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Immune-mediated Reactions to Vancomycin: A Systematic Case Review and Analysis

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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 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 growing healthcare 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 toxicity.[4] These

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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/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 I HSR (immunoglobulin [Ig]E)-mediated); organ specific reactions such as acute interstitial nephritis (AIN), typically a Type II HSR (antibody dependent); and other non-immediate HSRs, commonly type IV 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).

While 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), the Cochrane Library (1982-present). The base of the search used the medical subject heading vancomycin with a subheading limiter of “adverse effects.” Additionally, text word searches for vancomycin were matched against a list of HSR key words: hypersensitivity, allergic, urticaria, hives, rash, drug induced hypersensitivity syndrome, DIHS drug rash eosinophilia and systemic symptoms, eosinophilia, , bullous, dermatosis, IgA, IgE, anaphylaxis, nephritis, acute interstitial nephritis, and AIN.[8] We identified additional articles by reviewing references of included manuscripts. The last date searched was July 31, 2015.

Inclusion criteria 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. In order to synthesize clinical data, only publications with available full texts were included. Each case was identified and screened by one physician (JM). Inclusion of only convincing HSR reports was determined by a board-certified allergist/immunologist (KGB), with final case inclusion approved by all board-certified allergist co-investigators (KGB, PGW, AAL, AB). 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 toxicities (e.g., 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 one of the

following: (1) positive skin testing using a non-irritating concentration,[9,10] (2) immediate symptoms consistent with anaphylaxis[11] despite a red man syndrome protocol (slowed infusion and antihistamine premedication),[12,1314] or (3) symptoms consistent with IgE-mediated reaction during a vancomycin desensitization[15,16,17].

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 frequenciesand medians with interquartile ranges.

RESULTS

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

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

We identified seven cases of presumed IgE-mediated HSR to vancomycin (Table 1). Patients had median age of 43 years [IQR 39 years, 46 years] and females represented a majority (57%). Each patient exhibited immediate symptoms meeting definition of anaphylaxis. While skin findings were commonly present (n=5, 71%), 5 patients (71%) had respiratory symptoms and 4 patients (57%) had hypotension. In five patients, there was documentation of prior exposure to vancomycin. Patients had onset of reaction a median of two minutes [IQR 1 minute, 5 minutes] into the dose. Treatment included steroids and antihistamines, with epinephrine used in 4 patients (5 7%). Two of the reported cases required intubation, with one fatality, attributed to bilateral pneumonia and overwhelming sepsis.[18,19] After experiencing a HSR, 4 (57%) of patients underwent skin testing or a re-challenge. One patient had a positive skin test, that was defined by a wheal diameter of 3mm 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[20].[21] Two patients were desensitized to vancomycin with breakthrough symptoms. [19,22]

Thirty-four cases of LABD from vancomycin wereidentified(Table 2). Patients median age was 70 years [IQR 61 years, 76 years)] and men represented over half (56%) of cases. Patients reported with LABD developed the rash a median of 7 days [IQR 4 days, 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 biopsies 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 dapsoneThirty patients (88%) improved. The median time to resolution among 17 cases was 14 days [IQR 14 days, 21 days]. Sixpatients 18%) died, with 3 deaths directly related to LABD.

We identified 16 cases of DRESS syndrome from vancomycin (Table 3). Median age was 52 years [IQR 47 years, 61 years] and men represented a majority (56%). HSR occurred a median of 21 days [IQR 17 days, 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 [113 mg/dL, 337 mg/dL) and aspartate aminotransferase of 157 mg/mL [IQR 91 mg/mL, 313 mg/mL]. Of nine (56%) cases with renal involvement, eight reported peak Creatinine, with a median of 2.2 mg/dL [IQR 0.7 mg/dL, 4.2 mg/dL). The median absolute eosinophil count (AEC) among 16 cases was 3,180/mL [IQR 1,883/mL, 6,001/mL]. Four cases commented on atypical lymphocytes with three of them reporting they were present and one reported that they were absent. HHV6 reactivation was tested for in five cases, and elevated in only one case (1:320, Tamagawa).[23] Registry of Severe Cutaneous Adverse Reactions (regiSCAR) scoring methods were included in only four (25%) of reported cases. Thirteen patients (81%) were treated with steroids (intravenous and/or oral). Other agents used for treatment included cyclosporine (n=1)[24] and IVIG (n=1).[25] All patients experienced complete resolution of the HSR; among five cases 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 years, 68 years]and majority (75%) were male (Table 4). The median treatment time prior to HSRwas 26 days [IQR 7 days, 29 days]. Rash was present in six patients (75%), with more than half of the rashes described as maculopapular. Median peak Creatinine was a 6.6 mg/dL [IQR 3.5 mg/dL, 8.8 mg/dL].. Peripheral blood eosinophilia was quantified in 5 cases with a median peak AEC of 936/mL [IQR 861/mL, 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 five patients alsorequired renal replacement therapy. One patient received steroid-sparing agents cyclosporine and mycophenolate mofetilafter failing steroid treatment.[26] Complete resolution occurred in 6/8 (75%) of the patients, with four cases quantifying the median time to resolution (60 days [IQR 49 days, 165 days]). There were two deaths, both attributed to underlying infections..

