



Immune-mediated reactions to vancomycin

A systematic case review and analysis

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ABSTRACT

Background: Vancomycin is a broad-spectrum antibiotic whose use may be limited by adverse drug reactions (ADRs). Although vancomycin toxic effects are known, there are limited data on vancomycin hypersensitivity reactions (HSRs).

Objective: To understand the most commonly reported vancomycin HSRs through systematic case review.

Methods: We performed a literature search for English-language case reports and series from 1982 through 2015 (last search July 31, 2015) on Ovid MEDLINE and PubMed. The search included the subject heading *vancomycin* with the subheading *adverse effects* and separate text searches for *vancomycin* with a list of specified HSRs. References of identified articles were reviewed to find additional articles. Clinical data were collected and summarized.

Results: Of 201 identified articles, 84 were screened and 57 fully assessed; these 57 articles contained 71 vancomycin HSR cases that were included in analysis. Vancomycin HSRs were immediate (anaphylaxis, n = 7) and nonimmediate (n = 64). Nonimmediate HSRs included linear IgA bullous dermatosis (LABD, n = 34), drug rash eosinophilia and systemic symptoms (DRESS) syndrome (n = 16), acute interstitial nephritis (AIN, n = 8), and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN, n = 6). Median times of vancomycin therapy before HSR onset was 7 days (interquartile range [IQR], 4–10 days) for LABD, 9 days (IQR, 9–22 days) for SJS/TEN, 21 days (IQR, 17–28 days) for DRESS syndrome, and 26 days (IQR, 7–29 days) for AIN. Overall, 11 patients (16%) died, and 4 (6%) had deaths attributed to the HSR.

Conclusion: Vancomycin causes a variety of HSRs; the most commonly identified were nonimmediate HSRs, with LABD being most frequent. We observed a high frequency of HSR mortality. Further data are needed to understand the frequency and severity of vancomycin HSRs.

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Introduction

Vancomycin, a tricyclic glycopeptide,¹ is one of the oldest and most effective antibiotics used to treat gram-positive aerobic

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species. Vancomycin is the optimal parenteral treatment for many infections, including septicemia, pneumonia, cellulitis, endocarditis, and meningitis caused by methicillin-resistant *Staphylococcus aureus*. Orally, vancomycin is first-line treatment for the increasing health care–associated infection *Clostridium difficile* pseudomembranous colitis.² Vancomycin is also commonly used for treating infections in hospitalized patients and surgical patients with prior hypersensitivity to penicillins and/or cephalosporins.³

Clinicians are largely familiar with the adverse drug reactions (ADRs) that occur with vancomycin use, including nephrotoxicity, ototoxicity, and hematologic toxic effects.⁴ These ADRs are most pronounced among patients receiving extended courses of parenteral vancomycin therapy as outpatients, where the observed frequency of ADRs approaches 10%.⁵ Vancomycin is also known for causing red

man syndrome, an immediate reaction that is IgE independent, or pseudoallergic, in nature. Red man syndrome can affect between 4% and 47% of patients treated with vancomycin,⁶ and symptoms range from erythema to cardiovascular compromise or shock.

Vancomycin also has the potential to cause immune-mediated reactions, or hypersensitivity reactions (HSRs), which may be less frequently recognized. Vancomycin HSRs include immediate, type 1 HSRs (IgE-mediated); organ-specific reactions, such as acute interstitial nephritis (AIN), typically a type 2 HSR (antibody dependent); and other nonimmediate HSRs, commonly type 4 HSRs (cell mediated, delayed type). These HSRs include maculopapular rash, drug rash eosinophilia and systemic symptoms (DRESS) syndrome, linear IgA bullous dermatosis (LABD), and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).

Although syntheses of vancomycin ADRs have been reported,⁴ to our knowledge, no formal review of immune-mediated HSRs to vancomycin is available. Therefore, we aimed to identify the most commonly reported vancomycin HSRs through systematic case review.

Methods

We performed a systematic case report and case series review, with a protocol that adhered closely to the Preferred Reporting Items for Systematic Review and Meta-Analyses statement.⁷ The literature search was performed during January 2015 and included Ovid MEDLINE (1982–present), PubMed (1982–present), and the Cochrane Library (1982–present). The base of the search used the medical subject heading *vancomycin* with a subheading limiter of *adverse effects*. In addition, text word searches for vancomycin were matched against a list of HSR keywords and their abbreviations: *hypersensitivity, allergic, urticaria, hives, rash, drug-induced hypersensitivity syndrome, drug rash eosinophilia and systemic symptoms, eosinophilia, bullous, dermatosis, IgA, IgE, anaphylaxis, nephritis, and acute interstitial nephritis*.⁸ We identified additional articles by reviewing references of included manuscripts. The last date searched was July 31, 2015.

Inclusion and exclusion criteria were specified in advance. We included case reports and case series of vancomycin HSRs in English, or original work that was translated into English, from 1982 until present. To synthesize clinical data, only publications with available full texts were included. Each case was identified and screened by 1 physician (J.M.). Inclusion of only convincing HSR reports was determined by a board-certified allergist/immunologist (K.G.B.), with final case inclusion approved by all board-certified allergist coinvestigators (K.G.B., P.G.W., A.A.L., A.B.). Final inclusion necessitated a clear presentation of a patient with signs and symptoms of the HSR with appropriate causal logic in attribution of HSR to vancomycin. We excluded cases of ADRs that were possibly toxic effects (eg, cytopenias) and cases reporting immediate symptoms that were more likely red man syndrome than IgE. To distinguish from red man syndrome and to be included in possible IgE-mediated HSR, cases of immediate reactions needed to have at least 1 of the following: (1) positive skin test result using a nonirritating concentration,^{9,10} (2) immediate symptoms consistent with anaphylaxis¹¹ despite a red man syndrome protocol (slowed infusion and antihistamine premedication),^{12–14} or (3) symptoms consistent with IgE-mediated reaction during a vancomycin desensitization.^{15–17}

Clinical data were collected from each case and included patient characteristics, infection being treated, and reaction details, including timing of HSR onset, available subjective and objective clinical data confirming the HSR, and subsequent treatment and course. For each HSR, we performed summary descriptive statistics, including frequencies and medians with interquartile ranges (IQRs).

