

The importance of vancomycin in drug rash with eosinophilia and systemic symptoms (dress) syndrome

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ABSTRACT

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome characterized by fever, rash, eosinophilia, atypical lymphocytes, and multiorgan involvement has a significant mortality. Inpatient vancomycin use is increasing and appears to be emerging as an important etiology of DRESS syndrome. This study highlights the importance of vancomycin as a cause of DRESS syndrome. We reviewed all cases of DRESS syndrome among inpatients consulted by the Allergy & Immunology service at Massachusetts General Hospital (MGH) from July 2009 through December 2010. We also reviewed the use of inpatient parenteral vancomycin over the past 4 years at MGH. Six patients fulfilled clinical criteria for DRESS syndrome, including rash, fever, eosinophilia, and hepatitis, with five (83%) having vancomycin as the attributable cause. Onset of symptoms varied from 12 days to 4 weeks after start of vancomycin treatment. Systemic findings included atypical lymphocytes, lymphadenopathy, nephritis, hypotension, tachycardia, and pharyngitis. Treatment with corticosteroids was required in three cases. Recurrence of peripheral eosinophilia was a marker of disease relapse. In three of the five patients (60%), elevated human herpesvirus 6 (HHV6) IgG titers correlated with greater systemic involvement and prolonged time to resolution. MGH pharmacy records indicate a progressive increase in the number of patients treated with parenteral vancomycin over the last 4 years. Causative agents for DRESS syndrome in an inpatient setting is likely different from that seen in the general population. With increasing use of vancomycin, we are likely to see more cases of DRESS syndrome caused by vancomycin. Recognition of vancomycin as a common cause of inpatient DRESS syndrome is important.

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Drug-induced hypersensitivity syndrome (DIHS) was initially described by Chaiken *et al.* in 1950 as an adverse drug reaction to aromatic anticonvulsant therapy.¹ Current estimates are that 1 in 1000–10,000 exposures to anticonvulsant drugs result in DIHS.² In 2005, DIHS was renamed drug rash eosinophilia and systemic symptoms (DRESS) syndrome by Roujeau and colleagues^{3,4} and currently, there is persistence of both terms DIHS and DRESS without clear distinctions between them, although DIHS can be considered to be more severe than DRESS.⁵

Six to 10% of all adverse drug reactions have an immune basis, and immunologic drug reactions are responsible for 10% of fatal reactions.⁶ Although the exact pathogenesis is unknown, DRESS syndrome is believed to be a Gell and Coombs classification type IV reaction in which cytokine release from activated T cells contribute to many of the clinical features.⁷

DRESS syndrome has been associated with viral reactivation, mainly with human herpesvirus 6 (HHV6), but also human cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, and HHV7.^{8,9} Prior data suggest that up to 62% of patients with active DRESS showed an increase in HHV6 IgG titers.³

DRESS syndrome most commonly arises 2–4 weeks (range, 1–8 weeks) after exposure to the culprit drug. Clinical manifestations of DRESS syndrome can persist for months after discontinuation of the drug, and relapses have been described after initial remission.

Clinical criteria for the diagnosis of DRESS syndrome include fever, skin eruption, hematologic abnormalities, and systemic involvement. Ninety percent of patients with DRESS syndrome manifest with a rash, almost all cases (90–100%) involve fever, and periorbital or facial edema is observed in a quarter of patients.¹⁰ The most frequent hematologic findings include leukocytosis, eosinophilia, or atypical lymphocytes that are CD8⁺.¹¹ Hypogammaglobulinemia has also been reported in DRESS syndrome.¹² Systemic organ involvement can manifest in a multitude of ways, including hypotension, pharyngitis, lymphadenopathy, hepatitis, nephrotoxicity, cerebral edema, pneumonitis, pericardial effusion, myocarditis, or thyroiditis. Typically, organ involvement occurs 1–2 weeks after skin eruption.¹⁰ Clinically, the syndrome can mimic severe sepsis, viral infection such as measles or infectious mononucleosis, Still's

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Table 1 Clinical criteria for DRESS syndrome

DRESS syndrome	Roujeau criteria (2005) ^{3,4}	Suspicion of drug reaction Eosinophilia of >1500/mL and/or atypical lymphocytes Failure of at least two organ systems with skin being one of them
DRESS syndrome	Bocquert and colleagues' (1996) ¹¹	Cutaneous drug eruption Hematologic abnormalities (eosinophilia of >1500/mL or atypical lymphocytes) Systemic involvement including adenopathies of a >2-cm diameter, interstitial nephritis, interstitial pneumonia, or carditis
DIHS/DRESS	Kano and Shiohara (2006) ⁵	Maculopapular rash starting no longer than 3 wks after starting one of a limited number of drugs Prolonged clinical symptoms 2 wks after discontinuation of the causative drug Fever higher than 38°C Liver or renal abnormalities Leukocyte abnormalities Lymphadenopathy HHV6 reactivation

DIHS = drug-induced hypersensitivity syndrome; DRESS = drug rash with eosinophilia and systemic symptoms; HHV6 = human herpesvirus 6.

disease, or lymphoproliferation.^{5,13} Table 1 describes the clinical criteria put forth for DRESS syndrome and DIHS.