Of the six cases of vancomycin-induced SJS or TEN, .patients had a median age of 38 years [IQR 36 years, 46 years]and half were male (Table 5). The median treatment time prior to HSR was 9 days IQR [9 days, 22days]. All cases had biopsies consistent with SJS or TEN (e.g., revealing epidermal necrosis and blisters along the dermal-epidermal junction).

Steroids were used for treatment in two cases. Resolution occurred in four (67%) of cases, with time to resolution (reported in three cases), a median of 56 days [IQR 29 days, 57 days].Two patients (33%) died with one death attributed to HSR complications, and the other death being 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 non-immediate (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 or 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.[27] The current accepted skin testing protocol for IgE-mediated vancomycin allergy includes using a non-irritating concentration with skin prick concentration 50mg/mL and intradermal concentration 0.01 and 0.1 mcg/mL.[28,10] Although only one of our IgE-mediated HSRs to vancomycin cases used skin testing, other included cases had clinical courses that supports possible existence of an IgE mechanism; many had prior vancomycin exposure to account for sensitization and many failed red man syndrome protocols or desensitization. While severe red man syndrome is clinically indistinguishable from IgE-mediated anaphylaxis, IgE-independent reactions can often be overcome with premedication. Additionally, drug hypersensitivity literature previously reported that it is often patients with IgE-mediated reactions who have breakthrough reactions during desensitization procedures.[1213] We believe that this case review highlights the need for allergist involvement when patients fail red man syndrome protocols. 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 incidenceranges from 0.2 to 2.3 cases per million individuals per year.[29,30] Our data was similar to previous data, with patients commonly over 60 years old; however, our cases included eight patients who were 60 years old or younger.[29,31] This review highlights why this HSR can be confused with other HSRs, including SJS/TEN, erythema multiforme, maculopapular rash, and others. While only two cases did not present with a typical bullous eruption, cases included other exam 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.[3233] However, among the vancomycin DRESS cases synthesized, the majority 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 from 4-10%,[3435] our described DRESS cases had no fatalities. While there are no experimental trials evaluating the use of corticosteroids for the treatment of DRESS syndrome, our DRESS patients largely received steroids for DRESS syndrome and all experienced clinical recovery.

Because renal toxicity is at the forefront of a clinician's mind when treating patients with vancomycin who develop an acute change in creatinine,[36,37] AIN to vancomycin is likely underdiagnosed. However AIN is the cause of 10-27% of acute kidney injury without a clear cause.[38] AIN clinically presents with rash, peripheral eosinophilia, and/or eosinophiliuria. 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.[39] Several risk factors for developing vancomycin-induced AIN have been identified: concurrent treatment with aminoglycosides, elevated vancomycin trough >10mg/L, and prolonged treatment (>21 days).[40] We similarly found the median number of days of vancomycin therapy prior to AIN was >21 days (26 days); therefore. it may be useful to consider vancomycin AIN when patients develop a change in creatinine after a prolonged vancomycin course. There is limited prognostic data available for vancomycin-induced AIN. One case series found that patients' serum creatinine remained elevated in approximately 40% of patients and the mean recovery time of renal function was 1.5 months.[41] We found that 75% of the cases had recovery of their renal function, although five (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 (e.g., LABD) and more important for HSRs that relied on a clinical diagnosis (e.g., IgE-mediated, DRESS syndrome). The included cases may have suffered from misattribution; many of the patients were on other drugs concurrent 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 clinicians being more inclined to write-up cases with severe or dramatic 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 clinicians using vancomycin should have knowledge of, especially since vancomycin is commonly used in

the United States.[42] Our review reveals valuable clinical pictures of these HSRs, and highlights the need for improved diagnostic and reporting tools for rare HSRs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

IgE	Immunnoglobulin E
LABD	Linear IgA Bullous Dermatosis
DRESS	drug rash eosinophilia and systemic symptoms
AIN	acute interstitial nephritis
SJS/TEN	Stevens-Johnson’s syndrome/toxic epidermal necrolysis.

