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Vancomycin Hypersensitivity Reactions Documented in Electronic Health Records

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Abstract

Background: Vancomycin, the most common antimicrobial used in U.S. hospitals, can cause diverse adverse reactions, including hypersensitivity reactions (HSRs). Yet, little is known about vancomycin reactions documented in electronic health records (EHR).

Objective: To describe vancomycin HSR epidemiology from EHR allergy data.

Methods: Cross-sectional study of patients with ≥1 encounter from 2017–2019 and an EHR vancomycin drug allergy label (DAL) in two U.S. healthcare systems. We determined prevalence and trends of vancomycin DALs and assessed active DALs by HSR phenotype determined from structured (coded) and unstructured (free-text) data using natural language processing. We investigated demographic associations with documentation of vancomycin red man syndrome (RMS).

Results: Among 4,490,618 patients, 14,426 (0.3%) had a vancomycin DAL with 18,761 documented reactions (2,248 [12.0%] free-text). Quarterly mean vancomycin DALs added was 253 (SD 12) and deleted was 12 (SD 2). Of 18,761 vancomycin HSRs, 7,903 (42.1%) were immediate phenotypes and 3,881 (20.7%) were delayed phenotypes. Common HSRs were rash

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(32% of HSRs) and RMS (16% of HSRs). Anaphylaxis was coded in 6% of HSRs. Drug reaction eosinophilia and systemic symptoms (DRESS) syndrome was the most common coded vancomycin severe cutaneous adverse reaction. RMS documentation was more likely for males (OR 1.30, 95%CI 1.17–1.44) and less likely for blacks (OR 0.59, 95%CI 0.47–0.75).

Conclusions: Vancomycin causes diverse adverse reactions, including common (e.g., RMS) and severe (e.g., DRESS) reactions entered as DAL free-text. Anaphylaxis comprised 6% of documented vancomycin HSRs, although true vancomycin IgE-mediated reactions are exceedingly rare. Improving vancomycin DAL documentation requires more coded entry options, including a coded entry for RMS.

Keywords

Vancomycin; allergy; phenotype; hypersensitivity; infusion reaction; drug allergy label; electronic health record; red man syndrome; drug reaction eosinophilia and systemic symptoms syndrome; epidemiology

INTRODUCTION

Vancomycin is one of the most effective antibiotics for treating antibiotic-resistant Gram-positive infections. When administered parenterally, vancomycin is the first-line treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) including soft-tissue infections, bacteremia, osteomyelitis, and pneumonia.[1–4] Oral vancomycin is the first-line treatment for the growing healthcare-associated infection, *Clostridioides difficile* colitis.[5] Today, vancomycin is the most commonly used antimicrobial in United States (U.S.) hospitals.[6] Coinciding with the increased MRSA prevalence over the past two decades, vancomycin use increased by more than 30 percent between 2006 and 2012.[6,7]

Vancomycin causes several different types of adverse drug reactions (ADRs), including immediate and delayed hypersensitivity reactions (HSRs).[8,9] HSRs to vancomycin range from immune-mediated reactions, including immunoglobulin (Ig) E-mediated or T cell-mediated, to non-immune mediated reactions (i.e., IgE-independent).[10] The most common HSR to vancomycin is the non-immune-mediated rate-related infusion reaction, colloquially known as red man syndrome (RMS), which occurs from 4 to 47% of exposures.[11] RMS incidence estimates may vary because there is no precise RMS phenotype or documentation strategy.[12]

The allergy module in the electronic health record (EHR) is used to document all ADR types (e.g., HSRs, intolerances, and contraindications); HSRs account for approximately 20% of ADRs and may lack coded reactions for precise documentation.[13,14] While most EHRs have coded entries for “hives,” “rash,” “anaphylaxis,” and “angioedema,” many HSR phenotypes, including most severe cutaneous adverse reactions (SCARs), must be documented using free-text. Limited data suggest that the more detailed the documentation in the EHR drug allergy label (DAL), the higher likelihood that that specific drug class will be used in the future, presumably because greater reaction detail clarifies that the reaction was not allergic in origin.[15] As vancomycin DAL documentation may be particularly important for future vancomycin prescribing in U.S. hospitals, we investigated the epidemiology of vancomycin

immune-mediated and non-immune-mediated HSRs using coded and unstructured (free-text) data in the EHR allergy module of two large Northeastern U.S. healthcare systems.

