Antibacterial antibiotic-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a literature review

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Abstract

Background Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) is a delayed infrequent potentially life-threatening idiosyncratic drug reaction. Aromatic anticonvulsants and allopurinol are the most frequent causative agents. However, various reports of antibiotic-induced DRESS are available. In this review, we try to summarize reports of antibacterial antibiotic-induced DRESS focusing on characteristics of DRESS induced by each antibiotic group.

Methods The data were collected by searching PubMed/MEDLINE and ScienceDirect. The keywords used as search terms were “DRESS syndrome,” “drug-induced hypersensitivity syndrome (DIHS),” “antibiotics,” “antimicrobial,” and names of various antimicrobial groups. Finally, 254 relevant cases with a definite or probable diagnosis of DRESS based on RegiSCAR criteria were found until 30 May 2020 and reviewed.

Results and conclusion Totally, 254 cases of antibacterial antibiotic-induced DRESS are reported. Most of them are related to antituberculosis drugs, vancomycin, and sulfonamides, respectively. Rash and fever were most frequent clinical findings. Eosinophilia and liver injury were the most reported hematologic and visceral organ involvement, respectively. Most of the patients are managed with systemic corticosteroids. The death occurred in 16 patients which most of them experienced liver or lung involvement. The reactivation of various viruses especially HHV-6 is reported in 33 cases. The mean latency period was 29 days. It is necessary to perform thorough epidemiological, genetic, and immunological studies, also systematic case review and causality assessment, as well as well-designed clinical trials for better management of antibiotic-induced DRESS.

Keywords DRESS syndrome · Drug-induced hypersensitivity syndrome (DIHS) · Antibiotics · Antimicrobial agents

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug-induced hypersensitivity syndrome (DIHS), and DIDMOHS (drug-induced delayed multi-

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and cytomegalovirus (CMV) reactivation [2, 8]. HHV-6 is the most reported one [9].

DRESS reaction characterized by a generalized exanthematous morbilliform rash, fever, enlarged lymph nodes, internal organ involvement (usually the liver and kidneys), and hematologic findings including leukocytosis with hyperesinophilia [2, 3]. Skin presentations can be as exfoliative erythroderma, follicular, or nonfollicular pustules, purpuric lesions or blisters, and tense bullae induced by dermal edema. Typically involved sites are the face, upper trunk, and extremities [5]. Additionally, encephalitis, aseptic meningitis, myositis, bleeding, thyroiditis, respiratory distress syndrome, pericarditis, myocarditis, pneumonitis, colitis, pancreatitis, hypotension, interstitial nephritis, arthritis, arthralgia, and orchitis have been reported as organ involvements which typically occurs 1–2 weeks after skin eruption [5]. The pulmonary manifestation of DRESS presents in a wide spectrum from mild cough or dyspnea with nonspecific interstitial changes on chest imaging to acute respiratory distress syndrome (ARDS) with life-threatening hypoxic respiratory failure [10]. The mortality rate due to DRESS is reported between 10 and 30% [11]. However, Kardaun et al. reported a considerably lower rate in the acute phase, probably reflecting bias in published retrospective studies [12]. Fulminant hepatitis is the main cause of death associated with this syndrome, occurring in 5 to 10% of cases [13]. Myocarditis and respiratory failure are other main causes of death [10].

Various criteria have been established for the identification of DRESS syndrome. The Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR) and the European registry on severe cutaneous adverse drug reactions (RegiSCAR) are the most commonly used clinical diagnostic criteria [14]. RegiSCAR seems to be more accurate and comprehensive but the J-SCAR considered viral reactivation as a diagnostic criterion in contrast to RegiSCAR. Besides, there are some other accessory tools for its confirmation like the lymphocyte transformation test (LTT), the intradermal test (IDT), and skin biopsy [15]. LTT could not be used for diagnosis but skin biopsy besides using diagnostic criteria like RegiSCAR could be helpful.

Fortunately, this reaction is usually reversible, with a low incidence of residual damage or mortality, in the case of timely discontinuation of antibiotics and the use of topical or systemic corticosteroids [16, 17]. But the efficacy of systemic corticosteroids is unclear and randomized clinical trials are lacking [18]. Experts recommend this measure for patients with life-threatening hepatitis, pneumonia, or nephritis [16]. Immunosuppressive therapy with agents such as cyclophosphamide or cyclosporine may be even essential in steroid-resistant cases [19]. In severe DRESS, plasma exchange or intravenous immunoglobulin (IVIG) has also been used, although data on this is limited [16]. Supportive procedures are also helpful, including fluid and electrolyte management and antihistamines for cutaneous symptoms relief [16].

Aromatic anticonvulsant drugs (e.g., carbamazepine, phenytoin, and phenobarbital) and allopurinol are the most common offending medications. However, various reports of DRESS induced by antimicrobial agents including vancomycin, sulfonamides, β-lactams, minocycline, and anti-viral medications are available [1, 3, 4, 16]. A recently published case series proposed that 15–37% of DRESS syndrome may be caused by antibiotics [16]. In an electronic health record review in the USA, from 1980 to 2016, antibiotics were attributed to DRESS syndrome in 74% of cases (vancomycin [39%], β-lactams [23%], fluoroquinolones [4%], tetracyclines [4%], and sulfonamides [3%]) [20]. Overall, the severity of the antibiotic-induced DRESS in comparison with other culprits is controversial. Some studies reported that it was less severe than anticonvulsant or allopurinol-induced DRESS [21, 22]. But Trubiano et al. proposed that it is associated with high hospital admission and longer length of stay and higher mortality rate [23]. Many questions remain to be answered about the DRESS syndrome induced by antibiotics. In this review, we have collected all available reports of DRESS syndrome with antibacterial antibiotics agents.