Results

The search identified 201 possible publications, of which 84 were relevant to our topic and screened (Fig 1). Of these, 82 full-text articles were available of which 57 documented vancomycin HSRs and met inclusion quality standards for qualitative and quantitative analysis. The 57 articles included 71 cases of patients with a vancomycin HSR.

Overall, patients had a median age 60 years (IQR, 46–71 years), and 40 (56%) were male. HSRs were immediate (IgE/anaphylaxis, n = 7) and nonimmediate (n = 64). Nonimmediate HSRs identified were LABD (n = 34), DRESS syndrome (n = 16), AIN (n = 8), and SJS/TEN (n = 6) (Fig 2). HSR timing varied by HSR, with median latency of 7 days (IQR, 4–10 days) for LABD, 9 days (IQR, 9–22 days) for SJS/TEN, 21 days (IQR, 17–28 days) for DRESS syndrome, and 26 days (IQR, 7–29 days) for AIN (Fig 3A). Overall, 11 patients (16%) died, with 4 (6%) dying of HSR complications (Fig 3B).

We identified 7 cases of presumed IgE-mediated HSR to vancomycin (Table 1).^{10,18–23} Patients had median age of 43 years (IQR, 39–46 years), and 57% were female. Each patient exhibited immediate symptoms that met the definition of anaphylaxis. Although skin findings were commonly present (n = 5 [71%]), 5 patients (71%) had respiratory symptoms, and 4 patients (57%) had hypotension. In 5 patients, there was documentation of prior exposure to vancomycin. Patients had onset of reaction a median of

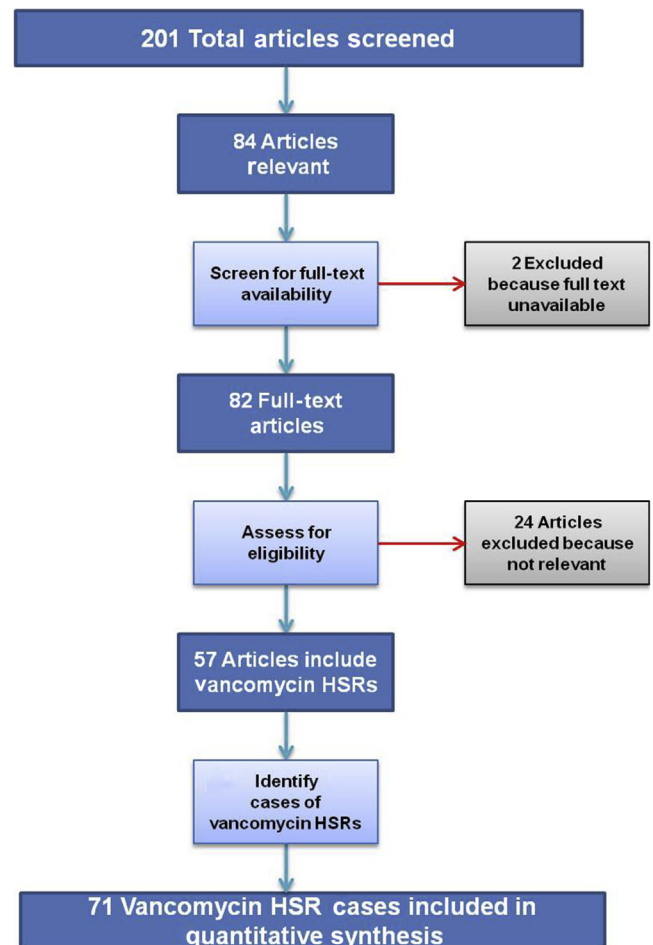


Figure 1. Flow chart of the methods for the studies chosen for the review. Of 201 identified publications, 84 were screened and 58 met the inclusion criteria. The 57 articles included 71 hypersensitivity reaction (HSR) cases.

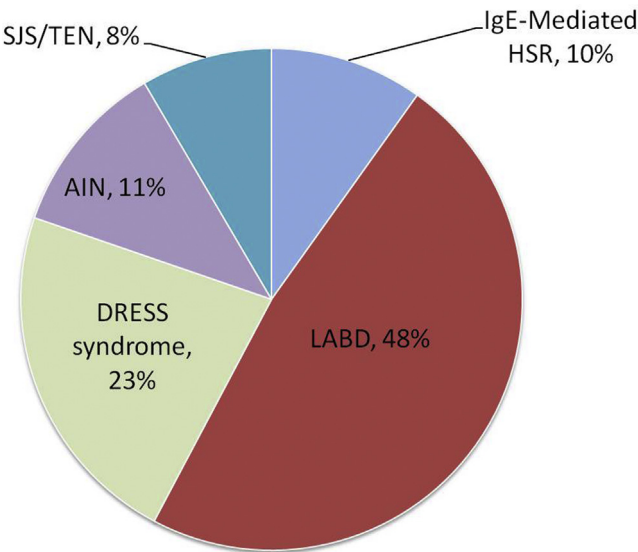


Figure 2. Hypersensitivity reactions (HSRs) were immediate (n = 7) and non-immediate (n = 64). Nonimmediate hypersensitivity reactions included linear IgA bullous dermatosis (LABD) (n = 34), drug rash eosinophilia and systemic symptoms (DRESS) syndrome (n = 16), acute interstitial nephritis (AIN) (n = 8), and Stevens-Johnson syndrome/toxic epidermal necrosis (SJS/TEN) (n = 6).