METHODS

We conducted an EHR-based cross-sectional study of patients with a vancomycin DAL who had at least one encounter at Johns Hopkins Health System Corporation (JHHS) or Mass General Brigham (MGB), formerly Partners HealthCare, between January 2017 and December 2019. Both JHHS and MGB uses Epic EHR; data from JHHS did not include John's Hopkins All Children's Hospital in St. Petersburg, Florida.

We determined vancomycin DAL prevalence rates by calculating the number of patients with an active vancomycin DAL considering the total number of patients who had an encounter at JHHS or MGB between January 2017 and December 2019. We considered both active and inactive DALs to assess vancomycin DALs entries (active labels) and deletions (inactive labels) during the same period, although the first quarter (January to March 2017) was excluded due to inaccurate findings resulting from the transition to Epic EHR.[16]

For active DALs, we determined the prevalence of documented vancomycin reactions by calculating the number of reactions by phenotype (HSR, non-HSR, other ADRs, unknown, null) considering the total number of documented reactions and both coded (structured) and uncoded (free-text) data. Free-text data were processed using a natural language processing (NLP) system called the Medical Text Extraction, Reasoning, and Mapping System (MTERMS, Figure 1).[17] MTERMS' value set is based on standard medical terminologies and other publicly available data sources.[18,19] MTERMS has previously demonstrated an overall F-measure of 90%.[20] In this study, we used MTERMS to identify and extract reactions in the free-text comments via lexicon look-up using a previously developed reaction value set.[18] To assess MTERMS performance at JHHS, we randomly selected a 5% subset of patients with free-text comments and measured its precision (0.96), recall (1.00) and F-measure (0.98).

We included in the reaction value set terms to identify RMS from free-text in a vancomycin DAL (e.g., variations including Red man, Redman, Red man's syndrome, Redman's, etc.). Prior to extraction, the free-text comments were pre-processed with MTERMS' misspelling detection and correction tool to capture spelling errors not included in the reaction value set. During extraction, the MTERMS negation detection module was applied to exclude negated reactions (e.g., "rash without itching"). Extracted reactions from the free-text that were already among the coded reactions for a given allergy entry were excluded. For example, if the coded reaction was "rash" and the free-text comments were "rash and swelling", only "swelling" was extracted. We classified documented reactions into their likely reaction types considering immune-mediated and non-immune-mediated HSRs and non-HSRs (e.g., renal liver toxicity, liver toxicity, ototoxicity).[21] In order to group HSRs, we assumed typical temporal onset of HSRs considering the symptoms and signs documented; however, we did not have timing of onset information in the EHR. For example, anaphylaxis and urticaria were considered immediate HSRs and SCARs were considered delayed HSRs. For rash

without any further specifications as a delayed HSR phenotype, given that maculopapular rash is a more common phenotype than IgE-mediated cutaneous reactions.[20,21]

For patients with free-text indicating RMS, we determined the number of associated coded reactions in their EHR (e.g., “flushing,” “rash,” etc.) excluding the code ‘other (see comments)’ which is the code used to signal that a free-text reaction exists at MGB. We identified the ten most common coded reactions associated with RMS free-text entries. While many patients had free-text that signaled a likely RMS, we did not assume RMS unless specified in this analysis. However, because a majority of rash, hives, itching, anaphylaxis, and flushing from vancomycin are likely indicative of RMS, we separately considered patients with these reactions to have “possible RMS.” Among “possible RMS” patients, we assessed the presence of free-text RMS documentation in the DAL by sex and race using logistic regression and presented odds ratios with 95% confidence intervals.

Finally, to determine if there was a disproportionately high frequency of free-text reaction entries in the vancomycin DAL, we assessed the frequency of “Other (see comments)” at MGB for vancomycin, and compared the frequency of vancomycin ‘other (see comments)’ to the frequencies of ‘other (see comments)’ for penicillin DALs and all antibiotics DALs. We used a chi squared test to compare these frequencies and considered a two-sided p-value of <0.05 considered statistically significant.

Statistical analyses were conducted using STATA/IC 15.0 software (StataCorp, College Station, Tex) and SAS 9.3 (SAS Institute Inc., Cary, NC). This study was approved by the Johns Hopkins in Medicine Institutional Review Board and the Partners Institutional Review Board.