**Methods**

The data were collected by searching in PubMed/MEDLINE and Scopus. The keywords used as search terms were “DRESS syndrome,” “drug-induced hypersensitivity reaction (DIHS),” “antibiotics,” “antimicrobial,” “β-lactams,” “penicillins,” “cephalosporines,” “aminoglycosides,” “macrolides,” “fluoroquinolones,” “vancomycin & teicoplanin,” “glycopeptides,” “tetracyclines,” “clindamycin,” “linezolid,” “sulfonamides,” and “antituberculosis.” Criteria for inclusion were as follows: full-text case reports/series available online, without a limit of the publication date on patients with a definite or probable diagnosis of antibacterial antibiotic induced DRESS based on RegiSCAR criteria (when RegiSCAR score was unavailable it was calculated by the authors based on the information from the case report). Criteria for exclusion were as follows: duplicate publications, unavailability of full-text, language other than English, and review articles. Data collection was carried out between October 2019 and 30 May 2020. By searching these databases, 299 articles were found. Corresponding and first authors performed the search process and initial selection of eligible studies. The first author checked the eligibility of the studies based on RegiSCAR criteria. After excluding unrelated (n = 29) and duplicated (n = 38) articles and also the review or general articles (n = 30), 202 eligible articles (case reports/series) were review. Out of 202 articles, two articles were excluded for full-text unavailability, 13 for not being available.
in English, 31 articles as reported antiviral or antifungal induced DRESS, and 18 articles as the DRESS diagnosis was not definite or probable based on RegiSCAR criteria. Finally, a total of 138 relevant articles up to the date of preparation (May 30, 2020) were included for review that 254 cases were reported in these articles (Fig. 1). The related articles are summarized in Table 1 supplementary file.

**Discussion**

There are reports of DRESS with various antimicrobial categories that are reviewed below in a classified manner. For better understanding of the differences between various antibiotic groups, we summarized the important information in 4 tables. In Table 1, the prevalence of DRESS with various antibacterial antibiotic categories are reported. In Table 2, mean latency period and percentage of eosinophilia occurrence are presented for each antibiotic group. In Table 3, visceral organ involvement of different antibiotic groups is

| Antibiotic category | Number of reported cases (%) |
|---------------------|-----------------------------|
| Penicillin          | 22 (8.66)                   |
| Cephalosporin       | 10 (3.94)                   |
| Carbapenem          | 3 (1.18)                    |
| Aminoglycoside      | 2 (0.79)                    |
| Antituberculosis    | 107 (42.13)                 |
| Macrolide           | 2 (0.79)                    |
| Fluoroquinolone     | 5 (1.97)                    |
| Glycopeptides       | 46 (18.11)                  |
| Tetracycline        | 21 (8.27)                   |
| Lincosamide         | 3 (1.18)                    |
| Sulfonamide         | 23 (9.06)                   |
| Nitrofurantoin      | 3 (1.18)                    |
| Linezolid           | 1 (0.39)                    |
| Daptomycin          | 1 (0.39)                    |
| Others              | 5 (1.97)                    |
| Total               | 254                         |

![Diagram of the study selection process](image)

Fig. 1  Diagram of the study selection process
defined. Finally, in Table 4, patients’ outcome for various antibiotics induced DRESS is accessible.

**Penicillins**

Out of total 254 cases summarized in this review, 22 cases were related to penicillins which were corresponded to 8.6% of all cases. Limited numbers of penicillin-induced DRESS reaction are reported. Among these 22 cases, 17 cases are occurred by co-amoxiclav and piperacillin-tazobactam (Pip/Taz), which are beta-lactam–beta-lactamase antibiotics. It could propose this hypothesis that combination of penicillins with beta-lactamase may be more prone for DRESS syndrome triggering.

The latency period differed between cases from days to more than 1 month for amoxicillin-clavulanic acid. Most of cases (85.71%) experienced liver involvement but recovered completely. There is also a report of DRESS with amoxicillin-clavulanic acid in a pregnant woman, who presenting with erythematous plaques on the abdomen, developing cardiac tamponade because of eosinophilic perimyocarditis and an interstitial pneumonitis 5 weeks after exposure. Her symptoms improved after oral corticosteroid therapy and she had an uncomplicated, on-time delivery [24].