2 minutes (IQR, 1–5 minutes) into the dose. Treatment included steroids and antihistamines, with epinephrine used in 4 patients (57%). Two of the reported cases required intubation, with 1 fatality, attributed to bilateral pneumonia and overwhelming sepsis.^{21,23} After experiencing an HSR, 4 patients (57%) underwent skin testing or a rechallenge. One patient had a positive skin test result, which was defined by a wheal diameter of 3 mm larger than the negative control to vancomycin (wheal, 10 mm; flare, 35 mm) using 50 mg/mL of vancomycin solution.¹⁰ One patient had symptoms despite a red man syndrome protocol.^{22,24} Two

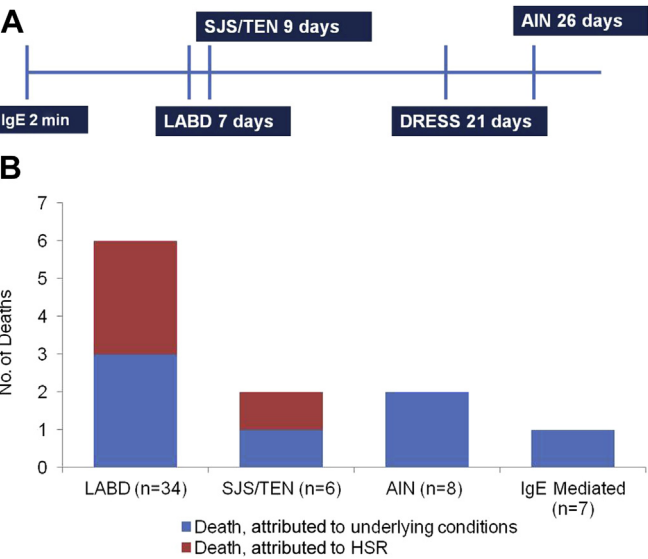


Figure 3. A, Median time to onset of hypersensitivity reactions varied by type. B, Overall, 11 patients (16%) with vancomycin HSRs died, with 4 deaths (6%) attributed to HSR. AIN indicates acute interstitial nephritis; DRESS, drug rash eosinophilia and systemic symptoms; LABD, linear IgA bullous dermatosis; and SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.

Table 1
Clinical Data for 7 Patients With IgE-Mediated Reactions to Vancomycin

Study	Age, y	Sex	No. of vancomycin doses previously	Infection treated	Reaction timing ^a	Symptoms	Treatment	Outcome	Skin testing or rechallenge	Justification for IgE
Otani et al, ¹⁰ 2015	60	F	NA	<i>Enterococcus faecalis</i>	8	Dyspnea, hypotension, skin erythema, flushing	Steroids Antihistamines Epinephrine	Improved	Yes	Positive skin test result
Bosse et al, ¹⁸ 2013	35	M	1	<i>Clostridium difficile</i> colitis	35	Dyspnea, throat tightness, laryngeal edema, facial erythema	Steroids, IVF, antihistamines, epinephrine, switched therapy	Improved	No	Convincing clinical diagnosis
Kupstaitte and Kadusevi, ¹⁹ 2010	23	M	1	Polymicrobial bacteremia, including <i>Enterococcus faecalis</i> and MRSA	1	Dyspnea, hypotension (blood pressure, 80/60 mm Hg), tachycardia, facial flushing, cold sweat, tremor	Steroids, IVF, antihistamines, switched therapy	Improved, negative repeat culture	No	Convincing clinical diagnosis
Kitazawa et al, ²⁰ 2005	43	M	1	MRSA abscess	1	Wheezing, flushing	Antihistamines	Improved	Yes	Breakthrough symptoms despite premedication and desensitization
Hasaballa et al, ²¹ 2000	45	F	NA	<i>Enterococcus</i> wound infection	1	Cardiac arrest, hypotension, flushing, tongue swelling, emesis, diaphoresis	Intubated, epinephrine, steroids, antihistamines, desensitized to vancomycin	Improved	No	Convincing clinical diagnosis
Chopra et al, ²² 2000	46	F	1	MRSA dialysis catheter infection	2	Respiratory distress, wheezing, cyanosis, pruritus, erythema	Steroids, antihistamines	Deceased, from sepsis	Yes	Severe reaction despite red man syndrome prophylactic administration
Vilavencio et al, ²³ 1998	43	F	1	MRSA wound infection	2	Hypotension, facial swelling, lip swelling	CPR, intubation, epinephrine	Improved	Yes	Severe reaction with breakthrough symptoms despite premedication and desensitization

Abbreviations: CPR, cardiopulmonary resuscitation; IVF, intravenous fluids; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not available.
^aTiming from vancomycin dose to reaction onset in minutes.

