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VANCOMYCIN-INDUCED DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS: A CASE REPORT

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Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a delayed, potentially fatal hypersensitivity reaction, and vancomycin has emerged as one of the antibiotics most often reported as a cause. This review draws on published case reports, case series and mechanistic studies to describe how vancomycin-associated DRESS presents, how it is diagnosed, and how it has been managed. Typical features include a latency of weeks, fever, rash, facial oedema, eosinophilia and hepatic or renal involvement, with herpesvirus reactivation and HLA-A*32:01 implicated in pathogenesis. Withdrawal of vancomycin and systemic corticosteroids are the mainstay of care. The literature consists largely of single reports, which limits conclusions on incidence and optimal treatment. No new patient data are presented.

1. INTRODUCTION

Few antibiotics are used as widely in hospital medicine as vancomycin. It is the standard glycopeptide for serious infection with meticillin-resistant *Staphylococcus aureus*, and it is given routinely for bone, bloodstream, device-related and some gastrointestinal infections [1, 2, 3]. Its adverse effect profile is well known to most prescribers: nephrotoxicity, ototoxicity, neutropenia and the infusion-related flushing once called red man syndrome. A delayed immune-mediated reaction that appears weeks into a course is far less familiar, and when it does appear it is easily put down to the underlying infection, to another drug the patient is taking, or to a viral illness.

The reaction in question is drug reaction with eosinophilia and systemic symptoms, better known as DRESS. The name emerged in the mid-1990s, when clinicians separated a drug-induced eruption accompanied by fever, lymph node enlargement, blood abnormalities and internal organ involvement from the pseudolymphoma group of reactions [4]. Later work showed that the same condition had been described under several labels, including drug-induced hypersensitivity syndrome, and that the clinical pattern was distinct enough to deserve its own diagnostic criteria [5, 6]. Aromatic anticonvulsants, allopurinol and sulfonamides were the first drugs to be recognised as typical triggers. Vancomycin has since taken a prominent place among reported antibiotic causes.

This article is a narrative review of published reports of vancomycin-induced DRESS. The title refers to a case report, but the text does not describe any individual patient and presents no new clinical data. Instead it brings together what the published case literature, case series and mechanistic work say about presentation, pathogenesis, diagnosis and treatment, and it sets the reports in the wider context of what is known about DRESS from larger registries [6, 7, 8]. The purpose is practical. A pharmacist or physician who recognises the pattern early, withdraws the drug and avoids further exposure can prevent a prolonged and sometimes life-threatening illness.

2. VANCOMYCIN AND ITS ADVERSE REACTIONS

Vancomycin is a large glycopeptide that binds the D-alanyl-D-alanine terminus of cell wall precursors and blocks peptidoglycan synthesis in Gram-positive bacteria. It is not absorbed from the gut and is given intravenously for systemic infection, with dosing individualised by renal function and, in many hospitals, by monitoring of trough or area-under-the-curve exposure [1]. Because courses for osteomyelitis, endocarditis or prosthetic joint infection can run for six weeks or longer, patients often receive the drug across the very period during which delayed hypersensitivity develops [2]. Long exposure is not a feature of the immune reaction itself, but it provides the time in which a reaction can declare itself.

The commonest immediate reaction is the vancomycin infusion reaction, which results from direct, non-immunological histamine release from mast cells and is related to the rate of infusion rather than to prior sensitisation [9]. It produces flushing, itching and sometimes hypotension, and it settles when the infusion is slowed or an antihistamine is given. A systematic review of case reports of immune-mediated reactions to vancomycin found a broad spread of phenotypes, including maculopapular exanthems, linear IgA bullous dermatosis, drug fever, interstitial nephritis, cytopenias and severe cutaneous adverse reactions, with DRESS and Stevens-Johnson syndrome among the more serious ones [10]. Such series are hard to interpret quantitatively, since they collect published curiosities instead of unselected cases.

Adverse drug reactions are traditionally divided into type A, which are dose-dependent and predictable from the pharmacology (the nephrotoxicity of vancomycin is the familiar example [11]), and type B, which are idiosyncratic and depend on host factors. DRESS belongs firmly to the second group. It does not follow the serum concentration of vancomycin and has been described in patients whose levels were therapeutic. Recognising this distinction matters in practice. A clinician used to adjusting vancomycin doses in response to rising creatinine may be tempted to lower the dose when a rash or abnormal liver tests appear, whereas in DRESS the drug needs to be stopped, since reducing the dose will not halt an immune response that has already been set in motion.