For Pip/Taz, the latency period was more than 2 weeks in all reported cases. In Cabanas et al., case series is stated that Pip/Taz is the principal cause of DRESS in their hospital, accounting for 26% of studied cases at the allergy department between 2006 and 2010 [3]. However, we just found 11 cases of Pip/Taz-induced DRESS (account for 4.33% of all collected antibiotic-induced DRESS). Circulating antigens derived from piperacillin and the drug-derived epitopes on proteins have been identified and completely described by Whitaker et al. [25] and proved that long-term treatment with very high doses of this reactive drug could be a risk factor for developing a T cell–mediated drug reaction. Drug–peptide conjugates derived from modified albumin clearly represent functional Ags for T cells and may indeed function as immunogens. As the half-life of modified human serum albumin is 19 days, it may also clarify why the meantime of skin symptom resolution is about 18 days, which is slightly shorter than that usually reported for DRESS syndrome (3–6 weeks; mean ± SD = 6.4 ± 9.4 weeks) [26].

The liver was the main involved internal organ in DRESS induced by Pip/Taz [35]. It seems that DRESS induced by piperacillin is milder, with a benign course and favorable prognosis [21, 22].

In a case of Pip/Taz-induced DRESS, which occurred with a 14-day latency period, patient reported numbness and paresthesia of the forearm during intravenous Pip/Taz infusion, 2 days before DRESS occurrence that may be the sign of upcoming DRESS [1].

Finally, a case could be mentioned that a patient experienced both acute generalized exanthematous pustulosis (AGEP) and DRESS with Pip/Taz, which is a rare finding [27].

Amoxicillin seems to have some role in triggering the DRESS in patients already showing signs of intolerance to sulfasalazine, but its role in the development of DRESS syndrome in people with no previous history remains unclear [4, 28–30]. Mardivirin et al. reported seven cases of DRESS flare with amoxicillin which was induced by other drugs. This reaction should be known because sometimes amoxicillin is considered as culprit drug, but the true offender drug had been taken for many weeks. It may cause a delay in the withdrawal of the true offending drug. It should be noted that complete manifestations of DRESS were too short after amoxicillin use to consider it as the culprit drug in these cases [31].

| Antibiotic category | Mean latency period (day) | Eosinophilia (%) | Mean eosinophil count (%) |
|--------------------|--------------------------|------------------|--------------------------|
| Penicillin         | 16.53                    | 81.8             | 32.94                    |
| Cephalosporin      | 19.4                     | 100              | 29.63                    |
| Carabapenem        | 4                        | 100              | 28.5                     |
| Aminoglycoside     | 31.5                     | 100              | 40                       |
| Antituberculosis   | 34.56                    | 95.33            | 32                       |
| Macrolide          | 5.5                      | 100              | 47                       |
| Fluoroquinolone    | 7.4                      | 100              | 49.75                    |
| Glycopeptides      | 21.23                    | 100              | 20.08                    |
| Tetracycline       | 28.48                    | 95.24            | 31.5                     |
| Lincomamide        | 12.33                    | 66.67            | 19.5                     |
| Sulfonamide        | 55.22                    | 91.3             | 16.5                     |
| Nitrofurantoin     | 5.33                     | 66.67            | –                        |
| Linezolid          | 7                        | 100              | –                        |
| Daptomycin         | 2                        | 100              | –                        |
The same reaction was reported after amoxicillin used in the patient with carbamazepine-induced DRESS, despite their chemical structure differences. The intradermal test to other beta-lactams was negative, defining a lack of cross-reactivity between amoxicillin and these drugs. Moreover, it should be noted that the second reaction usually is milder without organ involvement [32, 33].

In summary, clinicians should be cautious when prescribing amoxicillin to a patient with a previous history of DRESS syndrome. Skin tests to beta-lactams should be done in such a patient to define whether the patient can tolerate these drugs [34]. The pathophysiology of the reaction remains uncertain and HHV-6 and HHV-7 or EBV reactivation has been proposed as a mediating factor. Amoxicillin itself or viral reactivation might affect, through an immune-mediated mechanism

Table 3  Comparison of visceral organ involvement between different antibiotic groups

| Antibiotic category | Visceral organ involvement | Number (%) |
|---------------------|---------------------------|------------|
| Penicillin          | Liver                      | 21 (95.45) |
|                     | Kidney                     | 7 (31.82)  |
|                     | Lung                       | 1 (4.5)    |
|                     | Myocardium                 | 2 (9.09)   |
| Cephalosporin       | Liver                      | 8 (80)     |
|                     | Kidney                     | 3 (30)     |
|                     | Lung                       | 1 (10)     |
| Carbapenem          | Liver                      | 3 (100)    |
| Aminoglycoside      | Liver                      | 2 (100)    |
| Antituberculosis    | Liver                      | 77 (71.96) |
|                     | Kidney                     | 34 (31.78) |
|                     | Lung                       | 10 (9.35)  |
|                     | Myocardium                 | 1 (0.93)   |
|                     | CNS                        | 5 (4.67)   |
|                     | GI                         | 1 (0.93)   |
| Macrolide           | Liver                      | 1 (50)     |
|                     | Kidney                     | 2 (100)    |
| Fluoroquinolone     | Liver                      | 3 (60)     |
|                     | Kidney                     | 3 (60)     |
|                     | Lung                       | 1 (20)     |
| Glycopeptides       | Liver                      | 34 (73.91) |
|                     | Kidney                     | 34 (73.91) |
|                     | Lung                       | 12 (26.09) |
|                     | Myocardium                 | 1 (2.17)   |
| Tetracycline        | Liver                      | 20 (95.24) |
|                     | Kidney                     | 14 (66.67) |
|                     | Lung                       | 9 (42.86)  |
|                     | Myocardium                 | 4 (19.05)  |
|                     | Endocrine                  | 4 (19.05)  |
| Lincosamide         | Liver                      | 3 (100)    |
|                     | Kidney                     | 1 (33.33)  |
|                     | Lung                       | 1 (33.33)  |
| Pancreatitis        |                            | 1 (33.33)  |
| Sulfonamide         | Liver                      | 17 (73.91) |
|                     | Kidney                     | 4 (17.39)  |
|                     | Lung                       | 1 (4.35)   |
|                     | Myocardium                 | 1 (4.35)   |
|                     | Endocrine                  | 3 (13.04)  |
|                     | Serositis                  | 1 (4.35)   |
| Nitrofurantoin      | Liver                      | 3 (100)    |
|                     | Kidney                     | 3 (100)    |
|                     | Lung                       | 3 (100)    |
| Linezolid           | Liver                      | 1 (100)    |
|                     | Kidney                     | 1 (100)    |
| Daptomycin          | Liver                      | 1 (100)    |
|                     | Kidney                     | 1 (100)    |