Table 2

Clinical Data for 34 Patients With Linear IgA Bullous Dermatitis to Vancomycin^a

Study	Age, y	Sex	Infection treated	Reaction timing ^b	Skin sloughing	Mucosal involvement	Other rash atypical feature	Treatment	Outcome
Kakar et al, ²⁵ 2013	91	F	Acute cholecystitis, sepsis	2	40% BSA	Oral	Vesicles	Comfort measures only	Deceased, from HSR
Selvaraj and Khasawneh, ²⁶ 2013	70	F	Postoperative sepsis	5		Oral	Vesicles, palms affected	Discontinuation of vancomycin therapy	Full resolution within 14 d
Jawitz et al, ²⁷ 2011	78	F	Postoperative HAP	28				Topical steroids	Full resolution in 10 d
O'Brien et al, ²⁸ 2011	45	M	<i>Clostridium difficile</i> colitis	2				Discontinuation of vancomycin camphorylated moisturizer	Full resolution
McDonald et al, ²⁹ 2010	32	M	VAP	10				Discontinuation of vancomycin	Full resolution
Walsh et al, ³⁰ 2009	76	M	<i>Staphylococcus</i> bacteremia	9				Oral steroids, discontinuation of vancomycin therapy	Full resolution
Khan et al, ³¹ 2008	57	M	Liver and splenic abscesses Laparotomy	35	75% BSA		Palms and soles affected	Topical steroids, HD, IVIG	Deceased, from HSR
Senanayake et al, ³² 2008	68	M	Postoperative wound infection	4		Oral	Palms affected	Oral steroids, discontinuation of vancomycin therapy	Full resolution
Billet et al, ³³ 2008	70	M	Postoperative perihepatic abscess, MRSA, <i>Enterococcus</i>	5			No bullae	Oral steroids Dapsone	Clinically improved within 3 d
Billet et al, ³³ 2008	61	F	Postoperative wound abdominal infection	13			No bullae	Topical steroids, discontinuation of vancomycin therapy	Clinically improved in 6 d
Navi et al, ³⁴ 2006	73	M	ICD placement	3			Vesicles	Discontinuation of vancomycin therapy	Full resolution in 2 weeks
Waldman et al, ³⁵ 2004	77	M	CABG, complicated postoperative course	6	46% BSA			Silvadene dressing changes every 12 h, dapsone	Complete reepithelialization within 3 wk, deceased, from cardiac complications
Joshi et al, ³⁶ 2004	48	F	TVH complicated by pelvic abscess	10				Discontinuation of vancomycin therapy	Full resolution
Armstrong et al, ³⁷ 2004	81	M	AAA repair complicated by wound infection	3			Target lesions	Discontinuation of vancomycin therapy	Full resolution in 3 wk
Dellavalle et al, ³⁸ 2003	74	M	Pneumonia	4	90% BSA	Oral		Discontinuation of vancomycin therapy	Deceased, from septic shock
Neughbauer et al, ³⁹ 2002	52	F	<i>Escherichia coli</i> urosepsis	<1			Vesicles	Discontinuation of vancomycin therapy	Full resolution in 2 wk
Palmer et al, ⁴⁰ 2001	75	F	Infected varicose ulcer	6			Urticaria	Oral steroids Dapsone	Full resolution
Palmer et al, ⁴⁰ 2001	86	F	Fracture of femur after repair	4	"Diffuse"			Oral steroids	Deceased, from pneumonia and complications of HSR
Palmer et al, ⁴⁰ 2001	78	F	CABG complicated by MRSA wound infection	15			Urticaria	Topical steroids discontinuation of vancomycin therapy	Resolution of rash deceased, from renal failure
Klein et al, ⁴¹ 2000	65	M	Sepsis due to <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus</i> species	14				Discontinuation of vancomycin therapy	Full resolution in 4 wk
Mofid et al, ⁴² 2000	87	F	Urinary tract infection	11		Oral		IV steroids, discontinuation of vancomycin therapy	Full resolution
Danielsen et al, ⁴³ 1999	68	M	Culture-negative endocarditis	9			Vesicles	Topical steroids, discontinuation of vancomycin therapy	Full resolution within 10 d
Bernstein et al, ⁴⁴ 1998	60	F	Enterocutaneous fistula	10				Oral steroids, discontinuation of vancomycin therapy	Full resolution
Nousari et al, ⁴⁵ 1998	65	F	<i>P aeruginosa</i> <i>Staphylococcus epidermidis</i> sepsis	7				Discontinuation of vancomycin therapy	Full resolution within 30 d
Whitworth et al, ⁴⁶ 1996	63	M	Cardiac catheterization	1				Oral steroids, discontinuation of vancomycin therapy	Full resolution within 3 wk
Richards et al, ⁴⁷ 1995	72	F	Total pelvic exenteration for TCC of the bladder	2		Oral and genital	Target lesions Papules	Discontinuation of vancomycin therapy	Full resolution of eruptions in 2 wk

(continued on next page)

Table 2 (continued)

Study	Age, y	Sex	Infection treated	Reaction timing ^a	Skin sloughing	Mucosal involvement	Other rash atypical feature	Treatment	Outcome
Geismann et al. ⁴⁸ 1995	79	M	<i>S aureus</i> cellulitis	8		Oral and genital		Discontinuation of vancomycin	Full resolution
Kuehile et al. ⁴⁹ 1994	69	M	Draining sinus tract status-post CABG	14				Discontinuation of vancomycin therapy	Full resolution within 3 wk
Kuehile et al. ⁴⁹ 1994	74	F	Sternal wound infection after CABG	5d			Target lesions	Discontinuation of vancomycin therapy	Full resolution
							Palms affected		
Kuehile et al. ⁴⁹ 1994	67	M	Sternal wound infection after CABG	1			Vesicles	Discontinuation of vancomycin therapy	Full resolution
Carpenter et al. ⁵⁰ 1992	54	M	Bowel perforation	10				Discontinuation of vancomycin therapy	Full resolution within 9 mo
Carpenter et al. ⁵⁰ 1992	72	F	Intra-abdominal abscess	7			Palms and soles affected	Discontinuation of vancomycin therapy	Full resolution within 2 wk
Carpenter et al. ⁵⁰ 1992	54	M	Osteomyelitis	21				Vancomycin therapy continued for an additional 3 wk without worsening	Full resolution
Baden et al. ⁵¹ 1988	68	M	Postoperative <i>Escherichia coli</i> urosepsis (CABG)	9				Discontinuation of vancomycin therapy, twice daily compresses, bacitracin	Resolution within 2 wk

Abbreviations: AAA, abdominal aortic aneurysm; BSA, body surface area; CABG, coronary artery bypass graft; HAP, hospital-acquired pneumonia; HD, hemodialysis; HSR, hypersensitivity reaction; ICD, implantable cardioverter defibrillator; IV, intravenous; IVIG, intravenous immunoglobulin; MRSA, methicillin-resistant *Staphylococcus aureus*; TCC, transitional cell carcinoma; TVH, total vaginal hysterectomy; VAP, ventilator-associated pneumonia.

^aAll patients had characteristic skin biopsy findings and direct immunofluorescence with linear IgA deposition along the basement membrane/dermal-epidermal junction.