Renal handling is also relevant. Vancomycin is eliminated almost entirely by glomerular filtration, so its half-life lengthens considerably as kidney function falls, from a few hours in healthy adults to many days in advanced renal failure [1, 2]. A patient who develops interstitial nephritis as part of a hypersensitivity reaction therefore faces an extra problem: the drug accumulates just when the organ clearing it is injured, and exposure continues even after the last dose has been charted. This helps explain why

symptoms sometimes worsen for several days after withdrawal, and why dose-reduction strategies offer no safety margin once an immune reaction has begun.

3. DRESS: DEFINITION AND PATHOGENESIS

The most useful clinical description of DRESS comes from the RegiSCAR group, which collected cases prospectively across Europe and proposed a scoring system based on fever, enlarged lymph nodes, eosinophilia, atypical lymphocytes, skin involvement, organ involvement, duration and exclusion of other causes [5]. Scores classify a case as no, possible, probable or definite DRESS. The system gave the field a common language and replaced competing sets of criteria that had been used in Japan, France and elsewhere [5, 12]. It is a diagnostic aid, not a perfect test, and cases that score low can still be genuine if features have been masked by treatment or are not yet fully developed.

The pathogenesis is thought to involve three interacting elements: the drug, a genetically susceptible immune system and viral reactivation. A strong genetic link has been shown for vancomycin specifically. A case-control study reported that HLA-A*32:01 was present in a large majority of patients with vancomycin-induced DRESS but in only a small fraction of vancomycin-tolerant controls, a difference of a magnitude seldom seen in drug hypersensitivity [13]. Carriage is not required for disease and most carriers never develop it, so the allele is better seen as a risk marker than a predictor. Population frequency of the allele is highest in people of European ancestry, which may bear on screening ideas.

Reactivation of herpesviruses is the second pillar. Patients with DRESS often show reactivation of human herpesvirus 6, followed in some by Epstein-Barr virus, cytomegalovirus or human herpesvirus 7, in a sequence reminiscent of that seen in graft-versus-host disease [14, 15]. Studies of the T-cell response suggest that expanded populations of virus-specific and drug-specific cells are both found in the blood and skin of patients during the acute phase [16]. Whether the viruses drive the disease or simply respond to the immune dysregulation it causes is not settled. The debate has practical weight, because viral reactivation has been associated with prolonged courses, relapse and fatal outcomes, and it has been suggested that monitoring viral load could identify high-risk patients [17, 18].

How a drug as large as vancomycin triggers T cells is still debated. The classical hapten model proposes that a reactive drug or metabolite binds covalently to a self-protein, producing a neoantigen that is processed and presented. Vancomycin is not known to form such bonds easily. An alternative, the pharmacological interaction concept, suggests that a drug can bind non-covalently and directly to the T-cell receptor or to the HLA molecule, stimulating cells without processing [13]. The strong HLA-A*32:01 association fits the second idea, though it does not prove it, and functional studies of vancomycin-specific T cells remain few. Whichever mechanism proves correct, it will need to explain the unusual delay before disease appears.

Eosinophils contribute to tissue damage, and the cytokine milieu, including interleukin-5, is thought to explain the eosinophilia that gives the syndrome part of its name. Regulatory T cells appear to be transiently expanded and functionally impaired early in the illness, which may allow the broad immune activation that follows [16, 17]. Metabolic factors have been proposed as well, notably an inherited inability to detoxify reactive drug metabolites, a concept developed for anticonvulsant hypersensitivity [19]. For vancomycin, which is not extensively metabolised, such an explanation is less obvious, and the HLA association points more toward direct T-cell recognition of the parent drug presented by a particular major histocompatibility complex molecule [13].

4. CLINICAL FEATURES IN PUBLISHED VANCOMYCIN CASES

Published reports describe a fairly consistent picture. Fever is nearly universal and is usually the first sign that something is wrong, followed by a widespread morbilliform or maculopapular eruption that begins on the

face, upper trunk and arms and spreads downward. Facial oedema is a strong clue to the diagnosis and is much less common in simple drug exanthems [7, 8]. The rash may become infiltrated, scaly or purpuric, and erythroderma is reported in more severe cases. Lymph node enlargement, often in the neck and axillae, is another frequent finding. Mucosal involvement, when present, tends to be mild and mainly affects the lips, which helps set DRESS apart from Stevens-Johnson syndrome [6, 20].