RESULTS

Among 1,144,019 patients who had at least one encounter at JHHS between January 2017 and December 2019, 3,702 (0.32%) patients had an active vancomycin DAL. Of the 3,346,599 MGB patients who had at least one encounter between January 2017 and December 2019, 10,426 (0.31%) patients had an active vancomycin DAL. Between April 2017 and December 2019, the average number of added vancomycin DALs in the EHR was 253 (SD 12) per quarter. The average number of deleted (inactive) vancomycin DALs was 12 (SD 2) per quarter during the same time period (Figure 2).

There were 14,128 patients (0.31%) with a vancomycin DAL across both health care systems with 18,761 reconciled reactions by MTERMS (Table I). 7,268 (51%) were female and 8,713 (62%) were White, with a higher percentage of Black patients at JHHS than MGB (12% compared to 3%, respectively). Of the 18,761 total reactions, there were 7,903 (42.1%) immediate HSRs and 3,922 (20.9%) delayed HSRs (Table I). Reactions without a coded entry comprised 2,248 (12.0%) of reactions.

The most common HSRs were rash (31.3% of all HSRs), RMS (16.1% of all HSRs), hives (14.9% of all HSRs), itching (14.0% of all HSRs), flushing (9.4% of all HSRs), and anaphylaxis (6.1% of all HSRs). SCARs to vancomycin were uncommon (n = 136, 1.2% of

all HSRs) but drug reaction eosinophilia and systemic symptoms (DRESS) syndrome was the most common documented SCAR (n = 82, 60.3% of all SCARs).

There were 1,909 patients with specified RMS terms entered as free-text (Table II). The most common free-text entry was “Red man syndrome” (54.9%). Of the 1,909 patients, 967 (50.7%) had one associated coded reaction, 723 (37.9%) had two associated coded reactions, and 219 (11.5%) had three or more associated coded reactions in their DAL. In 489 (25.6%) patients, RMS patients did not have a coded reaction beyond “other (see comments).” RMS free-text was found most commonly in patients who had coded reactions of rash (48.5%), hives (20.3%), unknown (18.8%), itching (15.8%), anaphylaxis (9.5%), swelling (5.4%), and flushing (4.9%, Table III).

Considering the population of 10,051 patients with “possible RMS” (see methods), male patients were more likely to have RMS documentation than female patients (Odds Ratio [OR] 1.30, 95% CI 1.17–1.44). Compared to White patients, Black patients were less likely to have RMS documented (OR 0.59, 95% CI 0.47–0.75). After mutually adjusting for sex and race, neither the association of RMS documentation with male sex nor Black race changed (Table IV).

At MGB, the frequency of vancomycin DALs with free-text (n = 2358, 22.6%), was greater than the frequency of penicillin DALs with free-text (n = 49211, 12.9%; $p < 0.001$) and other antibiotics DAL with free-text (n = 110,506, 14.6%; $p < 0.001$).

DISCUSSION

We investigated the population epidemiology of vancomycin DALs documented in the EHRs of two large Northeastern U.S. healthcare systems using NLP to reconcile structured and free-text reactions.[17] We found the population estimate of a vancomycin DAL was 3 per 1,000 patients. The trend of vancomycin DALs steadily increased during the period studied, and deleted vancomycin DALs were rare suggesting DALs were not routinely re-evaluated. While we found rash to be the most common coded reaction, it was also the most common coded reaction accompanying RMS free-text; RMS itself was the second most common vancomycin HSR specified in the DAL. We identified that many vancomycin HSR were documented with free-text only; specific RMS documentation was not present in many coded reactions that were possible RMS (flushing, rash, and anaphylaxis), and RMS terminology may directly affect inconsistent or incomplete RMS documentation, particularly in female and black patients. Overall, free-text reactions were more commonly entered for vancomycin compared to penicillin antibiotics and other antibiotics at MGB. This study therefore suggests that there are substantial limitations to the EHR documentation of vancomycin HSRs; these limitations require improved reaction value sets, including a coded entry to reflect RMS potentially with more inclusive terminology (e.g., “infusion reaction” or similar).