Table 4  Comparison of patients’ outcome between various antibiotic groups

| Antibiotic category | Outcome               | N (%)   |
|---------------------|-----------------------|---------|
| Penicillin          | Death                 | 1 (4.55)* |
|                     | Complete resolution   | 20 (90.9) |
|                     | Partial resolution    | 1 (4.55)  |
| Cephalosporin       | Complete resolution   | 9 (90)  |
|                     | Partial resolution    | 1 (10)  |
| Carbapenem          | Complete resolution   | 3 (100) |
| Aminoglycoside      | Complete resolution   | 2 (100) |
| Antituberculosis    | Death                 | 7 (6.54)** |
|                     | Complete resolution   | 99 (92.52) |
| Macrolide           | Partial resolution    | 1 (0.94) |
| Fluoroquinolone     | Complete resolution   | 2 (100) |
| Glycopeptide        | Death                 | 2 (4.35) |
|                     | Complete resolution   | 43 (93.48) |
|                     | Partial resolution    | 1 (2.17)*** |
| Tetracycline        | Death                 | 4 (19.05) |
|                     | Complete resolution   | 16 (76.19) |
| Sulfonamide         | Death                 | 1 (4.35) |
|                     | Complete resolution   | 21 (91.3) |
|                     | Partial resolution    | 1 (4.35)*** |
| Nitrofurantoin      | Complete resolution   | 3 (100) |
| Linezolid           | Complete resolution   | 1 (100) |
| Daptomycin          | Partial resolution    | 1 (100)*** |

*Underlying pneumonia may be the reason of death
**Two deaths out of five were strongly related to DRESS
***She received liver transplant
****Disrupted LFT
or a direct toxic effect, a response against the components of the cytochrome P450 enzymes, reducing their detoxifying capacity [4]. It is also noteworthy that rash following administration of amoxicillin in patients with infective mononucleosis is important differential diagnosis and should be elaborated further.

As a summary, penicillin-induced DRESS accounts for less than 10% of reported antibiotic-induced cases. Liver was the most involved organ (in more than 90% of cases). However, two cases of myocarditis caused by co-amoxiclav were reported. The outcome was favorable in reported cases and no death happened due to DRESS (one death occurred in a patient who experienced Pip/Taz-induced DRESS; however, it seems to be related to underlying pneumonia).

**Cephalosporins**

Just 10 cases of DRESS syndrome with cephalosporins are reported until now (3.94% of all antibacterial antibiotic-reported DRESS cases) which most of them (n = 8) caused by third-generation cephalosporins. However, in a retrospective study from Korea in 2018, cephalosporins besides vancomycin and anti-TB medication are reported as the most common antimicrobial agents inducing DRESS [35]. Cefotaxime was known to cause the fewest adverse reactions among beta-lactam antibiotics [36]. However, some cases of DRESS are reported with this medication.

All patients managed with corticosteroid and antihistamines and just one case of cefuroxime-induced DRESS experienced hematuria for a long while after resolution of other symptoms. Moreover, like other beta-lactams, the liver and kidney were most reported organ involvements.

Fujiwaki et al. reported DRESS induced by cefotaxime and ampicillin. Fever occurred after 3 days but skin manifestation appears after 20 days [27]. There are some other case reports of cefotaxime-induced DRESS in adult and pediatric patients [37]. Aouam et al. reported a case of DRESS and also a case of DRESS-like syndrome (as no visceral involvement was found) [36].

Babu et al. reported the first case of cefpodoxime-induced DRESS syndrome, which the patient responded well to the steroid treatment [38].

The limited number of ceftriaxone-induced DRESS also is reported. In one case report, a 26-year-old patient who experienced DRESS with phenytoin reported sensitization to ceftriaxone after 2 months [33]. These kinds of reactions are reported in several cases with amoxicillin as mentioned above.

**Carbapenems**

Just three cases of carbapenem-induced DRESS are reported (1.18% of all 254 reported cases). All three patients experienced liver involvement and all of them survived after corticosteroid therapy. The latency period was almost shortest for carbapenem-induced DRESS cases in comparison with other antibacterial agents (4 days).