Blood tests show eosinophilia in most patients, though it may be absent early in the illness or masked by corticosteroids, and atypical lymphocytes are common. Liver involvement is the commonest internal organ manifestation in large series, usually as a rise in transaminases with a hepatocellular or mixed pattern, and in the most severe cases acute liver failure [21, 22, 23]. Renal involvement, from interstitial nephritis, is next most frequent and is especially relevant to vancomycin, where drug-related nephrotoxicity is already a concern [24, 25]. Lung, heart and gastrointestinal tract involvement are less common but carry a worse prognosis. Eosinophilic myocarditis is rare yet can be fatal, and any chest symptoms warrant prompt evaluation.

A recurring problem in the vancomycin reports is the overlap between DRESS and ordinary vancomycin nephrotoxicity. A rising creatinine in a patient on vancomycin has many causes, and a clinician reading the chart may conclude that the drug is damaging the kidney directly, which would prompt dose adjustment rather than withdrawal [1, 24]. The presence of rash, fever, eosinophilia and abnormal liver tests alongside renal dysfunction should shift thinking toward a hypersensitivity process. Case descriptions of interstitial nephritis with marked eosinophilia, including one with profound refractory eosinophilia, illustrate how the kidney can be a dominant organ in vancomycin DRESS [24]. Urinary eosinophils are neither sensitive nor specific, and biopsy is occasionally needed.

Some of the information in published case reports is summarised in table 1, which is arranged by diagnostic, organ, mechanistic and management themes instead of by individual patient. The distribution of entries is shown in fig. 1. The table makes a few points visible. Diagnostic criteria and descriptions of organ involvement are well supported by larger series, whereas observations specific to vancomycin rest on a handful of case reports and one genetic association study. Management statements are drawn largely from DRESS in general, since controlled treatment studies in vancomycin DRESS do not exist.

The course is often prolonged. Even after the culprit has been withdrawn, fever and organ abnormalities can wax and wane for weeks, and relapses occur as corticosteroids are tapered. A long-term follow-up series of patients with the closely related drug-induced hypersensitivity syndrome described flares and found that some patients went on to develop autoimmune conditions such as thyroid disease or type 1 diabetes months to years afterwards [18, 26]. Mortality in early series was around one in ten, driven mainly by liver failure and by cardiac or pulmonary involvement, although more recent registries suggest a somewhat lower figure when cases are recognised and treated early [6, 7, 22].

Putting the reports side by side suggests a typical timeline. The first two to three weeks of vancomycin pass without incident, apart from the infection being treated. A low-grade fever and itch then appear, often attributed to the infection or to another drug. Within days a rash spreads, blood tests show rising eosinophils and transaminases, and the patient is admitted or, if already in hospital, reviewed by dermatology [6, 27, 28]. The syndrome peaks over the following one to two weeks, and organ function recovers slowly once treatment has started. Describing this arc to junior staff is more useful than reciting the diagnostic score, because it teaches them what the early phase looks like.

Age and comorbidity colour the presentation. Older patients, those with chronic kidney disease and those receiving multiple medicines are well represented in reports of vancomycin DRESS, which probably reflects who receives prolonged courses of the drug and not an intrinsic susceptibility. Patients on immunosuppressive treatment may have

blunted eosinophilia or rash, delaying recognition. In a patient with bone infection who has already received several weeks of intravenous therapy, a new fever may be attributed to relapse of infection, and the antibiotic may even be escalated, which makes things worse [27, 28]. Awareness of this trap is probably the most useful single lesson that case reports offer.