The mortality associated with DRESS syndrome is high (10–40%) and increases to up to 50% with a diagnosis of hepatitis.^{14,15} Additionally, the severity of DRESS syndrome is associated with high HHV6 IgG titers.^{16–18}

The most important step in the treatment of DRESS syndrome is the identification and removal of the offending agent. Subsequent management is largely supportive, including fluid and electrolyte management. Cutaneous symptoms have been treated with steroids (topically, orally, or parenterally) and antihistamines. Experts recommend systemic glucocorticoids for patients with life-threatening hepatitis, pneumonia, or nephritis,^{19,20} although there are no controlled trials to support this management. Treatment with corticosteroids is often successful, although rapid taper is associated with reactivation of the syndrome.^{13,17} Viral reactivation, although associated with a more arduous clinical course, does not change the decision to initiate steroid treatment.⁷ In severe DRESS, intravenous immunoglobulin or plasma exchange has also been used, although data on this is limited.²¹

Several families of drugs have been implicated in DRESS syndrome including anticonvulsants, antimicrobials (including antibacterials, antivirals and antifungals), antidepressants, nonantimicrobial sulfones/sulfonamides, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, β -blockers, and others.^{5,13} Little is known about the relative fre-

quency of drugs causing DRESS syndrome, although most retrospective case reviews show anticonvulsants to be the most significant causative agents^{22,23} with antibiotics emerging as the second most common cause, as a recently published case series suggested that 15–37% of DRESS syndrome may be from antibiotics.^{22,23}

Vancomycin-associated DRESS syndrome was first described in single case reports in 2005 and 2006,^{24,25} and subsequent case reports characterized the diagnosis and its association with HHV6 reactivation.^{26–29} Experience with the diagnosis and treatment is growing.^{22,23,27}

METHODS

We reviewed all cases of DRESS syndrome among patients consulted by the Allergy and Immunology Service at the Massachusetts General Hospital (MGH) from July 2009 to December 2010. The protocol was approved by the Institutional Review Board at MGH. The fellows in Allergy and Immunology identified cases of DRESS syndrome from their inpatient consultations. In all cases, the Allergy and Immunology consultation diagnosed DRESS syndrome.

We also reviewed the use of inpatient parenteral vancomycin over the past 4 years at MGH. To address the frequency of treatment courses of parenteral vancomycin that could potentially result in DRESS syndrome, we excluded single doses of parenteral vancomycin.

RESULTS

There were six total cases of DRESS syndrome using currently established clinical criteria for diagnosis of DRESS syndrome (Table 1). Five of those cases (83%) were from parenteral vancomycin. One case (16%) was from lamotrigine.

Patient W.P.

W.P. was a 65 year-old Puerto Rican man with a history of diabetes mellitus type 2 and penicillin hypersensitivity. He was admitted with an esophageal perforation complicated by a β -hemolytic *Streptococcus* group B empyema, treated with a 7-day course of i.v. metronidazole, fluconazole, and vancomycin followed by a second course of therapy with i.v. metronidazole and vancomycin. Six days later, he developed a diffuse rash over his body, characterized by a centrally confluent, macular, blanching, erythroderma over his chest, abdomen, back, and extremities, as well as eosinophilia, mild hepatitis, and acute kidney injury. At this time, vancomycin was suspected as the likely causative agent and was stopped. Skin biopsy was notable for "spongiosis and interface dermatitis with dyskeratotic keratinocytes and superficial perivascular lymphocytic infiltrate with neutrophils" without any evidence of IgA, IgM, or IgG deposition. His course was complicated by progressive fevers, tachycardia, and hypotension on supportive pressors, respiratory failure requiring intubation, and progressively worsening rash with continued eosinophilia. After initiation of methylprednisolone therapy at 125 mg i.v. q.6 hours, his hemodynamic changes and cutaneous rash dramatically improved over 48 hours.

His DRESS syndrome gradually resolved over the following two and a half months, during which time he had two minor relapses characterized by pruritic rash and eosinophilia, requiring prolongation of steroid taper. He eventually had complete resolution of his laboratory abnormalities, including his eosinophilia, elevated creatinine, and hepatitis.