Overall, it could be concluded that beta-lactam-induced DRESS is typically benign mostly involving the liver and could be completely reversed with corticosteroid therapy.

**Aminoglycosides**

There are just two cases of confirmed DRESS with aminoglycosides (AGs) to the best of our knowledge (0.79% of all 254 antibiotic-related DRESS cases). Passeron et al. reported DRESS induced by streptomycin when it was used as an antituberculosis agent beside isoniazid, rifampicin, and ethambutol. Fever, lymphadenopathy, and morbilliform rash, followed by exfoliative dermatitis with stomatitis, hypereosinophilia, atypical lymphocytes, and signs of hepatitis were the clinical manifestations. Streptomycin was the most probable causative agent, as the cutaneous rash and itching increment followed by fever and rise in hepatic enzymes noted promptly after its reintroduction [39].

It is noteworthy that despite AGs’ bad reputation for nephrotoxicity, none of these two cases experienced kidney involvement. Both of them experienced hepatic involvement with completed resolution. The mean latency period also was longer than most of other antibiotic classes like beta-lactams.

**Antituberculosis**

As anti-TBs are well known for their hepatic and skin adverse effects independently, antituberculosis drug-associated DRESS has possibly been underdiagnosed and underreported for a few years [40]. However, actually, they compromised the largest part of antibacterial-reported DRESS cases, based on our searches. Out of total 254 cases summarized in this review, 107 cases were related to anti-TBs, which correspond to 42.13% of all cases. Rifampin (RIF) was the most reported offending agent among this category, followed by isoniazid (INH), ethambutol, and pyrazinamide, respectively [18, 40]. In a case series (n = 76), Allouchery et al. reported RIF (n = 60) and INH (n = 32) as the most common suspected drugs. However, excluding patients with a diagnosis other than tuberculosis who received RIF, INH was in the first place (n = 32), followed by RIF (n = 30), then pyrazinamide (n = 25), and finally by ethambutol (n = 22). No dose-dependent pattern was found in this study. The mortality rate of DRESS was about 3%, which is slightly higher than the previously reported rate (1.7%). This may be due to delayed diagnosis since antituberculosis drugs are not the first to be suspected [40].

However, Jung et al. study reported a different frequency. They proposed ethambutol as the most common causative anti-TB (53.5%), followed by RIF (26.7%).
latency of DRESS occurrence was 42 days. Moreover, there was a significant quantitative correlation between the RegiSCAR score and peak eosinophil count and a negative relationship between the RegiSCAR score and latency [41]. Based on this review, although the culprit medication for DRESS occurrence was not defined clearly in all collected case reports, considering reported data, rifampin followed by INH were most accused antituberculosis.

In another case series, 7 of the 11 studied patients were ethnically native South Americans, who are slow acetylator phenotypes for INH and a higher incidence of toxic hepatitis predominated. So, a genetic predisposition to DRESS syndrome may occur in this population [42].

As there is limited number of medication for the treatment of TB and they are used concomitantly in multi-drugs regimen, sometimes re-challenge is necessary to determine the exact culprit so treatment for TB can be continued. The drug re-challenging test is usually accepted as the gold standard for confirming the offending drug and minimizes unnecessary antituberculosis treatment discontinuation. In Palmero et al.’s study after drug discontinuation, they were reintroduced with a quarter of the initial dose and increased proportionally up to full dosage. The first medication was usually levofloxacin, followed by ethambutol. Only when these drugs were tolerated, reintroduction of INH and RIF were tried. It should be mentioned that a relapse of DRESS after the reintroduction of a culprit drug must be interpreted with caution [42]. Antituberculosis drugs could not be reintroduced until after the eosinophilia, rash, and toxic hepatitis had almost resolved. In comparison with the standard anti-TB regimen, the regimens after the resolution of DRESS syndrome comprised fewer drugs, with inferior antituberculosis activity [42].

Considering the differences in the chemical structure of antituberculosis medications, it is unlikely that there was cross-reactivity between them [40]. Lehloenya et al.’s study reported that the risk of cross-reactivity of isoniazid and ethionamide in DRESS syndrome is low [43].

Based on this review, the latency period is more than 1 month in average for anti-TB-induced DRESS and as these medications administered for several months in TB, the risk of DRESS occurrence is high. Moreover, various types of organ involvements other than liver and kidney are reported by these medication and mortality rate is almost higher in comparison with most of other antibiotic-induced DRESS (6.54%).

Macrolides

Some reports of adults and pediatric patients with infectious mononucleosis or Epstein-Barr virus infection (IM; EBV) who developed generalized eruptions following treatment with azithromycin are available [44]. The incidence of skin rash is higher in the antibiotic-treated IM patients than those who do not take antibiotics and it is proposed that many of the previously noted cutaneous eruptions of IM were antibiotic eruptions in the setting of an altered immune state resulting from the EBV infection [45, 46]. Amoxicillin was one of the first antibiotics which were connected to skin eruptions in IM. However, other antibiotics such as penicillin G or tetracycline also cause these reactions with much lower incidence. Later, other antibacterial drugs were also related to skin symptoms in IM, such as amoxicillin, talampicillin, or methicillin and few cases were reported about cephalixin, levofloxacin, erythromycin, and azithromycin [46]. The eruptions usually occur 2–10 days after starting the antibiotic treatment which is shorter than usual latency period for DRESS. Besides, no organ involvement occurs. This may result in a hypersensitivity reaction to an antigen, which in the case of antibiotics could manifest as a drug eruption [47]. Both the clinical and histological features confirm a delayed type hypersensitivity reaction [46].