Table 1: Features of vancomycin-associated DRESS drawn from published reports and related DRESS literature

Feature	Reported finding	Ref.
Diagnostic scoring RegiSCAR	Scores fever, nodes, eosinophils, atypical lymphocytes, rash, organs and exclusion of other causes	[5, 6]
Latency time to onset	Usually weeks after starting; vancomycin reports often describe two to four weeks	[6, 27, 28]
Skin and face rash, oedema	Widespread eruption with facial oedema; mucosal change mild if present	[7, 20]
Liver hepatic injury	Most frequent organ involvement; severe cases progress to acute liver failure	[21, 23]
Kidney interstitial nephritis	May be mistaken for vancomycin nephrotoxicity; eosinophilia can be marked	[22, 24]
Genetics HLA association	HLA-A*32:01 strongly associated with vancomycin DRESS in a case-control study	[13]
Viral reactivation herpesviruses	HHV-6 and others reactivate in sequence; linked to prolonged and severe disease	[14, 15]
Corticosteroids first-line therapy	Prolonged taper commonly used; benefit inferred from retrospective series	[29, 30]
Ciclosporin second-line option	Rapid improvement in small series; allows early steroid withdrawal	[31]
Alternative antibiotics MRSA cover	Daptomycin non-inferior in bacteraemia; teicoplanin generally avoided	[32, 33]
Late sequelae follow-up	Autoimmune thyroid disease and diabetes reported months to years later	[18, 26]

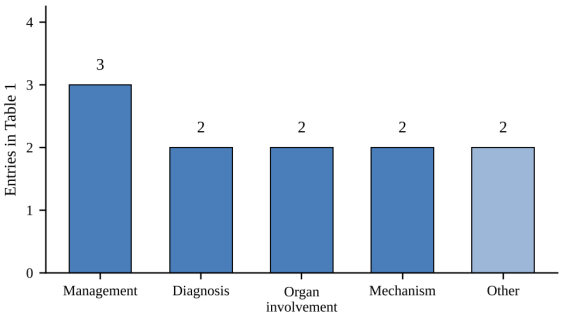


Fig. 1: Number of entries in table 1 by theme

5. DIAGNOSIS AND CAUSALITY ASSESSMENT

A diagnosis of DRESS depends on clinical recognition and exclusion of mimics. The differential includes viral exanthems, Epstein-Barr virus infection, sepsis, lymphoma, hypereosinophilic syndromes, vasculitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, and systemic infection with the organism being treated [8, 20, 34]. Baseline investigation usually comprises a full blood count with differential, liver and renal function tests, urinalysis, creatine kinase, troponin and an electrocardiogram when cardiac involvement is suspected, and chest imaging if there are respiratory symptoms. Serology and polymerase chain reaction for viruses are often added, partly to exclude other causes and partly to look for reactivation [6, 7].

Skin biopsy is not diagnostic but helps to exclude other conditions. Histology in DRESS is variable, with perivascular lymphocytic infiltrates, eosinophils, spongiosis and sometimes interface change, and the findings do not distinguish it from a simple drug exanthem [8, 20]. The RegiSCAR score is therefore the central tool, and it should be recalculated as results come in because it may change over days. Eosinophil counts above the upper limit of normal, along with atypical lymphocytes, contribute to the score, so it is worth recording the nadir and peak values and repeating the count after the first week [6, 35].

Causality assessment aims to decide which drug is responsible, and it is more difficult in DRESS than in immediate reactions because several suspects, a long latency and delayed onset are typical. Structured algorithms such

as the French imputability method, which scores chronology and semiology of the reaction together with alternative causes, are widely used in case reports, though it was designed with simpler reactions in mind [36]. Tools developed for severe cutaneous reactions, such as algorithms based on drug notoriety, latency and dechallenge, may fit better. A thorough drug history with start and stop dates, plotted against symptom onset, remains the most informative single step in any investigation [36].

Monitoring policies provide a practical safeguard. Guidelines on therapeutic drug monitoring focus on trough or exposure targets and creatinine, but patients on courses longer than two weeks also warrant periodic full blood counts with differential and liver tests, which are already part of routine care in many bone and joint infection services [1]. A rising eosinophil count, even before rash, is a signal to review the drug list. The cost of an additional blood test is small compared with that of a missed hypersensitivity reaction, and pharmacists who review these results at ward rounds are well placed to spot patterns that individual clinicians may not.

Confirmatory testing is limited. Patch testing performed several months after recovery can identify the culprit in a proportion of patients and is regarded as safe when done by an experienced centre, though the sensitivity differs between drugs and is not well characterised for vancomycin [8, 29]. Lymphocyte transformation tests and in vitro T-cell assays are available in specialised laboratories. Oral or intravenous rechallenge is contraindicated because of the risk of a more severe recurrence. Where HLA typing is accessible, detection of HLA-A*32:01 may add supporting evidence in a patient of European descent, but a negative result does not exclude the diagnosis [13].