RMS was one of the most commonly documented vancomycin reactions, representing at least 16% of vancomycin HSRs. This 16% notably did not include patients with documented coded reactions such as rash, hives, itching, flushing, and anaphylaxis, which may have been

RMS ("possible RMS" patients were 5-fold more than patients where RMS was specified in the DAL free-text). Accurate documentation of RMS is critical for patient care, since RMS is not a contraindication to future vancomycin use as it can be prevented by slow infusion and anti-histamines.[22] Although 6% of vancomycin reactions were coded as anaphylaxis, true IgE-mediated reactions to vancomycin are exceedingly rare, reported only in case reports.[23,24] A recent systematic case review from 1982 through 2015 found only seven presumptive cases of IgE-mediated reactions to vancomycin based on a positive skin test, immediate symptoms despite slow infusion and anti-histamines, or symptoms during vancomycin desensitization.[8] Still, an IgE mechanism was not proved. We believe that even the patients with vancomycin DAL indicating anaphylaxis may have had RMS. When RMS is not diagnosed or documented appropriately, patients will be assumed to have a true, IgE-mediated reaction to vancomycin; this will result in strict vancomycin avoidance, potentially even when vancomycin is the optimal treatment.[25]

We found that female and Black patients were less likely to have RMS documented in their DAL despite similar reactions/symptoms among the "possible RMS" group. This finding may represent a limitation to the current terminology, potentially reflecting a bias in the healthcare provider documenting the reaction. Alternatively, erythema may not be comparably identified on black skin compared to white skin. Although RMS is a commonly used and historic terminology broadly recognized among diverse healthcare professionals, this study identifies notable terminology limitations, particularly given it is not a coded reaction and was not as likely to be used for patients who are female or black. While a coded entry for RMS is optimal, a renaming and rebranding of RMS to "infusion reaction" or "non-IgE-mediated HSR" may ultimately be preferable to limit documentation bias and extend similar documentation to drugs beyond vancomycin that can cause similar reactions.[26,27] Ultimately, improving vancomycin DALs may require point-of-use clinical decision support (CDS) that guides clinicians to identify vancomycin immediate IgE-independent reactions when entering coded reactions such as rash, hives, itching, and flushing. A similar CDS tool could also assist in the accurate documentation of other drugs that cause immediate IgE-independent reactions, such as neuromuscular blocking agents, opioids, and quinolones.[26,27]

Vancomycin can cause delayed HSRs including DRESS, linear IgA bullous dermatosis, and Stevens-Johnson syndrome/toxic epidermal necrolysis.[28,29] In our study, we found that SCARs to vancomycin were rare, although among 136 documented SCARs, the most commonly documented was DRESS Syndrome with 82 cases documented. A prior MGB study identified 69 validated DRESS syndrome cases from the DAL and noted that vancomycin was the most common drug culprit.[30] This study finding is important given the morbidity and mortality associated with DRESS syndrome, and the growing number of inpatients treated with vancomycin, many of whom may be discharged on prolonged parenteral vancomycin for MRSA as part of outpatient parenteral antibiotic therapy programs.[31,32] Accurate documentation will additionally facilitate genetic studies, since vancomycin-induced DRESS was recently found to be strongly associated with HLA-A*32:01 in a population of predominantly European ancestry.[33,34]

Recent efforts related to antibiotic allergy evaluation as antimicrobial stewardship focus on β-lactam antibiotics given the large numbers of patients carrying clinically insignificant penicillin DALs.[35] However, for large urban hospitals, reported vancomycin allergies may also carry substantial adverse consequences. We found that the trend of vancomycin DALs has been steadily increasing between April 2017 and December 2019. Yet, the number of deleted vancomycin allergy entries during the same period of time was significantly lower, likely secondary to the common misconception that a drug allergy is a permanent diagnosis.[13] For inpatients in these healthcare systems, vancomycin may be optimal treatment preferred over alternatives for MRSA such as ceftaroline, daptomycin and linezolid which have a higher associated cost.[25] Our data suggest that the coded reaction options in the allergy module of the EHR requires substantial modifications with CDS enhancements to accurately capture common and important vancomycin reactions. Improving vancomycin DALs may indeed prove to be important for optimal and cost-conscious antibiotic treatment in large urban hospital systems such as JHHS and MGB.

This study has important limitations. We studied data within vancomycin DALs that suggest HSRs, although they are not verified vancomycin HSRs. We assumed typical temporal onset of HSRs by phenotype considering the symptoms and signs documented in the vancomycin DAL, but timing of HSR onset was not available. Even the immune-mediated HSRs were merely suggestive of HSRs without being confirmed by allergy or dermatology specialists nor diagnostic testing (e.g., biopsies, skin testing). However, we used an established NLP system used previously for EHR allergy epidemiology assessments and HSRs and confirmed its validity in JHHS data.[20,21] This NLP system, however, has not been previously validated for non-EPIC EHR systems. We included only free-text entries that specified RMS and may have missed cases describing RMS using alternative terminology. While we were able to appreciate that there was more free-text in the DALs of vancomycin compared to other antibiotics at MGB, comparable data at JHHS was not available. These data also come from two large healthcare systems in urban U.S. areas (Boston, Baltimore), and thus, these population may not be representative to other U.S. populations. However, findings related to vancomycin DALs were markedly similar between the two insitutions studied.