Patient D.N.

D.N. was a 40-year-old white man with history of a traumatic shoulder injury treated with placement of a prosthetic shoulder complicated by *Propionibacterium* and *Peptostreptococcus* infection, who presented with fevers, chills, a pruritic diffuse rash, diaphoresis, profound malaise, drenching sweats, nausea, and anorexia during his 4th week of treatment with parenteral vancomycin. On physical exam, he had a diffuse, flat, erythematous, blanching, macular nonpurpuric rash, with superficial desquamation on his face. He had cervical and submandibular lymphadenopathy, splenomegaly, and pitting edema. Laboratory evaluation revealed eosinophilia, acute kidney injury, hepatitis, and increased

inflammatory markers (erythrocyte sedimentation rate of 14 mm/hour and c-reactive protein of 65.7 mg/L). Blood and urine cultures were negative. During his hospitalization, his eosinophilia peaked at a total eosinophil count of 3890/mL (35% of total white blood cell count). He had peripheral blood atypical lymphocytes and a high HHV6 IgG antibody titer at 1:640.

Despite replacement of vancomycin with linezolid, he developed fluid-responsive low-grade hypotension, anasarca, acute renal failure with eosinophiluria, and odynophagia with a grossly normal-appearing esophagus on endoscopy. Radiological studies noted splenomegaly and cervical lymphadenopathy, with reactive hyperplasia on fine-needle aspiration. He was treated with methylprednisolone at 80 mg i.v. q.12 hours, with resolution of his eosinophilia, fevers, elevated creatinine, and tachycardia within the first 2 days. He was then placed on oral prednisone at 80 mg q.12 hours with taper. An acute exacerbation of the syndrome with pruritic rash, eosinophilia, and hepatitis 5 days after changing to an oral taper necessitated an increased dose of prednisone and slower taper.

His oral steroid taper continued for 6 months and was complicated by secondary adrenal insufficiency. He had complete resolution of his laboratory abnormalities, with an HHV6 IgG antibody titer decreased to 1:320 at 4 months after onset of his DRESS syndrome and continued negative HHV6 load.

Patient N.C.

N.C. was a 48-year-old woman with history of left shoulder injury who developed a coagulase-negative *Staphylococcus* infection of her shoulder replacement, and one month into her vancomycin course, she developed a pruritic rash on her abdomen, legs, ankles, and hands. Laboratory evaluation showed eosinophilia and mild hepatitis. Despite cessation of her vancomycin and transition to linezolid, her clinical features continued to progress, with development of a flat erythematous rash on her upper trunk, face, and back; fever to 100.1°F; shortness of breath; nausea; diarrhea; and worsening eosinophilia to 1200 eosinophils/mL. Her symptoms gradually resolved with supportive care including antihistamines. About 1 week later, she developed an acute shortness of breath with chest heaviness and was found to have a right lower lobe pulmonary embolus without signs of deep vein thrombosis. Although her rash was resolving at this point, her laboratory evaluation was still notable for eosinophilia (1900 eosinophils/mL; 14%), as well as hepatitis. She was not given systemic corticosteroids for management. She completed her antibiotic course with doxycycline. HHV6 serology showed low positive IgG antibody titers at 1:80 with negative HHV6 DNA viral load.

Table 2 Clinical summary of case series of DRESS syndrome from parenteral vancomycin

	Patient W.P.	Patient D.N.	Patient N.C.	Patient N.S.	Patient E.W.
Duration of therapy before onset of DRESS syndrome	12 days	4 wks	4 wks	3 wks	3 wks
Maximum recorded temperature	101.8°F	102°F	100.1°F	103.2°F	103.9°F
Peak eosinophilia (absolute count eosinophils/mL)	10% (3460)	35% (3890)	14% (1900)	36% (6550)	18% (1620)
Urine eosinophils (or eosinophiluria)	Positive	Not tested	Not tested	Positive	Not tested
Atypical lymphocytes	3%	4%	None	3%	7%
Hepatitis	AST 440 ALT 105 Alk Phos 378 T Bili 1.8 D Bili 1.1 Complete resolution of all except persistently elevated Alk Phos	AST 122 ALT 178 Alk Phos 181 Complete resolution	AST 85 ALT 137 Alk Phos 308 Complete resolution	ALT 170 AST 75 Alk Phos 293 Complete resolution	AST 107 ALT 347 Alk Phos 310 Complete resolution
Nephritis	Cr 2.11 from baseline 0.54	Cr peak 2.19 from baseline 0.89	None	Cr peak 2.29 from baseline 1.4	None
HHV6	Complete resolution	Complete resolution		Complete resolution	
Reactivation	Not tested IgG 1:640 DNA <500	IgM <1:20 IgG 1:80	IgM <1:20 IgG 1:320	IgM <1:20	DNA <500
Hypotension	Pressor- dependent hypotension	Fluid-responsive hypotension	None	None	None
Lymphadenopathy	Unknown	Cervical and submandibular	Unknown	Axillary	Unknown
Allergy history	Angioedema to penicillin	Angioedema and rash to penicillin	History of childhood food allergies and nickel dermatitis	None	Asthma, skin prick positive to animal dander, and history of angioedema with NSAIDs and aspirin