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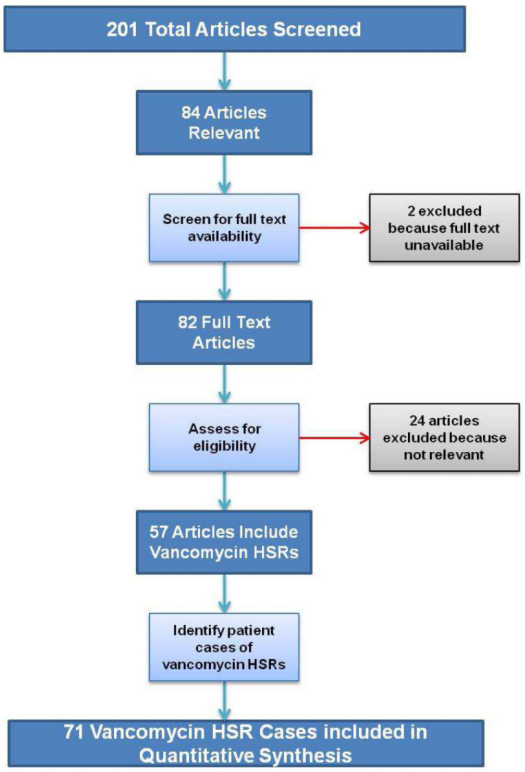

Figure 1.

Flow chart of methodology for studies chosen for the review

Legend. Of 201 identified publications; 84 were screened and 58 met inclusion criteria. The 58 articles included 71 HSR cases.

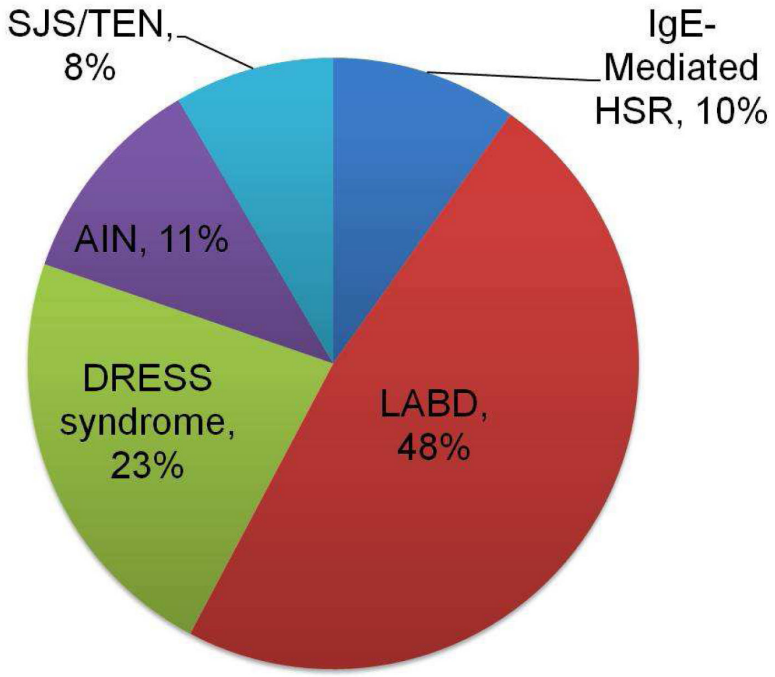

Figure 2.
Cases of Immune-Mediated Hypersensitivity Reactions to Vancomycin

Legend. HSRs were immediate (n=7) and non-immediate (n=64**).** Non-immediate hypersensitivity reactions included LABD (n=34), DRESS syndrome (n=16), acute interstitial nephritis (n=8), and SJS/ TEN (n=6).