Just two cases of probable DRESS with azithromycin are reported (0.79% of 254 reviewed cases) and it seems that macrolides rarely are culprits for DRESS. Both reported cases occurred shortly after medication use (mean 5.5 days) and experienced kidney involvement but it resolved after corticosteroid therapy and supportive care.

Fluoroquinolones

Just 5 reports are available regarding DRESS induced by ciprofloxacin and levofloxacin (1.97% of all 254 reviewed cases). The shorter latency period is a unique characteristic of (FQ) fluoroquinolone-induced DRESS syndrome. Alkhateeb et al. presented a case of ciprofloxacin-induced DRESS syndrome with a beginning of symptoms only 2 days after drug exposure [48]. It is interesting to note that the same finding is observed in idiosyncratic ciprofloxacin-induced liver injury [49]. However, based on this review, the mean latency period was 7.7 d. Moreover, it seems that FQ-induced DRESS is mild and eventually is controlled a few days after drug discontinuation in many cases without any other intervention. However, the same outcome is reported in some other antibiotic groups like macrolides, aminoglycoside, carbapenems, and nitrofurantoin. Among visceral involvement, liver injury meaningfully less commonly occurred by FQs. Just 3 patients (60%) experienced liver involvement, which occurred in more than 70% for DRESS induced by the other antibiotic groups except macrolides. It should also be mentioned that three patients experienced kidney involvement and one patient lung injury. The highest liver involvement frequency is reported by clindamycin and nitrofurantoin (three out 3 cases); however, considering the number of reported DRESS cases, it could be concluded that tetracyclines induced lots of liver injury and other organ involvements and had the highest mortality rate (19.05%).
Glycopeptides

Vancomycin may cause different adverse reactions including the “red man syndrome,” erythema multiforme, vasculitis, allergic exanthema, anaphylaxis, agranulocytosis, thrombocytopenia, linear IgA bullous disease, and Stevens-Johnson syndrome/toxic epidermal necrolysis and also DRESS. Out of total 254 cases summarized in this review, 46 cases were related to vancomycin which corresponds to 18.11% of all cases. Most of the reported glycopeptide-induced DRESS belonged to vancomycin.

Cacoub et al.’s literature review found 2% of reported DRESS cases occurred with vancomycin [2]. It was first described in single case reports in 2005 and 2006, and subsequent case reports characterized the diagnosis and its association with HHV-6 reactivation. Moreover, the patient with the highest HHV-6 titers had a prolonged and severe clinical course [16]. Besides, Konvinse et al. proposed that HLA-A*32:01 is severely associated with vancomycin-induced DRESS in a population of predominantly European ancestry [50].

DRESS syndrome happened within 2–5 weeks after starting vancomycin treatment [17]. In this review, we found a mean time of 21.23 days, which is shorter than anti-TBs and sulfonamides but much longer than beta-lactam latency time.

The age of patients who experienced DRESS with vancomycin is mentioned to be higher than other culprit drugs [35]. Risk factors for vancomycin-induced DRESS are prolonged therapy with vancomycin (> 7 days) and age > 40 years [51].

In comparison with other antibacterial groups, vancomycin DRESS seems to have more renal involvement and is reported in about 75% of cases [52]. This is near to the percentage we found in this review (73.91%). Vancomycin typically attributed to acute interstitial nephritis (AIN), and less usually has been associated with acute tubular necrosis (ATN) during DRESS. One case of vancomycin-induced ATN as a complication of DRESS is reported by Kim et al. [53]. Vancomycin trough levels > 15 mg/L are an independent predictor of nephrotoxicity, but any relationship with DRESS has not been examined [54]. Based on our review, just in 3 cases out of 13 patients who trough level of vancomycin was reported for them, the level was higher than recommended range (23.08%). So, it seems that they may not be related. Pulmonary involvement was reported in 5% of vancomycin-induced DRESS [55]. Based on our data, kidney and liver involvements had the same prevalence (73.91%), followed by lung damage (26.09%) which is much higher than abovementioned prevalence. Kidney injury is a little bit more common with vancomycin which may be somewhat related to its nephrotoxic nature. However, contrary to this hypothesis, the nephrotoxic antibiotics, aminoglycosides, did not cause renal involvement as a complication of DRESS.

DRESS may be followed by antibody deficiency and autoimmune phenomena with other medications. For example, Wendland et al. reported that in a patient who experienced DRESS induced with vancomycin and daptomycin, agranulocytosis occurred with ceftobiprole, a fifth-generation cephalosporin [56].

Withdrawal of vancomycin and the use of systemic corticosteroids improved both cutaneous and systemic appearances of DRESS syndrome in most cases [16, 17]. Just two deaths related to DRESS are reported by glycopeptides (4.35%), both of them caused by vancomycin.

It is important to note that the clinical presentation of DRESS may mimic ongoing or worsening sepsis, and consideration of alternative diagnoses such as DRESS beside sepsis is vital for optimal outcomes [16].