6. MANAGEMENT AND OUTCOME

Prompt withdrawal of the suspected drug is the first and most important step, and it should be accompanied by a search for an alternative agent for the infection if treatment must continue. Supportive care follows from the organ pattern: fluid and electrolyte management, skin care with emollients and topical corticosteroids, antipyretics, and monitoring of liver, kidney and cardiac function [8, 29]. Patients with extensive skin involvement, marked organ dysfunction or haemodynamic instability are managed in a high-dependency or burns setting. Allergy documentation should be completed before discharge so that vancomycin is not restarted by another team, and the patient should be told clearly which drugs to avoid.

Systemic corticosteroids are the usual treatment for patients with significant organ involvement. Retrospective series suggest that prednisolone or equivalent at about 0.5 to 1 mg/kg daily, tapered over several weeks, is common practice, and rapid tapering is associated with relapse [29, 30]. Evidence for benefit rests on observation and is confounded by indication, because the sickest patients are the ones most likely to receive steroids. A French retrospective study of 38 patients also reported that milder cases could sometimes be managed with potent topical corticosteroids alone, reserving systemic therapy for those with organ involvement [30]. Randomised trials are lacking, so practice varies from centre to centre, and steroid exposure itself adds risks of infection, hyperglycaemia and mood disturbance in patients already unwell.

Second-line therapies are reserved for steroid-dependent or refractory disease and for patients in whom steroids are risky. Ciclosporin has been reported to produce rapid improvement in small series, with the advantage of a short course and quick steroid withdrawal [31]. Intravenous immunoglobulin, plasmapheresis, rituximab and anti-interleukin-5 antibodies are described in case reports. Where reactivation of cytomegalovirus is documented with organ disease, antiviral drugs such as ganciclovir have been used, and some authors favour antiviral cover in patients with severe disease and rising viral loads [17, 18]. All of these options carry risks and are best chosen with specialist input.

Choosing an alternative antibiotic is a pharmacy question as much as a clinical one. For MRSA infections, the options include daptomycin, linezolid, ceftaroline and, in some settings, teicoplanin [3, 33].

Daptomycin has shown non-inferiority to standard therapy in bacteraemia and right-sided endocarditis caused by *S. aureus* and is a common substitute, but it is not suitable for pneumonia and requires creatine kinase monitoring [33]. Teicoplanin is structurally related to vancomycin, and cross-reactivity has been reported in other delayed reactions, so it is generally avoided after DRESS unless allergy specialists agree otherwise [10, 32]. Whatever is chosen, the new drug should be monitored for fresh signs of hypersensitivity.

The infection that required vancomycin does not go away because the drug is stopped, and balancing the two problems is one of the harder parts of care. Source control, such as drainage of an abscess or removal of an infected device, may reduce how long antibiotics are needed. Infectious diseases consultation is usually sought. Corticosteroids and other immunosuppressants add to the infective risk, and viral reactivation can mimic worsening sepsis [3, 17]. For these reasons the antibiotic plan, the immunosuppressive plan and the monitoring plan are best agreed together by the dermatology, infectious diseases and pharmacy teams, so that one decision does not undermine another.

Outcomes depend on the organ involved and the speed of recognition. Most patients recover completely within weeks to a few months, but a minority are left with chronic problems. Late complications reported after DRESS include autoimmune thyroiditis, type 1 diabetes mellitus, haemolytic anaemia and, rarely, lupus-like disease, so follow-up should extend over a year or more, with thyroid function and glucose checked periodically [18, 26]. Patients should be told that relapses may occur even when no drug exposure has taken place, as reactivation of latent virus can rekindle the disease. A clear written record of the reaction in the health record helps others to avoid re-exposure.

Prevention is limited but not absent. Screening for HLA-A*32:01 before vancomycin is not currently advised, given that most carriers tolerate the drug and that the test is not widely available, though the cost-effectiveness question has been raised for populations in which carriage is common [13]. Stewardship offers a more practical route. Avoiding unnecessarily long courses, reviewing the need for vancomycin at 48 to 72 hours against culture results and making an early switch to narrower agents lower exposure and the opportunity for reactions [1]. When a delayed rash appears in a patient on long-term therapy, the question of DRESS should be asked at once and not after the rash has spread.