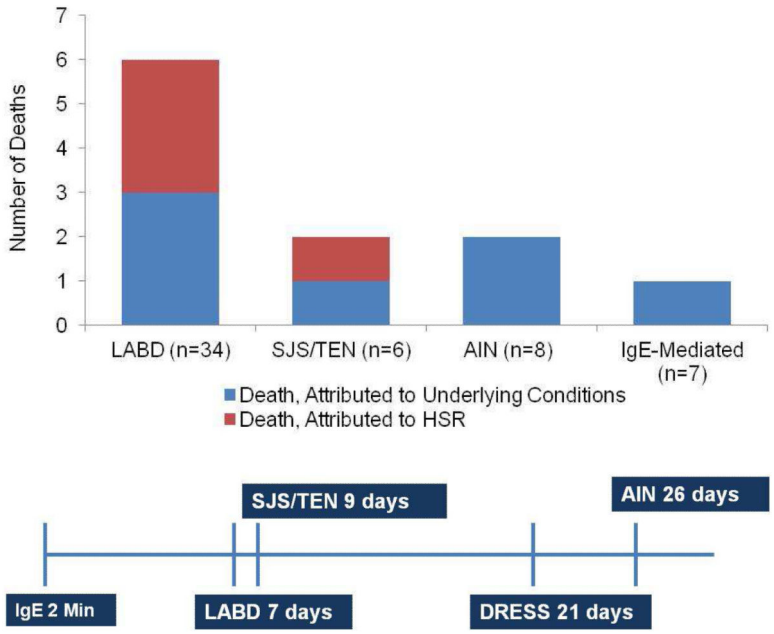

Figure 3.

Immune-mediated Hypersensitivity Reactions to Vancomycin. (a) Timing of Hypersensitivity Reactions (b) Observed fatalities by Hypersensitivity Reaction

Legend: (A) Median time to onset of hypersensitivity reactions varied by type. (B) Overall 11 (16%) of patients with vancomycin HSRs died, with 4(6%) of deaths attributed to HSR.

Table 1

Clincal data for cases of IgE-mediated reactions to vancomycin (n=7)

	Age (yrs)	Gender (M/F)	Number of vancomycin doses previously	Infection treated	Reaction timing* (minutes)	Symptoms	Treatment	Outcome	Skin-testing or re-challenge	Justification for IgE
Otani et al. 2015	60	F	NA	*Enterococcus faecalis*	8m	Dyspnea Hypotension Skin erythema Flushing	Steroids Antihistamines Epinephrine	Improved	Yes	Skin testing positive
Bosse et al. 2013	35	M	1	*Clostridium difficile* colitis	35m	Dyspnea Throat tightness, laryngeal edema, Facial erythema	Steroids IVF Antihistamines Epinephrine Switched therapy	Improved	No	Convincing clinical diagnosis
Kupstaie et al. 2010	23	M	1	Polymicrobial bactermia including *Enterococcus* faecalis and *MRSA*	1m	Dyspnea Hypotension (80/60) Tachycardia Facial flushing, cold sweat, tremor	Steroids IVF Antihistamines Switched therapy	Improved, negative repeat culture	No	Convincing clinical diagnosis
Kitazawa et al. 2005	43	M	1	*MRSA* abscess	1m	Wheezing Flushing	Antihistamines	Improved	Yes	Breakthrough symptoms despite premedication and desensitization
Hassaballa et al. 2000	45	F	NA	*Enterococcus* wound infection	1m	Cardiac arrest Hypotension Flushing Tongue swelling Emesis, Diaphoresis	Intubated Epinephrine Steroids Antihistamines Desensitized to vancomycin	Improved	No	Convincing clinical diagnosis
Chopra et al. 2000	46	F	1	*MRSA* dialysis catheter infection	2m	Respiratory distress, Wheezing, Cyanosis, Pruritus, Erythema,	Steroids Antihistamines	Deceased, from sepsis	Yes	Severe reaction despite red man syndrome prophylactic administration
Vilaviciencio et al. 1998	43	F	1	*MRSA* wound infection	2m	Hypotension, Facial swelling, Lip Swelling	CPR Intubation Epinephrine	Improved	Yes	Severe reaction with breakthrough symptoms despite premedication and desensitization

Abbreviations: NA: not available; IVF: intravenous fluids; MRSA: methicillin-resistant *Staphylococcus aureus*; CPR: cardiopulmonary resuscitation

* Timing from vancomycin dose to reaction onset

Table 2

Clinical data for cases of Linear IgA bullous dermatosis to vancomycin (LABD, n=34). All patients had characteristic skin biopsy findings and direct immunoflourescence with linear IgA deposition along the basement membrane/dermal-epidermal junction.