^bTiming from vancomycin dose to reaction onset in days.

patients were desensitized to vancomycin with breakthrough symptoms.^{20,23}

Thirty-four cases of LABD from vancomycin were identified (Table 2).^{25–51} The median age of the patients was 70 years (IQR, 61–76 years), and men represented more than half (56%) of the cases. Patients with LABD developed the rash a median of 7 days (IQR, 4–10 days) into vancomycin course. Thirty-two patients (94%) had bullous eruptions. Two patients (6%) had macules and papules only. The rash among cases of LABD included skin sloughing (n = 5 [15%]), mucosal involvement (n = 7 [21%]), urticaria (n = 2 [6%]), vesicles (n = 6 [18%]), target lesions (n = 3 [9%]), and involvement of palms and soles (n = 5 [15%]). All patients had biopsy specimens with characteristic subepidermal bulla with neutrophilic abscesses in the papillary dermis with direct immunofluorescence confirming a linear pattern of IgA deposition along the basement membrane zone. Treatment included topical and/or oral steroids. Three patients (9%) were treated with dapson. Thirty patients (88%) improved. The median time to resolution among 17 cases was 14 days (IQR, 14–21 days). Six patients (18%) died, with 3 deaths directly related to LABD.

We identified 16 cases of DRESS syndrome from vancomycin (Table 3).^{52–61} Median age was 52 years (IQR, 47–61 years), and most (56%) were men. HSRs occurred a median of 21 days (IQR, 17–28 days) into the patient's treatment course. Symptoms included edema (63%), lymphadenopathy (19%), and fever (81%). Cases with liver involvement (n = 13 [81%]), reported median peak alanine aminotransferase of 163 mg/dL (IQR, 113–337 mg/dL) and aspartate aminotransferase of 157 mg/mL (IQR, 91–313 mg/mL). Of 9 patients (56%) with renal involvement, 8 reported a peak creatinine, with a median of 2.2 mg/dL (IQR, 0.7–4.2 mg/dL). The median absolute eosinophil count among 16 patients was 3,180/mL (IQR, 1,883–6,001/mL). Four patients commented on atypical lymphocytes, with 3 of them reporting that they were present and 1 reporting being absent. Human herpesvirus 6 reactivation was tested for in 5 cases and elevated in only 1 case (1:320).⁵⁹ Registry of Severe Cutaneous Adverse Reactions (regiSCAR) scoring methods were included in only 4 reported cases (25%). Thirteen patients (81%) were treated with steroids (intravenous and/or oral). Other agents used for treatment included cyclosporine (n = 1)⁶⁰ and intravenous immunoglobulin (n = 1).⁵³ All patients experienced complete resolution of the HSR; among 5 patients reporting time to resolution, there was a median time to resolution of 7 days [IQR 5 days, 60 days].

Among 8 AIN cases patients had median age of 58 years (IQR, 42–68 years), and most (75%) were male (Table 4).^{62–69} The median treatment time before HSR was 26 days (IQR, 7–29 days). Rash was present in 6 patients (75%), with more than half of the rashes described as maculopapular. Median peak creatinine level was 6.6 mg/dL (IQR, 3.5–8.8 mg/dL). Peripheral blood eosinophilia was quantified in 5 cases with a median peak absolute eosinophil count of 936/mL (IQR, 861–979/mL). All biopsied cases were proven AIN by kidney biopsy, including interstitial edema, with eosinophils, and mononuclear infiltrations. Five patients (63%) received steroid treatment, and 5 patients also required renal replacement therapy. One patient received steroid-sparing agents cyclosporine and mycophenolate mofetil after steroid treatment failed.⁶⁶ Complete resolution occurred in 6 of 8 patients (75%), with 4 patients quantifying the median time to resolution (60 days; IQR, 49–165 days). There were 2 deaths, both attributed to underlying infections.

Of the 6 cases of vancomycin-induced SJS/TEN, patients had a median age of 38 years (IQR, 36–46 years), and half were male (Table 5).^{28,70–74} The median treatment time before HSR was 9 days (IQR, 9–22 days). All cases had biopsy results consistent with SJS/TEN (eg, revealing epidermal necrosis and blisters along the dermal-epidermal junction). Steroids were used for