Table 2 Continued

	Patient W.P.	Patient D.N.	Patient N.C.	Patient N.S.	Patient E.W.
Steroid use in management	Intravenous Solu-Medrol followed by long prednisone taper	Family history of sister with severe seasonal allergies and brother with eczema Intravenous Solu-Medrol followed by long prednisone taper	Family history of a brother with asthma and eczema None	Family history of a son with eczema None	Intravenous Solu-Medrol followed by long prednisone taper
Relapses	Yes	Yes	No	No	No
DRESS = drug rash with eosinophilia and systemic symptoms; HHV6 = human herpesvirus 6; NSAIDs = nonsteroidal anti-inflammatory drugs; AST = aspartate transaminase; ALT = alanine aminotransferase; Alk Phos = alkaline phosphatase; T Bili = total bilirubin; D Bili = direct bilirubin.					

Patient N.S.

N.S. was a 74-year-old man with a history of type 2 diabetes and chronic kidney disease who had a traumatic hand injury, complicated by an infection with Gram-positive cocci in clusters. He was initially empirically treated with a parenteral vancomycin and cefepime, which was subsequently changed to a course of parenteral vancomycin and ciprofloxacin. Three weeks into his course of antibiotic treatment, he developed a pruritic rash on his chest and the antibiotics, including vancomycin, were stopped. Nine days later, the patient presented to an outside hospital with fever (103.2°F); rash over his trunk, legs, and face; facial and peripheral edema; hypotension; and tachycardia. Although his cultures were unrevealing, laboratory evaluation was notable for eosinophilia and hepatitis. Given the concern for sepsis, he was started on i.v. fluids and parenteral piperacillin/tazobactam.

Seven days later, he came to our hospital with ongoing rash, diarrhea, and low-grade fevers. His physical examination was remarkable for axillary lymphadenopathy and a fine scaling on his face, abdomen, hands, and legs. His edema had resolved. Laboratory evaluation was notable for eosinophilia of 5040 eosinophils/mL (23%) with eosinophiluria, and hepatitis. He did not require treatment with corticosteroids and did not have any recurrence of his symptoms or eosinophilia on follow-up. His HHV6 IgG and IgM titers were negative.

Patient E.W.

E.W. was a 51-year-old Puerto Rican man with systemic lupus erythematosus and asthma who was treated with parenteral vancomycin, ciprofloxacin, and metronidazole for osteomyelitis of his finger after trimethoprim/sulfamethoxazole treatment failure. Approximately 3 weeks after starting this regimen, he developed a pruritic, erythematous maculopapular rash over his torso and face accompanied by periorbital swelling, chest tightness, nausea, headache, fever, chills, and lightheadedness. At presentation, he had a peripheral eosinophilia of 640 eosinophils/mL (10%), which peaked at 1620 eosinophils/mL (18%), as well as atypical lymphocytosis that peaked at 7% and hepatitis. His antibiotic regimen was changed to linezolid and ertapenem, without any further complications. He was treated with corticosteroid therapy, with subsequent improvement in his rash and eosinophilia. HHV6 titers are not available.

Detailed findings from these cases are summarized in Table 2.

Inpatient Use of Parenteral Vancomycin

More patients are being exposed to parenteral vancomycin over time at the MGH. The number of inpa-

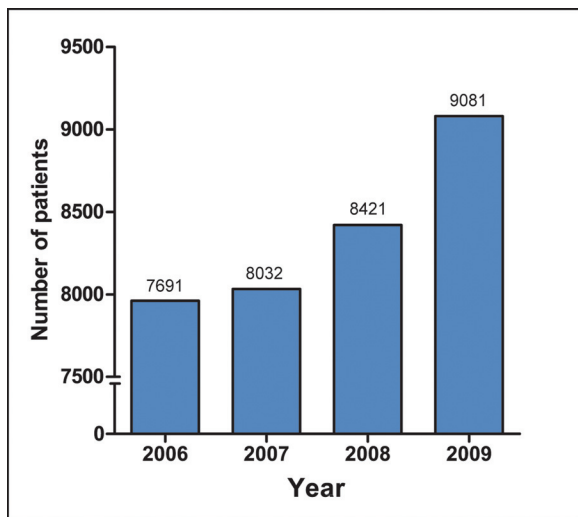


Figure 1. In patient vancomycin use at Massachusetts General Hospital. The number of patients treated with a course of vancomycin has been rising over the past four years.