Counselling at discharge is easy to overlook. Patients and families need to know what the reaction was, that it was not an ordinary rash, and that it can return in the weeks after recovery. They should carry written information naming vancomycin as the suspected cause and listing any drugs that were also stopped, so that a future prescriber in a different hospital can make an informed choice. Some centres also advise avoidance of other glycopeptides until specialist assessment has been done, and of starting new medicines in the early recovery phase unless there is a clear need, because new exposures during this period are poorly understood [10, 32].

7. LIMITATIONS AND FUTURE DIRECTIONS

The literature on vancomycin DRESS has obvious weaknesses. It is dominated by individual case reports, which carry publication bias, vary in how thoroughly they exclude alternatives, and generally do not report negative outcomes or cases managed uneventfully [27, 28]. Case series with a handful of patients are somewhat better but still lack denominators. Estimates of incidence are essentially unavailable. Without them it is impossible to say whether vancomycin DRESS is truly rare or underrecognised, or whether its frequency is rising with greater use of the drug and better awareness of the syndrome.

Several research questions follow. Large prospective registries that include all vancomycin exposures would permit estimation of risk and identification of non-genetic risk factors, such as prolonged treatment, renal impairment and co-medication. Replication of the

HLA-A*32:01 association in non-European populations, together with a cost-effectiveness analysis of targeted screening, would show whether genotyping has a place [13]. Biomarkers that distinguish DRESS from simple exanthems early in the illness would help, as would trials of steroid-sparing regimens. Better characterisation of cross-reactivity within the glycopeptide class would also help prescribers who must pick an alternative.

Pharmacists have a particular part to play. They are often the first to see the complete medication timeline, they review allergy records and they handle adverse event reporting. Structured causality assessment with a recognised tool, entry of a precise reaction description in the allergy field rather than a vague label of drug allergy, and communication with the patient's primary care team all reduce the risk of re-exposure [36, 37]. Over-labelling carries costs too, since patients wrongly recorded as vancomycin allergic may be pushed toward less effective or more toxic alternatives. Accurate documentation of both the reaction and the evidence for it serves the patient better than either silence or overstatement.

Finally, there is a communication problem. Delayed reactions are often missed because the interval between starting the drug and the first signs is long, and the early features are mild and non-specific. Education of pharmacists, nurses and junior doctors to ask about rash, fever and abnormal blood tests in patients on prolonged antibiotics could shorten time to diagnosis. Electronic decision support that flags eosinophilia or rising transaminases in patients on vancomycin is an obvious next step, though its value would need testing, as alert fatigue is a real hazard in busy wards [37].

8. CONCLUSION

Vancomycin can cause DRESS, and published reports show a pattern that is recognisable once it has been seen: fever and widespread rash, facial oedema, eosinophilia, liver or kidney involvement, and onset several weeks into treatment [6, 7, 27]. Genetic susceptibility through HLA-A*32:01 and herpesvirus reactivation help explain why a minority of patients react in this way, and why the course may be prolonged [13, 14]. The practical message is that a new rash with organ dysfunction in a patient on vancomycin should prompt consideration of DRESS before any adjustment of the dose. Early recognition is the one intervention clearly within the control of the ward team.

Management rests on stopping the drug, supportive care and, when organs are involved, corticosteroids, with ciclosporin and other agents kept for refractory disease [29, 30, 31]. Substitute antibiotics should be chosen with attention to cross-reactivity and monitored closely [32, 33]. The evidence is weak by the usual standards, built from case reports and from DRESS research in general, and it will remain so until registries and trials supply denominators and comparisons. In the meantime, careful documentation, causality assessment and reporting by clinical pharmacists add real value [17, 36]. Follow-up for late autoimmune complications should not be forgotten once the acute illness is over [26].

9. ABBREVIATIONS

ADR-Adverse drug reaction, DRESS-Drug reaction with eosinophilia and systemic symptoms, HHV-Human herpesvirus, HLA-Human leukocyte antigen, MRSA-Meticillin-resistant Staphylococcus aureus, RegiSCAR-Registry of Severe Cutaneous Adverse Reactions, IgA-Immunoglobulin A, IDSA-Infectious Diseases Society of America, AUC-Area under the curve

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11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

13. REFERENCES

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