Table 3

Clinical Data for 16 Patients With DRESS Syndrome to Vancomycin

Study	Age, y	Sex	Infection treated	Reaction timing ^a	Clinical signs and symptoms	Laboratory findings	Treatment	Outcome
Young et al, ⁵² 2014	24	M	<i>Corynebacterium jeikeium</i> septic arthritis	21	MP rash, arthralgia, lymphadenopathy, fever	AEC, 2,900/L; AST, missing; ALT, 270 mg/dL; no nephritis; RegiSCAR score 7	IV steroids with a prednisone taper	Clinically improved with resolution of symptoms
Young et al, ⁵² 2014	48	F	L5/S1 osteomyelitis	14	MP rash, facial edema, odynophagia, fever, chills	AEC, 2,200/L; AST, missing; ALT, 337 mg/dL; no nephritis; RegiSCAR score 6	IV steroids with prolonged prednisone taper	Clinically improved within 5 d
Young et al, ⁵² 2014	59	F	MRSA wound infection	21	MP rash, fever and facial edema	AEC, 10,400/L; AST, missing; ALT, 113 mg/dL; no nephritis; RegiSCAR score 6	Oral and topical steroids, antihistamines	Clinically improved
Della-Torre et al, ⁵³ 2013	75	M	Culture-negative endocarditis	27	MP rash, fever	AEC, 0.6 × 10 ⁹ ; AST, 45 mg/dL; ALT, 264 mg/dL; Cr, baseline missing; maximum, 1.31 mg/dL; RegiSCAR score >7	IV steroids, antihistamines IVIG	Clinically improved, laborator results normalized
Blumenthal et al, ⁵⁴ 2013	65	M	β-Hemolytic <i>Streptococcus</i> group B empyema	12	MP rash	AEC, 3,460/L; AST, 440 mg/dL; ALT, 105 mg/dL; Cr, baseline, 0.5; maximum, 2.1 mg/dL; atypical lymphocytes, none	IV steroids	Clinical improvement within 48 h, DRESS resolved after 2 mo
Blumenthal et al, ⁵⁴ 2013	40	M	<i>Propionibacterium</i> and <i>Peptostreptococcus</i> prosthetic joint infection	28	MP rash, fever, cervical lymphadenopathy, splenomegaly, pitting edema	AEC, 3,890/L; AST, 178 mg/dL; ALT, 122 mg/dL; Cr, baseline, 0.8 mg/dL; maximum, 2.2 mg/dL; HHV6 IgG, <1:20	IV steroids, followed by 6-mo oral taper	Clinical improvement within 2 d
Blumenthal et al, ⁵⁴ 2013	48	F	Coagulase-negative <i>Staphylococcus aureus</i> prosthetic joint infection	28	MP rash, fever	AEC, 1,900/L; AST, 85 mg/dL; ALT, 137 mg/dL; no nephritis; HHV6 IgG, <1:20	No steroids used in management, antihistamines	Gradual clinical improvement with supportive care
Blumenthal et al, ⁵⁴ 2013	74	M	Gram-positive cocci cellulitis after traumatic hand injury	21	MP rash, fever, facial and peripheral edema, hypotension, tachycardia	AEC, 6,550/L; AST, 75 mg/dL; ALT, 170 mg/dL; Cr, baseline, 1.4 mg/dL; maximum, 2.3 mg/dL; HHV6 IgG, <1:20	No steroids used in management, IVF, switched therapy	Clinically improved
Blumenthal et al, ⁵⁴ 2013	51	M	Osteomyelitis	21	MP rash, periorbital edema, chest tightness, nausea, fever, chills, lightheadedness	AEC, 1,620/L; AST, 107 mg/dL; ALT, 347 mg/dL; no nephritis; HHV6 DNA <600	IV steroids, switched therapy	Clinically improved
Dauby et al, ⁵⁵ 2012	54	F	Methicillin-resistant <i>Staphylococcus epidermis</i> catheter associated bacteremia (febrile neutropenia in setting of chemotherapy for breast cancer)	7	MP rash, fever, chills	AEC, 6,380/L; AST, 31 mg/dL; ALT, 45 mg/dL; no nephritis	Topical steroids, antihistamines, antipyretic, switched therapy	Clinically improved
O'Meara et al, ⁵⁶ 2011	66	M	ORIF complicated by MRSA	28	MP rash, fever, facial edema, lymphadenopathy	AEC, 3,620/L; AST, 163 mg/dL; ALT, 144 mg/dL; Cr, baseline, 1.3 mg/dL; maximum, 4.9 mg/dL	IV steroids	Clinically improved after prolonged treatment course
Boet et al, ⁵⁷ 2009	38	F	<i>Streptococcus oralis</i> endocarditis	30	MP rash, fever, facial edema	AEC, 2,820/L; no nephritis	IV steroids	Clinically improved, discharged within few weeks
Vauthey et al, ⁵⁸ 2008	60	F	MRSA cellulitis after amputation	18	MP rash, fever, periorbital edema	AEC, 1,251/L; Cr Cl, 30 mL/min	IV steroids, topical steroids, antihistamines	Gradually improved, discharged after 2 mo
Tamagawa-Mineoka et al, ⁵⁹ 2007	52	M	Cholesteatoma after tympanoplasty (MRSA infection from ear wound)	4	MP rash, fever, facial edema	AEC, 1,832/L; AST, 358 mg/dL; ALT, 547 mg/dL; Cr, baseline, NA; maximum, 3.58 mg/dL; HHV6 DNA, 1:320	IV steroids followed by prednisone taper	Clinically resolved
Zuliani et al, ⁶⁰ 2005	45	F	Coagulase-negative endocarditis	18	MP rash, fever, facial edema	AEC, 1,474/L; AST, 385 mg/dL; ALT, 599 mg/dL; Cr, baseline, 0.8 mg/dL; maximum, 5.3 mg/dL	IV steroids with prednisone taper, antihistamines, hemodialysis, cyclosporine	After two cutaneous relapses, clinically improved
Marik et al, ⁶¹ 1997	51	M	Culture-negative endocarditis	30	MP rash, palpitations, malaise, dyspnea and rigors	AEC, 5,875/L; Cr, baseline, 1.0 mg/dL; maximum, 7.8 mg/dL	IV steroids	Clinically improved in 1 wk, hospital course complicated by urosepsis

Abbreviations: AEC, absolute neutrophil count; Cl, clearance; Cr, creatinine; DRESS, drug rash eosinophilia with systemic symptoms; HHV6, human herpesvirus 6; IV, intravenous; IVF, intravenous fluids; IVIG, intravenous immunoglobulin; MP, maculopapular; MRSA, methicillin-resistant *Staphylococcus aureus*; ORIF, open reduction internal fixation; RegiSCAR, Registry of Severe Cutaneous Adverse Reactions.