It should be considered that vancomycin used in bone cement does not have a significant role in the development of HSS/DRESS syndrome [57].

Teicoplanin, another glycopeptide antibiotic, also caused DRESS syndrome in limited number of patients. The onset of teicoplanin-induced DRESS ranges from 3 to 28 days. Reported cases have good outcomes, with all patients surviving after the instant withdrawal of the teicoplanin and supportive symptom treatment [58]. We found 7 cases with average latency period of 11.71 days and all of patients survived. Allergic cross-reactivity between vancomycin and teicoplanin has been reported infrequently [59]. Thus, hypersensitivity to vancomycin is not a contraindication to the use of teicoplanin if it was necessary [19]. However, Miyazu et al. described a case of DRESS with rash, interstitial pneumonitis, and eosinophilia caused by cross-reactivity between vancomycin and the following teicoplanin administration [59]. So, it is better to be cautious.

Tetracyclines

There were 21 cases of tetracycline-induced DRESS (8.27% of antibiotic-induced DRESS cases) which most of them are related to minocycline, with long latency period in most of the cases (mean latency period of 28.48 days). Despite general safety records, doxycycline has been reported to have caused side effects, such as pseudotumor cerebri, AGEP, DRESS, and also Stevens-Johnson syndrome [60]. Just two cases of doxycycline-induced DRESS are reported to the best of our knowledge.

Minocycline-induced DRESS is related to various organ involvements including the liver, kidney, myocardium, lung, and endocrine system. Two concerning minocycline-associated adverse reactions are autoimmunity and DRESS [61]. Although it has anti-inflammatory characteristics, the drug has been linked to many autoimmune disorders, including drug-induced lupus erythematosus, serum sickness–like reactions, vasculitis, and autoimmune hepatitis [62].
Minocycline-induced DRESS occurs generally in patients with Fitzpatrick skin phototypes V and VI. Patients with these phototypes had significant plasma and skin levels of minocycline even as long as several months after discontinuation of minocycline therapy. Melanin-minocycline complex formation may be the cause of this reaction in these patients [63]. Lung involvement seems to be more common in minocycline-induced DRESS [64]. We also found pulmonary involvement in about half of patients with tetracycline-induced DRESS (42.86%). However, the recent systematic review on pulmonary manifestations of DRESS syndrome has not found this association. They mentioned that lungs are less frequently involved in DRESS syndrome, but it may be related to a more severe clinical course and higher mortality [10]. Based on our review also, one-third of patients with lung involvement died (3/9).

In Brown et al.’s study, the patient experienced type 1 diabetes mellitus, Graves’ disease, and positive antinuclear and anti-Smith antibodies during several months after minocycline exposure, suggesting a long-term immune system changes following DRESS rather than a short-term acute effect of minocycline [62]. It is believed that T regulatory (T-reg) cells play an important role and significantly increased during the acute stage of DRESS. Consequently, it increased immune suppression and at least in part have contributed to the autoimmunity. The combination of nonfunctional T-reg cells and viral reactivation can synergistically promote autoimmunity in an organ-specific or systemic manner. Moreover, some studies have linked DQA1*0303, DQB1*0401, and HLAB62 with fulminant T1DM after DRESS. Inherent immunomodulatory effect of minocycline is also important [65].

Hypersensitivity myocarditis, also known acute eosinophilic myocarditis (giant cell myocarditis [GCM]), is a rare potentially fatal manifestation of minocycline-induced DRESS reaction, and seven cases are reported until now. These specific organ failures lead to high mortality rate in comparison with other antibiotics induced DRESS (20%).

Finally, it should be noted that there is a possibility of tetracycline cross-reactivity with DRESS, and any tetracycline including tigecycline should be avoided in patients with a history of tetracycline-associated DRESS [7].

### Lincosamide

There is three reports of clindamycin induced DRESS out of all 254 reported cases (1.18%). Tian et al. reported clindamycin induced DRESS without organ involvement which was successfully treated by oral prednisolone [66].

In a clindamycin induced DRESS case reported by Nakamura et al., there was no evidence of HHV-6, EBV, and CMV reactivation, but there is a probability that HHV-7 reactivation may contribute to the development of the reaction. As this patient had hypogammaglobulinemia, IVIG in addition to intravenous corticosteroid was prescribed. They expected that IVIG compensates for the decreased immunoglobulin concentration and besides the therapeutic effect of IVIG may be partially due to the presence of anti-viral IgG in it [67].

However, Quidley et al. represented a much more severe clindamycin induced DRESS syndrome that finally resulted in death. She developed an early rash and presented with concomitant renal and hepatic involvement. Her condition rapidly deteriorated despite the fast discontinuation of the medication and even IVIG administration. Hepatic involvement is proposed a predictor of poor prognosis in this patient [68]. However, the two other cases also experienced liver involvement but survived. Multi-organ failure including liver, kidney, pancreas and lung may cause death in this patient.

### Sulfonamides

Sulfonamide antibiotics, particularly cotrimoxazole, are extensively associated with DRESS. Out of total 254 cases summarized in this review, 23 cases were related to sulfonamides, which correspond to 9.06% of all cases. However, the non-antibiotic sulfonamides like furosemide have not frequently been reported to cause DRESS syndrome. Different metabolic pathways of several sulfâ±containing compounds which lead to dissimilar reactive metabolites with specific immunogenic reactivity could be a possible reason for abovementioned finding [69].