	Age (yrs)	Sex (M/F)	Infection treated	Reaction timing	Skin Sloughing	Mucosal Involvement	Other rash atypical feature	Treatment	Outcome
Kakar et al. 2013	91	F	Acute cholecystitis Sepsis	2d	40% BSA	Oral	Vesicles	Comfort measures only	Deceased, from HSR
Selvaraj et al. 2013	70	F	Post-operative sepsis	5d		Oral	Vesicles Palms affected	Discontinuation of vancomycin	Full resolution within 14d
Jawitz et al. 2011	78	F	HAP post-op	28d				Topical steroids	Full resolution in 10d
O'Brien et al. 2011	45	M	*Clostridium dificile* colitis	2d				Discontinuation of vancomycin Camphorylated moisturizer	Full resolution
McDonald et al. 2010	32	M	VAP	10d				Discontinuation of vancomycin	Full resolution
Walshe et al. 2009	76	M	*Staphylococcus* bacteremia	9d				Oral steroids Discontinuation of vancomycin	Full resolution
Khan et al. 2008	57	M	Liver and splenic abscesses Laparotomy	35d	75% BSA		Palms and Soles affected	Topical steroids HD IVIG	Deceased, from HSR
Senanayake et al. 2008	68	M	Post-op wound infection	4d		Oral	Palms affected	Oral steroids Discontinuation of vancomycin	Full resolution
Billet et al. 2008	70	M	Post-op perihepatic abscess, MRSA, Enterococcus	5d			No bullae	Oral steroids Dapsone	Clinically improved within 3d
Billet et al. 2008	61	F	Post-op wound abdominal infection	13d			No bullae	Topical steroids Discontinuation of vancomycin	Clinically improved in 6d
Navi et al. 2006	73	M	ICD placement	3d			Vesicles	Discontinuation of vancomycin	Full resolution in 2 weeks
Waldman et al. 2004	77	M	CABG, complicated post-op course	6d	46% BSA			Silvadene dressing changes q12h Dapsone	Complete re-epithelialization within 3 weeks Deceased, from cardiac complications
Joshi et al. 2004	48	F	TVH c/b pelvic abscess	10d				Discontinuation of vancomycin	Full resolution
Armstrong et al. 2004	81	M	AAA repair c/b wound infection	3d			Target lesions	Discontinuation of vancomycin	Full resolution in 3 weeks
Dellavalle et al. 2003	74	M	Pneumonia	4d	90% BSA	Oral		Discontinuation of vancomycin	Deceased, from septic shock

	Age (yrs)	Sex (M/F)	Infection treated	Reaction timing	Skin Sloughing	Mucosal Involvement	Other rash atypical feature	Treatment	Outcome
Neughbauer et al. 2002	52	F	*Escherichia coli* urosepsis	<1d			Vesicles	Discontinuation of vancomycin	Full resolution in 2 weeks
Palmer et al. 2001	75	F	Infected varicose ulcer	6d			Urticaria	Oral steroids Dapsone	Full resolution
Palmer et al. 2001	86	F	Fracture of femur s/p repair	4d	"Diffuse"			Oral steroids	Deceased, from pneumonia and complications of HSR
Palmer et al. 2001	78	F	CABG c/b MRSA wound infection	15d			Urticaria	Topical steroids Discontinuation of vancomycin	Resolution of rash Deceased, from renal failure
Klein et al. 2000	65	M	Sepsis due to *Klebsiella pneumoniae, P.aeruginosa, Staphylococcus* species	14d				Discontinuation of vancomycin	Full resolution in 4 weeks
Mofid et al. 2000	87	F	Urinary tract infection	11d		Oral		IV steroids Discontinuation of vancomycin	Full resolution
Danielsen et al. 1999	68	M	Culture negative endocarditis	9d			Vesicles	Topical steroids Discontinuation of vancomycin	Full resolution within 10d
Bernstein et al. 1998	60	F	Enterocutaneous fistula	10d				Oral steroids Discontinuation of vancomycin	Full resolution
Nousari et al. 1998	65	F	*P.aeruginosa S.epidermidis* sepsis	7d				Discontinuation of vancomycin	Full resolution within 30 days
Whitworth et al. 1996	63	M	Cardiac catherization	1d				Oral steroids Discontinuation of vancomycin	Full resolution within 3 weeks
Richard et al. 1995	72	F	Total pelvic ex-enteration for TCC of the bladder	2d		Oral and genital	Target lesions Papules	Discontinuation of vancomycin	Full resolution of eruptions over 2 weeks
Geismann et al. 1995	79	M	*S. aureus* cellulitis	8d		Oral and genital		Discontinuation of vancomycin	Full resolution
Kuechle et al. 1994	69	M	Draining sinus tract status-post CABG	14d				Discontinuation of vancomycin	Full resolution within 3 weeks
Kuechle et al. 1994	74	F	Sternal wound infection status-post CABG	5d			Target lesions Palms affected	Discontinuation of vancomycin	Full resolution
Kuechle et al. 1994	67	M	Sternal wound infection status-post CABG	1d			Vesicles	Discontinuation of vancomycin	Full resolution