^aTiming from vancomycin dose to reaction onset in days

Table 4
Clinical Data for 8 Patients With AIN to Vancomycin

Study	Age, y	Sex	Infection treated	Reaction timing ^a	Symptoms	Laboratory data	Biopsy	Treatment	Outcome
Htike et al, ⁶² 2012	79	F	Coagulase-negative <i>Staphylococcus</i> bacteremia	7	Malaise, fatigue	Cr (baseline, 0.9 mg/dL; maximum, 11.7 mg/dL; 92.3% change), no urine eosinophils	ATN changes: loss of tubular cells, tubular dilatation; AIN changes: interstitial edema, eosinophils, mononuclear infiltrate	Oral steroids for 2 wk	Renal function resolved in 4 wk
Salazar et al, ⁶³ 2010	51	M	MRSA osteomyelitis	28	Rash	Cr (baseline, 0.9 mg/dL; maximum, 2.2 mg/dL; 59.0% change), AEC, 2,318/L	Interstitial edema, eosinophils, mononuclear infiltrations	Oral steroids	One recurrence, followed by resolution
Michail et al, ⁶⁴ 2009	35	M	<i>Staphylococcus aureus</i> empyema	4	MP rash, arthralgia	Cr (baseline, normal; maximum, 6.5 mg/dL), no urine eosinophils	Mononuclear inflammatory infiltration	Furosemide HD, switched therapy	Renal function resolved in 10 mo
Hong et al, ⁶⁵ 2007	44	M	Polymicrobial wound infection with <i>S aureus</i> , group B streptococci, and <i>Streptococcus mitis</i>	28	Rash, fever, hypotension	Cr (baseline, 3.1 mg/dL; maximum, 8.5 mg/dL; 63.5% change), AEC, 640/L	Giant cell granulomas, mononuclear interstitial infiltration	After failed IV and oral steroids once every 1 wk, switched to cyclosporine and mycophenolate mofetil, HD, switched therapy	Renal function improved with cyclosporine, mycophenolate mofetil and HD for 2m
Hsu et al, ⁶⁶ 2001	70	M	MRSA abscess	23	Fever, MP, rash	Cr (baseline, 2.0 mg/dL; maximum, 3.5 mg/dL; 42.9% change), AEC, 936/L	Interstitial edema, eosinophils, mononuclear infiltrations	Oral steroids, CVVH, switched therapy	Several readmissions followed by death from polymicrobial sepsis
Wai et al, ⁶⁷ 1998	64	M	MRSA sternal wound dehiscence after CABG	39	Fever, MP, rash	Cr (baseline, 1.1 mg/dL; maximum, 9.5 mg/dL; 88.4% change), AEC, 979/L	Interstitial mononuclear infiltrations, granulomata	Oral steroids HD for 2 wk, switched therapy	Renal function Improved, several readmissions and complicated postoperative course
Codding et al, ⁶⁸ 1989	67	M	<i>S aureus</i> endocarditis	30	Fever, MP, rash	Cr (baseline, 1.5 mg/dL; maximum, 6.6 mg/dL), AEC, 861/L	Interstitial mononuclear infiltration, granulomata	HD, switched therapy	Clinically deteriorated, deceased from septic shock
Bergman et al, ⁶⁹ 1988	34	F	Endometritis, <i>S aureus</i>	6	Fever, pedal edema	Cr (baseline, 1.5 mg/dL; maximum, 3.4 mg/dL), AEC, normal	Refused renal biopsy	Discontinued vancomycin therapy	Renal function resolved within 15 d

Abbreviations: AEC, absolute eosinophil count; AIN, allergic interstitial nephritis; ATN, acute tubular nephrosis; CABG, coronary artery bypass graft; Cr, creatinine; CVVH, continuous-veno-venous hemofiltration; HD, hemodialysis; IV, intravenous; MP, maculopapular; MRSA, methicillin-resistant *Staphylococcus aureus*.

^aTiming from vancomycin dose to reaction onset in days.

Table 5
Clinical Data for 6 Patients With Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis to Vancomycin

Study	Age, y	Sex	Infection treated	Reaction timing ^a	Rash description	Laboratory data	Biopsy	Treatment	Outcome
Changela et al, ⁷⁰ 2013	35	M	MRSA abscess	9	Dusky purpuric plaques and multiple fluid filled blisters on the trunk, upper and lower extremities, 30% of BSA	IgA, 154 mg/dL	Necrotic epidermis, severe blisters at DE junction, necrotic keratocytes	IV steroids for 4 d, oral steroid taper	Clinically improved
O'Brien et al, ⁷¹ 2011	46	F	Respiratory failure	A few	Epidermal sloughing, erosions and blisters over 40% BSA, positive Nikolsky sign		Epidermal necrosis, minimal interface, and perivascular lymphocytic infiltrate	Discontinuation of vancomycin therapy	Terminally ill, deceased
Bouaziz et al, ⁷² 2006	38	F	Fistula	9	MP rash, fever, oral, ocular and mucous membrane erosions, diffuse blisters, positive Nikolsky sign, 50% epidermal skin detachment	Serum drug level, 20 mg/L	Follicular necrosis DE detachment	IV fluids, anti-infectious therapy, nutritional support, skin care	Deceased day 13, from HSR
Chan-Tack, ⁷³ 2000	46	F	Infected hip joint prosthesis	8	Diffuse flaccid bullae covering 50% BSA, necrotic epidermis		Epidermal necrosis and detachment	Whirlpool therapy, topical antimicrobial, nutritional support, pain control	Clinically improved, discharged after 8 wk
Alexander et al, ⁷⁴ 1996	36	M	Endocarditis	17	MP rash involving torso, abdomen, legs and arms; lymphadenopathy, pharyngeal irritation, lip swelling, and conjunctival irritation	ANC, 1; 911/mm ³ ; eosinophilia (13%–28%)	Epidermal necrosis, DE junction blisters, dermal infiltration	Steroid therapy	Clinical improvement within 24 h
Vidal et al, ⁷⁵ 1992	28	M	<i>Staphylococcus aureus</i> sepsis (history of AIDS)	27	MP rash, fever, oral mucosa and genitals involved, positive Nikolsky sign	ESR, 78 mm/h; ANC, 1,349/mm ³	Lymphocytic and neutrophilic subdermal infiltration	Switched therapy	Recovered, discharged after 57 d

Abbreviations: ANC, absolute neutrophil count; BSA, body surface area; DE, dermal-epidermal; ESR, erythrocyte sedimentation rate; HSR, hypersensitivity reaction; IV, intravenous; MP, maculopapular; MRSA, methicillin-resistant *Staphylococcus aureus*.

^aTiming from vancomycin dose to reaction onset in days.

treatment in 2 cases. Resolution occurred in 4 cases (67%), with time to resolution (reported in 3 cases) of a median of 56 days (IQR, 29–57 days). Two patients (33%) died, with 1 death attributed to HSR complications and the other death attributed to terminal illness.