We described the epidemiology of vancomycin HSRs documented in the EHRs of two large health systems and illustrated the limitations of the EHR allergy module documentation of some of the most common (e.g., immediate IgE-independent reactions, RMS) and the most severe (e.g., DRESS) vancomycin HSRs. Improved vancomycin reaction documentation and targeted CDS is needed to facilitate optimal inpatient care and improve vancomycin allergy epidemiologic research.

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Abbreviations:

MRSA	Methicillin-resistant *Staphylococcus aureus*
U.S.	United States
ADR	Adverse drug reaction
HSR	Hypersensitivity reactions
Ig	Immunoglobulin
RMS	Red man syndrome
EHR	Electronic health record
SCAR	Severe cutaneous adverse reactions
DAL	Drug allergy label
NLP	Natural language processing
MTERMS	Medical Text Extraction, Reasoning, and Mapping System
DRESS	Drug reaction eosinophilia and systemic symptoms
CDS	Clinical decision support

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Highlights Box:

What is already known about this topic?

Vancomycin is a commonly used antimicrobial that can cause diverse adverse reactions, including immune-mediated HSRs and non-immune-mediated HSRs such as red man syndrome (RMS).

What does this article add to our knowledge?

RMS was one of the most commonly documented vancomycin reactions (16% of HSRs) despite requiring free-text entry. Anaphylaxis comprised 6% of documented vancomycin HSRs, although true vancomycin IgE-mediated HSRs are exceedingly rare. RMS may be underrecognized and underdocumented, particularly for female and black patients.

How does this study impact current management guidelines?

Given the frequency with which vancomycin is administered in the U.S., EHR documentation of vancomycin HSRs requires more coded entries, including an entry to represent RMS.