	Age (yrs)	Sex (M/F)	Infection treated	Reaction timing	Skin Sloughing	Mucosal Involvement	Other rash atypical feature	Treatment	Outcome
Carpenter et al. 1992	54	M	Bowel perforation	10d				Discontinuation of vancomycin	Full resolution within 9 months
Carpenter et al. 1992	72	F	Intra-abdominal abscess	7d			Palms and soles affected	Discontinuation of vancomycin	Full resolution within 2 weeks
Carpenter et al.	54	M	Osteomyelitis	21d				Vancomycin continued for an additional 3 weeks without worsening	Full resolution
Baden et al. 1988	68	M	*E.coli* urosepsis Post-op (CABG)	9d				Discontinuation of vancomycin Twice daily compresses Bacitracin	Resolution within 2 weeks

* Timing from vancomycin dose to reaction onset

Abbreviations: d: days; BSA: body surface area; HSR: hypersensitivity reaction; HAP: hospital acquired pneumonia; VAP: ventilator associated pneumonia; HD: hemodialysis; IVIG: intravenous immunoglobulins; MRSA: methicillin-resistant *Staphylococcus aureus*; ICD; implantable cardioverter defibrillator; CABG: coronary artery bypass graft; h: hours; TVH: total vaginal hysterectomy; c/b: complicated by; AAA: abdominal aortic aneurysm; s/p: status-post; IV: intravenous; TCC: transitional cell carcinoma

Table 3

Clinical data for cases of Drug Rash Eosinophilia and Systemic Symptoms (DRESS) syndrome to vancomycin (n=16)

	Age (yrs)	Gender (m/f)	Infection treated	Reaction timing*	Clinical signs and symptoms	Laboratory findings	Treatment	Outcome
Young et al. 2014	24	M	*Corynebacterium jeikeium* septic arthritis	21d	MP rash, arthralgia, lymphadenopathy, fever	AEC: 2,900/L AST M/ALT 270mg/dL No nephritis RegiSCAR score 7	IV steroids with a prednisone taper	Clinically improved with resolution of symptoms
Young et al 2014	48	F	L5/S1 osteomyelitis	14d	MP rash, facial edema, odynophagia, fever, chills	AEC: 2,200/L AST M/ALT 337mg/dL No nephritis RegiSCAR score 6	IV steroids with prolonged prednisone taper	Clinically improved within 5 days
Young et al. 2014	59	F	MRSA wound infection	21d	MP rash, fever and facial edema	AEC: 10,400/L AST M/ALT 113mg/dL No nephritis RegiSCAR score 6	Oral and topical steroids Antihistamines	Clinically improved
Della-Torre et al. 2013	75	M	Culture negative endocarditis	27d	MP rash, fever	AEC: 0.6×10^9 AST 45/ALT 264mg/dL Cr. (bl M, max 1.31mg/dL) RegiSCAR score > 7	IV steroids Antihistamines IVIG	Clinically improved, labs normalized
Blumenthal et al. 2013	65	M	β-hemolytic *Streptococcus* group B empyema	12d	MP rash	AEC: 3460/L AST 440mg/dL/ALT 105mg/dL Cr. (bl 0.5, max 2.1mg/dL) Atypical lymphocytes: none	IV Steroids	Clinical improvement within 48h DRESS resolved after 2 months
Blumenthal et al. 2013	40	M	*Propionibacterium* and *Peptostreptococcus* prosthetic joint infection	28d	MP rash, fever, cervical lymphadenopathy, splenomegaly, pitting edema	AEC:3,890/L AST 178mg/dL/ALT 122mg/dL Cr (bl 0.8mg/dL,max 2.2mg/dL) HHV6 IgG <1:20	IV steroids, followed by 6 month oral taper	Clinical improvement within 2 days
Blumenthal et al. 2013	48	F	Coagulase negative *S.aureus* prosthetic joint infection	28d	MP rash, fever	AEC:1,900/L AST 85mg/dL/ALT 137mg/dL No nephritis HHV6 <1:20	No steroids used in management Antihistamines	Gradual clinical improvement with supportive care
Blumenthal et al. 2013	74	M	Gram positive cocci cellulitis after traumatic hand injury	21d	MP rash, fever, facial and peripheral edema, hypotension, tachycardia	AEC: 6,550/L AST 75mg/dL/ALT 170mg/dL Cr (bl 1.4 mg/dL,max 2.3mg/dL) HHV6 <1:20	No steroids used in management IVF Switched therapy	Clinically improved