Discussion

We performed a systematic case review of vancomycin HSRs and found 71 cases representing a variety of HSRs, including IgE-mediated, LABD, DRESS syndrome, AIN, and SJS/TEN. The most frequently observed HSRs from vancomycin were nonimmediate ($n = 64$), with LABD the most frequently reported vancomycin HSR ($n = 34$). We were able to appreciate some variability in case diagnosis and treatment that may inform future care of these patients and encourage standard case reporting for rare HSRs. We observed a high frequency of case fatality, which in some cases was directly related to the HSR, indicating a need for increased awareness of vancomycin HSRs.

The most challenging HSR to identify in our review was IgE-mediated vancomycin HSRs because it was difficult to diagnose and distinguish from red man syndrome. There are no serum tests that exist, skin testing is not validated, and vancomycin is known to be a direct mast cell activator.⁷⁵ The current accepted skin testing protocol for IgE-mediated vancomycin allergy includes using a nonirritating concentration with a skin prick concentration of 50 mg/mL and intradermal concentration of 0.01 and 0.1 μ g/mL.^{10,76} Although only 1 of our patients with IgE-mediated HSRs to vancomycin underwent skin testing, other included patients had clinical courses that support the possible existence of an IgE mechanism, many had prior vancomycin exposure to account for sensitization, and many failed red man syndrome protocols or desensitization. Although severe red man syndrome is clinically indistinguishable from IgE-mediated anaphylaxis, IgE-independent reactions can often be overcome with premedication. In addition, drug hypersensitivity literature previously reported that it is often patients with IgE-mediated reactions who have breakthrough reactions during desensitization procedures.^{12,13} We believe that this case review highlights the need for allergist involvement when red man syndrome protocols fail. Such patients may benefit from vancomycin skin testing, and future doses may need to be given by a desensitization procedure.

LABD was the most commonly identified vancomycin HSR, although overall LABD incidence ranges from 0.2 to 2.3 cases per million individuals per year.^{77,78} Our data were similar to previous data, with patients commonly older than 60 years; however, our cases included 8 patients who were 60 years or younger.^{77,79} This review highlights why this HSR can be confused with other HSRs, including SJS/TEN, erythema multiforme, maculopapular rash, and others. Although only 2 cases did not present with a typical bullous eruption, cases included other examination features, such as target lesions, vesicles, skin desquamation, and/or mucous membrane involvement. Our findings reinforce the importance of skin biopsy in the diagnosis of cutaneous HSRs.

DRESS syndrome is a morbid, systemic HSR that includes rashes, hematologic abnormalities, lymphadenopathy, and internal organ involvement, most commonly the liver and/or kidneys. DRESS syndrome is a clinical diagnosis, usually of exclusion, and is ideally diagnosed using the regiSCAR clinical score developed by European investigators in surveillance studies.^{80,81} However, among the vancomycin DRESS syndrome cases synthesized, most did not report the regiSCAR score. Beyond its usefulness in the clinical care of patients with potential DRESS syndrome, using objective scoring is the best available method to convey diagnostic clinical certainty when publishing a case report. Finally, although DRESS syndrome has a reported

mortality rate of 4% to 10%,^{82,83} our described DRESS cases had no fatalities. Although there are no experimental trials evaluating the use of corticosteroids for the treatment of DRESS syndrome, our patients with DRESS syndrome largely received steroids, and all experienced clinical recovery.

Because renal toxic effects are at the forefront of a clinician's mind when treating patients with vancomycin who develop an acute change in creatinine,^{84,85} AIN to vancomycin is likely underdiagnosed. However, AIN is the cause of 10% to 27% of acute kidney injury without a clear cause.⁸⁶ AIN clinically presents with rash, peripheral eosinophilia, and/or eosinophiluria. By microscopy, the urine may have white blood cell casts. However, the diagnosis of AIN is made with a kidney biopsy, and because there is rarely a clinical need to perform a biopsy, there are few cases of biopsy-proven acute interstitial nephritis.⁶² Several risk factors for developing vancomycin-induced AIN have been identified: concurrent treatment with aminoglycosides, elevated vancomycin trough greater than 10 mg/L, and prolonged treatment (>21 days).⁸⁷ We similarly found that the number of days of vancomycin therapy before AIN was more than 21 days (mean, 26 days); therefore, it may be useful to consider vancomycin AIN when patients develop a change in creatinine after a prolonged vancomycin course. There are limited prognostic data available for vancomycin-induced AIN. One case series found that patients' serum creatinine levels remained elevated in approximately 40% of patients, and the mean recovery time of renal function was 1.5 months.⁸⁸ We found that 75% of the cases had recovery of their renal function, although 5 (63%) required renal replacement therapy, and, overall, recovery generally took a number of months.

Our review has a number of important limitations. The first limitation concerns bias within the studies themselves. Although we established clinical case standards, all cases of HSRs to vancomycin are naturally limited by our clinical diagnostic tools in drug allergy. This is less important for HSRs that were biopsy proven (eg, LABD) and more important for HSRs that relied on a clinical diagnosis (eg, IgE-mediated, DRESS syndrome). The included cases may have been misattributed; many of the patients were taking other drugs concurrently with vancomycin, and we had to rely on the primary case author's causality assessment. Another limitation with this type of analysis is that there is bias across studies, including publication bias and selective reporting. Although we found the most cases of LABD, we cannot determine that this observed frequency is related to the actual frequency of the HSR. Our findings may be due to physicians being more inclined to report cases with severe or extreme outcomes, which could also explain the high overall mortality. Nevertheless, HSRs from vancomycin are occurring and can be severe.

In summary, we identified a variety of HSRs to vancomycin that all physicians using vancomycin should have knowledge of, especially because vancomycin is commonly used in the United States.⁸⁹ Our review reveals valuable clinical pictures of these HSRs and highlights the need for improved diagnostic and reporting tools for rare HSRs.

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