tients who received vancomycin was 7961 between August 2006 and July 2007, 8032 between August 2007 and July 2008, 8421 between August 2008 and July 2009, and 9081 between August 2009 and July 2010. Figure 1 shows this increase between 2007 and 2010.

DISCUSSION

From July 1, 2009 to December 30, 2010, the Allergy and Immunology Service at this hospital was consulted on six cases of DRESS syndrome. Here, we describe those five cases that share parenteral vancomycin as a likely causative agent. This is noteworthy for three reasons. First, the pattern of causative agents for DRESS syndrome in an inpatient setting is likely different from that seen in the general population, with antibiotics, such as parenteral vancomycin in the setting of systemic infections, likely accounting for a majority of cases. Second, as discussed, the clinical presentation may mimic ongoing or worsening sepsis, and consideration of alternative diagnoses such as DRESS syndrome is important for optimal outcomes. Third, as more patients are being exposed to parenteral vancomycin, we are likely to see increasing cases of DRESS syndrome caused by vancomycin.

These cases of DRESS syndrome related to vancomycin all fulfill currently established clinical criteria for DRESS syndrome, and patient D.N. also meets criteria for DHIS. DRESS syndrome occurred between 12 days and 4 weeks into treatment with vancomycin. All patients except N.C. had atypical lymphocytes. All patients had hepatitis of varying degrees, which largely resolved. All patients except N.C. and E.W. had nephritis that resolved completely. Two of our patients had previous IgE-mediated drug reactions to penicillin.

The use of corticosteroids in DRESS remains controversial. As noted previously, cutaneous manifestations improve with corticosteroid treatment. In our experience, the use of corticosteroids improved both cutaneous and systemic manifestations of DRESS syndrome.

HHV6 has been suggested to be a prognostic factor in previous reports of DHIS.²⁹ Our patient with the highest HHV6 titers had a severe and prolonged clinical course. Peripheral eosinophilia might be a useful marker of disease relapse, because recurrence of symptoms was associated with an acute rise in eosinophilia in two of our cases.

Large, multicenter studies have shown that vancomycin use is increasing dramatically,^{30–32} with one study showing vancomycin to be the single-most commonly used antibiotic in their sample of hospitals from 2004 to 2006.³⁰ Our experience with increasing use of vancomycin at our hospital is consistent with increasing use of vancomycin nationwide.

Both community and hospital prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) is rising.^{33,34} Recently, our hospital's microbiology laboratory reported that 39% of our *S. aureus* is methicillin resistant, which includes all inpatient and outpatient specimens.³⁵ Because vancomycin is the first-line parenteral agent for MRSA, it is not surprising that vancomycin use has been increasing in our hospital.

There are a number of limitations of this study. First, although this case series represents the largest case series of vancomycin-associated DRESS syndrome to date larger systematic evaluations may provide further disease insights. Furthermore, data on vancomycin-associated DRESS syndrome before July 2009 at MGH is limited; therefore, we can not evaluate a trend over time of DRESS syndrome from vancomycin. We do know, however, that since December 2010, we have continued to diagnose DRESS syndrome from parenteral vancomycin. Because the patients recruited in this case series were referred for Allergy and Immunology consultation at a tertiary care academic institution, there may be both a qualitative and quantitative bias in our case description. It is possible that milder cases of DRESS syndrome might not be referred to our service or our institution. Also, our experience may not be representative, especially if hospitals have less MRSA in their communities. The absence of any specific ICD coding for DRESS syndrome has limited our review of hospital case records further.

Identification of DRESS syndrome secondary to parenteral vancomycin use is likely to occur with increasing frequency. Although features of DRESS syndrome such as fever, hypotension, and tachycardia can be mistaken for sepsis, early recognition and treatment is critical, because there is a high mortality rate and removal of the offending agent is paramount for treatment. Without a high clinical suspicion and an appro-

appropriate laboratory evaluation, this syndrome could be overlooked or misclassified. We report our experience here to foster an increased awareness of this type of hypersensitivity syndrome to vancomycin and encourage a comprehensive evaluation for this syndrome, in patients on parenteral antibiotics who develop cutaneous and systemic manifestations.

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