	Age (yrs)	Gender (m/f)	Infection treated	Reaction timing*	Clinical signs and symptoms	Laboratory findings	Treatment	Outcome
Blumenthal et al. 2013	51	M	Osteomyelitis	21d	MP rash, periorbital edema, chest tightness, nausea, fever, chills, lightheadedness	AEC: 1,620/L AST 107 mg/dL/ALT 347mg/dL No nephritis HHV6 DNA <600	IV steroids Switched therapy	Clinically improved
Dauby et al. 2012	54	F	Methicillin-resistant *Staphylococcus epidermis* catheter associated bacteremia (febrile neutropenia in setting of chemotherapy for breast cancer)	7d	MP rash, fever, chills	AEC: 6,380/L AST 31mg/dL /ALT 45 mg/dL No nephritis	Topical steroids Antihistamines Antipyretic Switched therapy	Clinically improved
O'Meara et al. 2011	66	M	ORIF c/b MRSA	28d	MP rash, fever, facial edema, lymphadenopathy	AEC: 3,620/L AST 163mg/dL /ALT 144mg/dL Cr (bl 1.3mg/dL,max 4.9mg/dL)	IV steroids	Clinically improved after prolonged treatment course
Boet et al. 2009	38	F	*Streptococcus oralis* endocarditis	30d	MP rash, fever, facial edema	AEC: 2820/L No nephritis	IV steroids	Clinically improved, discharged within few weeks
Vauthey et al. 2008	60	F	MRSA cellulitis after amputation	18d	MP rash, fever, periorbital edema	AEC: 1,251/L Cr Cl 30mL/min	IV steroids Topical steroids Antihistamines	Gradually improved, discharged after 2 months
Tamagawa-Mineoka et al. 2007	52	M	Cholesteatoma s/p tymanoplasty (MRSA infection from ear wound)	4d	MP rash, fever, facial edema	AEC: 1,832/L AST 358 mg/dL/ALT 547mg/dL Cr (bl NA, max 3.58 mg/dL) HHV6 DNA 1:320	IV steroids followed by prednisone taper	Clinically resolved
Zuliani et al. 2005	45	F	Coagulase negative endocarditis	18d	MP rash, fever, facial edema	AEC: 1,474/L AST 385 mg/dL/ALT 599 mg/dL Cr (bl 0.8 mg/dL,max 5.3 mg/dL)	IV steroids with prednisone taper Antihistamines Hemodialysis Cyclosporine	After two cutaneous relapses, Clinically improved
Marik et al. 1997	51	M	Culture negative endocarditis	30d	MP rash, palpitations, malaise, dyspnea and rigors	AEC: 5,875/L Cr (bl 1.0 mg/dL, max 7.8 mg/dL)	IV steroids	Clinically improved in 1 week. Hospital course c/b urosepsis

Abbreviations: d: days; MP: maculopapular; AEC: absolute neutrophil count; M: missing; RegiSCAR: registry of severe cutaneous adverse reactions; IV: intravenous; MRSA: methicillin-resistant *Staphylococcus aureus*; Cr: creatinine; bl: baseline; IVIG: intravenous immunoglobins; DRESS: drug rash eosinophilia with systemic symptoms; HHV6: human herpesvirus 6; IVF: intravenous fluids; ORIF: open reduction internal fixation; c/b: complicated by; Cl: clearance;

* Timing from vancomycin dose to reaction onset

Table 4

Clinical data for cases of acute interstitial nephritis (AIN) to vancomycin (n=8)