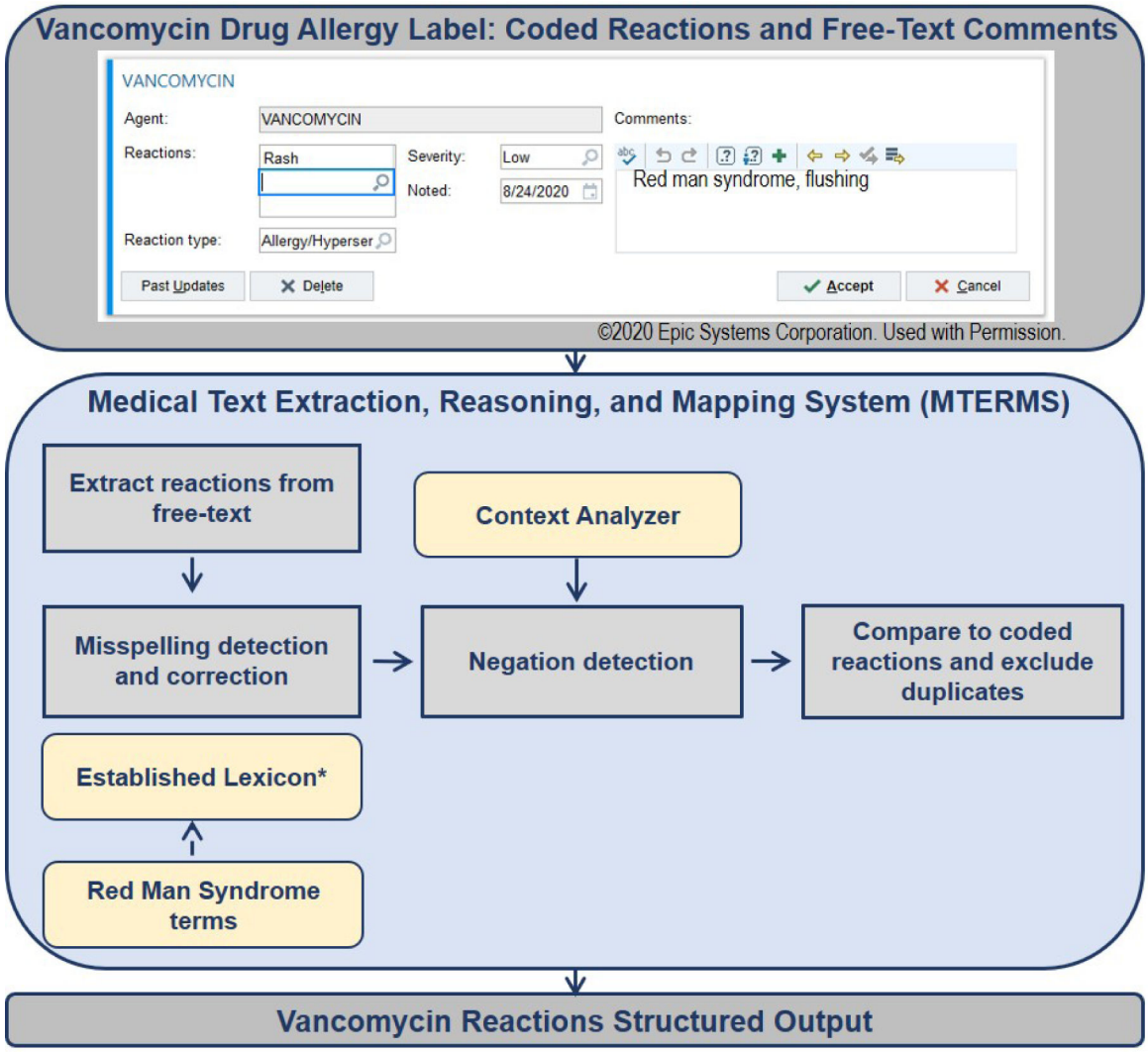

Figure 1.

Medical Text Extraction, Reasoning, and Mapping System (MTERMS) components used to extract vancomycin reactions including value set terms to identify “red man syndrome” (RMS) from unstructured (free-text) data.

*MTERMS lexicon includes terms from standard terminologies (e.g., UMLS, RxNorm, and SNOMED CT).[19,36,37]