The liver was the main involved internal organ; however, a DRESS with multi-organ involvement was reported by dapson. It is also noteworthy that in about half of the cases a viral reactivation was also present.

Gastrointestinal and hypersensitivity reactions are the main adverse reaction of trimethoprim/sulfamethoxazole (TMP/SMX) and Stevens-Johnson syndrome, interstitial nephritis, toxic epidermal necrolysis, DRESS, agranulocytosis, and aplastic anemia are the most severe ones [70]. SMX is perhaps the responsible drug as it is a member of the sulfa groups of drugs, which can cause DRESS in association with HHV-6 [71]. N-acetyl-SMX, a SMX metabolite, is part of a potential route that makes immune cells more susceptible to react to certain drugs, resulting in the development of DRESS [70].

As mentioned above, TMP/SMX-induced fulminant hepatitis is a component of DRESS syndrome, occurring as soon as 1 day, or up to 6 weeks after first exposure and it managed usually successfully with corticosteroid and antihistamine use [72]. However, based on our review, the shortest latency period for TMP/SMX was 7 days.

Rueda-Valencia et al. reported a 4-year-old case with sickle cell anemia that experienced DRESS induced by TMP/SMX. The hypertransfusion treatment received by the patient might act as a predisposing factor [73].
Dapsone (4, 4′-diamino-diphenyl sulfone) is generally used in the treatment of inflammatory disease and infections such as Pneumocystis jiroveci pneumonia in patients with HIV infection, neutrophilic dermatoses, dermatitis herpetiformis, leprosy, and autoimmune bullous disease [74]. Dapsone-induced DRESS rate is 0.2–0.5% and it has the longest latency period among antibiotics that induced DRESS (mean time 131 days based on available cases). The fever is almost reported in all patients who experienced DRESS induced by dapsone. Hepatitis, lymphadenopathy, and atypical lymphocytosis were also common [35]. In nonleprosy patients, the HLA-B*13:01 allele was severely associated with dapsone-induced DRESS [74]. This allele is mostly absent in Europeans and Africans, but it has an allele frequency of 1–12% in Indians, 2–4% in Southeast Asians, 1.5% in Japanese, and a markedly high prevalence of up to 28% in Australian Aborigines, Taiwanese, and Papuans [75].

It also should be mentioned that in one case of dapsone-induced DRESS, it causes thyroiditis or myocarditis which are not common with most of the other antimicrobial agents [76]. Yusef reported a case of DRESS syndrome in a patient with toxoplasmosis infection, appearing during 8 weeks beginning of sulfadiazine [77].

It seems that no cross-reactivity occurred between different sulfonamides regarding DRESS syndrome [78].

**Other antibiotics**

Linezolid generally is well tolerated, except its thrombocytopenia and gastrointestinal side effects. A case of linezolid-induced DRESS happened after 7 days of use. The relatively short latency period in this report could be explained by earlier exposure to a single dose of linezolid on day 5 of hospitalization [79].

Three cases of nitrofurantoin induced DRESS are reported with liver, kidney, and lung involvements (1.18% out of 254 reported antibiotic-induced DRESS cases). These reactions occurred shortly after nitrofurantoin use and completely resolved by routine measures. One report of daptomycin-induced DRESS is also available which occurred just 2 days after its administration with kidney and liver involvement. The patients’ LFT did not completely resolve in follow-up period [80].

There are also many other cases of antimicrobial antibiotic induced DRESS, which are not mentioned in this review directly, but all of them are summerized in a table, presented as a supplementary file [81, 82–170].

**Limitations**

As we just included the English manuscripts, from limited electronic databases, a number of eligible studies may be missed out resulting in a selection bias. Moreover, as in some articles, the RegiSCAR score was not mentioned, and for the confirmation of the diagnosis, we decided to score the cases by ourselves. So, it is possible that in 15 omitted studies based on the criteria, some necessary information for the RegiSCAR score calculation were not mentioned in the article, and maybe they were definite or probable cases. Moreover, the RegiSCAR of reported cases are checked just by first author which was better to be done by two separate authors to minimize the selection bias.

**Conclusion**

In this review, 254 cases of antimicrobial antibiotic-induced DRESS with definite or probable diagnosis based on RegiSCAR criteria are collected. Most cases are related to anti-TBs, glycopeptides, and sulfonamides, respectively. The mean latency period was 29.26 days (range 2–300 days). The longest latency period was related to sulfonamides and anti-TBs. Eosinophilia was the most reported hematologic involvement which occurred in about 93.7% of patients. Liver injury is the most defined type of organ damage (194 cases). Renal involvement was in the next place, which usually mild and recovered after medication discontinuation without permanent sequelae. The death occurred in 16 patients which most of them experienced hepatitis and/or pneumonitis. The highest mortality rate belonged to tetracyclines and anti-TB antibiotics. The reactivation of various viruses especially HHV-6 is reported in 33 cases. It is necessary to perform thorough epidemiological, genetic, and immunological studies, also systematic case review and causality assessment, as well as well-designed clinical trials for improving management of antibiotic-induced DRESS.

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