	Age (yrs)	Gender (m/f)	Infection treated	Reaction timing*	Symptoms	Lab data	Biopsy	Treatment	Outcome
Htike et al. 2012	79	F	Coagulase-neg *Staphylococcus* Bacteremia	7d	Malaise, fatigue	Cr (bl 0.9 mg/dL,max 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 weeks	Renal function resolved over 4 weeks
Salazar et al. 2010	51	M	MRSA osteomyelitis	28d	Rash	Cr (bl 0.9 mg/dL, max 2.2,59.0% change) AEC: 2318/L	Interstitial edema Eosinophils Mononuclear infiltrations	Oral steroids	One recurrence Followed by resolution
Michail et al. 2009	35	M	*S. aureus* empyema	4d	MP rash, arthralgia	Cr (bl normal, max 6.5 mg/dL) No urine eoisinophils	Mononuclear inflammatory infiltration	Furosemide HD Switched therapy	Renal function resolved over 10m
Hong et al. 2007	44	M	Polymicrobial wound infection with *Staphylococcus aureus*, Group B *Streptococci*, and *S.mitis*	28d	Rash, fever, hypotension	Cr (bl 3.1 mg/dL, max 8.5 mg/dL, 63.5% change AEC: 640/L	Giant cell granulomas Mononuclear interstitial infiltration	After failed IV and oral steroids x 1w, switched to cyclosporine and MMF HD Switched therapy	Renal function improved with cyclosporine, MMF and HD for 2m
Hsu et al. 2001	70	M	MRSA abscess	23d	Fever, MP rash	Cr (bl 2.0 mg/dL, max 3.5 mg/dL,42.9 % change) AEC: 936	Interstitial edema Eosinophils Mononuclear infiltrations	Oral steroids CVVH Switched therapy	Several readmissions followed by death from polymicrobial sepsis
Wai et al. 1998	64	M	MRSA sternal wound dehiscence s/p CABG	39d	Fever, MP rash	Cr (bl 1.1 mg/dL,max 9.5 mg/dL,88.4 % change) AEC: 979/L	Interstitial mononuclear infiltrations Granulomata	Oral steroids HD over 2 weeks Switched therapy	Renal function improved Several readmissions and complicated post-operative course
Codding et al. 1989	67	M	*Staphylococcus aureus* endocarditis	30d	Fever, MP rash	Cr (bl 1.5 mg/dL, max 6.6mg/dL) AEC: 861	Interstitial mononuclear infiltration Granulomata	HD Switched therapy	Clinically deteriorated Deceased from septic shock
Bergman et al. 1988	34	F	Endometritis, *Staphylococcus aureus*	6d	Fever, pedal edema	Cr (bl 1.5 mg/dL,max 3.4 mg/dL) AEC: normal	Refused renal biopsy	Discontinued vancomycin	Renal function resolved within 15 days

Abbreviations: d: days; Cr: Creatinine; bl: baseline; max: maximum; ATN: acute tubular nephrosis; AIN: allergic interstitial nephritis; MRSA: methicillin-resistant Staphylococcus aureus; AEC: absolute eosinophil count; MP: maculopapular; HD: hemodialysis; IV: intravenous; w: weeks; MMF: mycofenolate mofetil; m: months; CVVH: continuous-veno-venous hemofiltration; s/p: status-post; CABG: coronary artery by-pass graft

* Timing from vancomycin dose to reaction onset

Table 5

Clinical data for cases of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) to vancomycin (n=6)

	Age (yrs)	Sex (m/f)	Infection treated	Reaction timing*	Rash description	Lab data	Biopsy	Treatment	Outcome
Changela et al. 2013	35	M	MRSA abscess	9d	Dusky purpuric plaques and multiple fluid filled blisters on the trunk, upper and lower extremities. 30% of BSA	IgA: 154mg/dL	Necrotic epidermis Severe blisters at DE junction Necrotic keratocytes	IV steroids for 4d Oral steroid taper	Clinically improved
O'Brien et al. 2011	46	F	Respiratory failure	"few" d	Epidermal sloughing, erosions and blisters over 40% BSA. Nikolsky sign positive		Epidermal necrosis, minimal interface, and perivascular lymphocytic infiltrate	Discontinuation of vancomycin	Terminally ill, deceased
Bouaziz et al. 2006	38	F	Fistula	9d	MP rash, fever, oral, ocular and mucous membrane erosions, diffuse blisters, Nikolsky sign positive, 50% epidermal skin detachment	Serum drug level 20mg/L	Follicular necrosis DE detachment	IV fluids Anti-infectious therapy Nutritional support Skin care	Deceased day 13, from HSR
Chan-Tack 2000	46	F	Infected hip joint prosthesis	8d	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 weeks
Alexander et al. 1996	36	M	Endocarditis	17d	MP rash involving torso, abdomen, legs and arms. Lymphadenopathy, pharyngreal 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 24h
Vidal et al. 1992	28	M	*S. aureus* sepsis (history of AIDS)	27d	MP rash, fever, oral mucosa and genitals involved. Nikolsky's sign positive	ESR: 78mm/hour ANC: 1,349/mm^3	Lymphocytic and neutrophilic subdermal infiltration	Switched therapy	Recovered, discharged after 57d

Abbreviations: MRSA: methicillin-resistant staphylococcus aureus; d: days; BSA: body surface area; DE: dermal-epidermal; IV: intravenous; MP: maculopapular; HSR: hypersensitivity reaction; ANC: absolute neutrophil count; AIDS: acquired immunodeficiency syndrome; ESR: erythrocyte sedimentation rate

*Timing from vancomycin dose to reaction onset