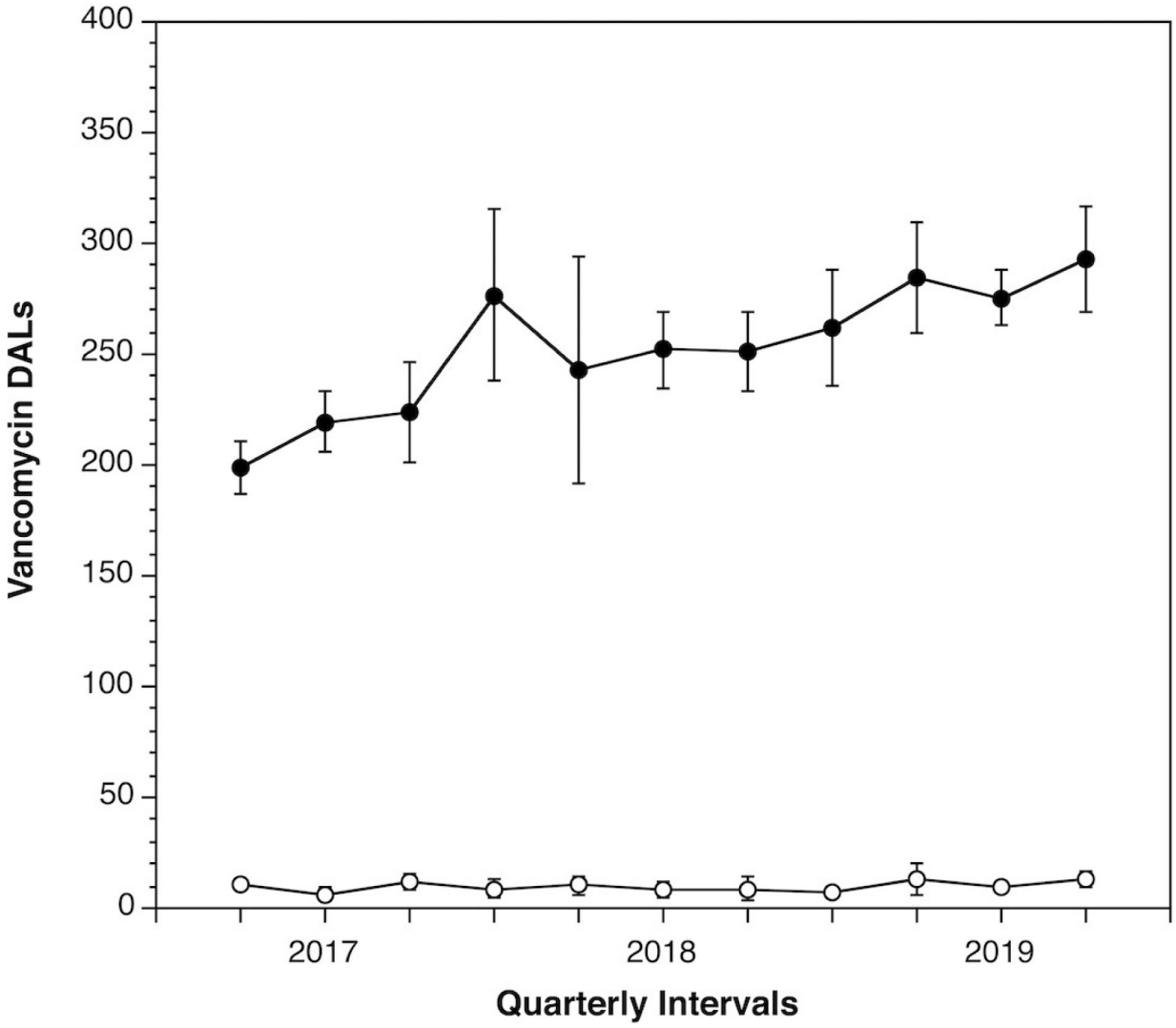

Figure 2.

Vancomycin drug allergy label (DAL) entries (•) and deletions (○) between April 2017 and December 2019. First quarter (January to March 2017) was not included because of transition to a different EHR system. Values are given as mean and vertical bars display the standard deviation.

Table 1.

Prevalence of vancomycin drug allergy labels (**n = 18,761**) by healthcare system considering (A) reaction phenotypes, and (C) other adverse drug reactions. Data are represented by n(%).

A. HSRs	Total (n = 11,825)	JHHS (n = 3,213)	MGB (n = 8,612)
Immediate HSR phenotypes	***7,903 (66.8)***	***2,327 (72.4)***	***5,576 (64.7)***
Red man syndrome *	1,909 (16.1)	417 (13.0)	1,492 (17.3)
Hives	1,759 (14.9)	484 (15.1)	1,275 (14.8)
Itching	1,651 (14.0)	517 (16.1)	1,134 (13.2)
Flushing	1,106 (9.4)	488(15.2)	618 (7.2)
Anaphylaxis	708 (6.1)	193 (6.0)	515 (6.0)
Angioedema	490 (4.1)	159 (4.9)	331 (3.8)
Respiratory reactions †	280 (2.4)	69 (2.1)	211 (2.5)
Delayed HSR phenotypes	***3,922 (33.2)***	***886 (27.6)***	***3,036 (35.3)***
Rash	3,710 (31.3)	849 (26.4)	2,861 (33.2)
DRESS	82 (0.7)	8 (0.2)	74 (0.9)
Dermatitis	41 (0.3)	16 (0.5)	25 (0.3)
SJS	34 (0.3)	4 (0.1)	30 (0.3)
Fixed drug eruption	21 (0.2)	6 (0.2)	15 (0.2)
AGEP	18 (0.2)	1 (0.03)	17 (0.2)
LABD	14 (0.1)	2 (0.1)	12 (0.1)
TEN	2 (0.02)	0	2 (0.02)
B. Non-HSRs	**Total (n = 536)**	**JHHS (n = 108)**	**MGB (n = 428)**
Contraindications	***306 (57.1)***	***44 (40.7)***	***262 (61.2)***
Blood dyscrasias ‡	141 (26.3)	7 (6.5)	134 (31.3)
Renal toxicity	87 (16.2)	28 (25.9)	59 (13.8)
Ototoxicity	63 (11.8)	8 (7.4)	55 (12.9)
Liver toxicity	15 (2.8)	1 (0.9)	14 (3.3)
Intolerances	***230 (42.9)***	***64 (59.3)***	***166 (38.8)***
GI symptoms §	191 (35.6)	53 (49.1)	138 (32.2)
Headache	39 (7.3)	11 (10.2)	28 (6.5)
C. Other ADRs	**Total (n = 6,400)**	**JHHS (n = 2,200)**	**MGB (n = 4,200)**
Other reactions ¶	***1,301 (20.3)***	***420 (19.1)***	***881 (21.0)***
Unknown	***1,557 (24.3)***	***523 (23.8)***	***1,034 (24.6)***
Null #	***3,542 (55.3)***	***1,257 (57.1)***	***2,285 (54.4)***

JHHS, Johns Hopkins Health System Corporation; MGB, Mass General Brigham; HSRs, Hypersensitivity reactions; DRESS, Drug reaction with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; AGEP, Acute generalized exanthematous pustulosis; LABD, Linear IgA bullous dermatosis; TEN, Toxic epidermal necrolysis; GI, gastrointestinal

Grey shading represents reactions without a structure code and that were identified in the free-text comments using the Medical Text Extraction, Reasoning, and Mapping System (MTERMS).

* Red man syndrome reactions were detected by applying natural language processing on free-text comments in the vancomycin DAL.

[†]Respiratory reactions included bronchospasm, stridor, wheezing, and/or shortness of breath.

[‡]Blood dyscrasias included thrombocytopenia, leukopenia, neutropenia, and/or anemia.

[§]GI symptoms included vomiting, nausea, and/or diarrhea.

[¶]Other reactions included reactions that were not included in HSRs or non-HSRs (e.g., fever [n=239], mental status change [n=32], chest pain [n=13]).

[#]Null indicates patients with no reaction listed in the DAL.

Table II.

"Red Man Syndrome" (RMS) free-text terms identified in the allergy module of the EHR by healthcare system. Data are presented as n(%).

Term (free-text comments)	Number of entries (n = 1909)	JHHS (n = 417)	MGB (n = 1,492)
Red man syndrome	1048 (54.9)	206 (54.9)	842 (44.1)
Redman syndrome	197 (10.3)	39 (10.3)	158 (8.3)
Red man's syndrome	184 (9.6)	61 (9.6))	123 (6.4)
Red man	153 (8.0)	22 (8.0)	131 (6.9)
Redman's syndrome	104 (5.4)	24 (5.4)	80 (4.2)
Red mans syndrome	56 (2.9)	8 (2.9)	48 (2.5)
Red man's	51 (2.7)	16 (2.7)	35 (1.8)
Redmans	47 (2.5)	11 (2.5)	36 (1.9)
Redman	42 (2.2)	7 (2.2)	35 (1.8)
Redmans syndrome	27 (1.4)	8 (1.4)	19 (1.0)

Table III.

Top 10 coded reactions associated with ‘Red Man Syndrome’ free-text entries

Coded reaction	Number of entries n (%) (n = 1909)
Rash	926 (48.5)
Hives	387 (20.3)
Unknown	359 (18.8)
Itching	302 (15.8)
Anaphylaxis	181 (9.5)
GI Upset	151 (7.9)
Swelling	103 (5.4)
Flushing	94 (4.9)
Mental Status Change	74 (3.9)
Other (see comments) *	1361 (71.3)

GI, gastrointestinal

* Coded commonly chosen to indicate there is a free-text reaction entrered

Table IV.

Demographic associations of having RMS specified as free-text in patients with a vancomycin DAL coded as hives, itching, flushing, swelling, anaphylaxis, bronchospasm, rash, other, and unknown (n=10,051).

Patient characteristics	RMS entered as free-text	
	Unadjusted Odds ratio (95% CI)	Adjusted Odds ratio (95% CI)*
Sex		
Female	[ref]	[ref]
Male	1.30 (1.17, 1.44)	1.30 (1.17, 1.44)*
Race		
White	[ref]	[ref]
Black	0.59 (0.47, 0.75)	0.59 (0.47, 0.75)
Hispanic	1.16 (0.82, 1.53)	1.16 (0.83, 1.64)
Asian	0.78 (0.54, 1.13)	0.78 (0.54, 1.12)
Other	1.00 (0.67, 1.22)	1.00 (0.77, 1.28)
Mixed race†	1.38 (0.67, 2.83)	1.40 (0.68, 2.88)
Unknown‡	0.91 (0.67, 1.22)	0.90 (0.67, 1.22)

RMS, Red man syndrome

*Adjusted for sex and race

†Patients with more than one race/ethnicity coded in their electronic health records

‡Patients without a race/ethnicity listed in their electronic health records