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Concise Communication

Antimicrobial never events: Objective application of a framework to assess vancomycin appropriateness

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Abstract

To address appropriateness of antibiotic use, we implemented an electronic framework to evaluate antibiotic "never events" (NEs) at 2 medical centers. Patient-level vancomycin administration records were classified as NEs or non-NEs. The objective framework allowed capture of true-positive vancomycin NEs in one-third of patients identified by the electronic strategy.

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Although various methodologies exist to quantify hospital antibiotic consumption, few have focused on patient-level appropriateness.[1-3] Recent studies investigating inappropriate antibiotic use have been successful in classifying inappropriateness burden; however, these strategies have not been used for antimicrobial stewardship interventions.[4,5] Furthermore, some studies have employed laborious medical record review, and results may not be readily extrapolated. Thus, the development of a generalizable, reproducible tool that is sensitive for capturing and intervening on inappropriate antibiotic events is urgently needed. We have recently proposed the antibiotic "never events" (NEs) framework to serve as a metric for quality of prescribing.[6] This framework allows clear definition of antibiotic administrations that should never occur, that is, when the risk of harm significantly outweighs potential benefit. In this study, we evaluated an analytical framework for the identification of NEs as a measure of vancomycin inappropriateness and NEs in 2 hospital systems.

Methods

Pre-existing electronic health records (EHRs) were extracted either from data warehouses or available medical record systems at Northwestern Memorial Hospital (NMH) and Henry Ford Hospital (HFH) (January 2014 through October 2017) (Fig. S2). Briefly, only the first vancomycin course within the index hospital admission (encounter) was included, and subsequent vancomycin courses (first dose at least 96 hours from the previous dose) were excluded. Data elements were reconciled to vancomycin records via unique encounter identification numbers (index admission). Specific data preprocessing is described in the Supplementary Materials (online). This study was approved by the institutional review boards of NMH and HFH.

A generalizable framework with data elements standardized across all participating settings was applied to all included patients and data elements. The framework consisted of an algorithm with binary decision points (Fig. 1), classifying each instance as electronically identified NEs or non-NEs (Supplementary Materials online). As a representative sample, a minimum of 300 patients with NEs and non-NEs were randomly selected and underwent manual adjudication against electronic outputs from the algorithm. We evaluated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) from the electronic predictions via manual EHR review of NE versus non-NE instances. The same non-NE subgroup was reutilized to assess performance characteristics at HFH.

Results

At NMH, 197 NEs (106 type 1 and 91 type 2) were identified among 38,232 vancomycin courses (0.5%), which corresponded to 2 NEs per 1,000 vancomycin therapy days (see Summary Demographics in the Supplementary Materials online). In total, 200 patients underwent manual review (type 1, n = 50; type 2, n = 50; non-NE, n = 100). Of the 100 patients identified with NEs via the electronic algorithm, 35 cases were true positives (18 type 1 and 17 type 2). Performance characteristics were similar between type 1 and type 2 NEs (Table 1). Aggregating both NE types, sensitivity and specificity were 94.6% and 60.1%, respectively. False-positive type 1 NEs were primarily due to *Enterococcus* spp in asymptomatic bacteriuria (ASB) (n = 23), and others were misclassified primarily due to concurrent infections (n = 8). One type 1 NE was reclassified as a type 2 NE. Similarly, false-positive type 2 NEs (n = 33) were primarily associated with concomitant infections requiring vancomycin therapy (n = 10), the presence of *Enterococcus* spp in ASB (n = 8), and unclear allergy

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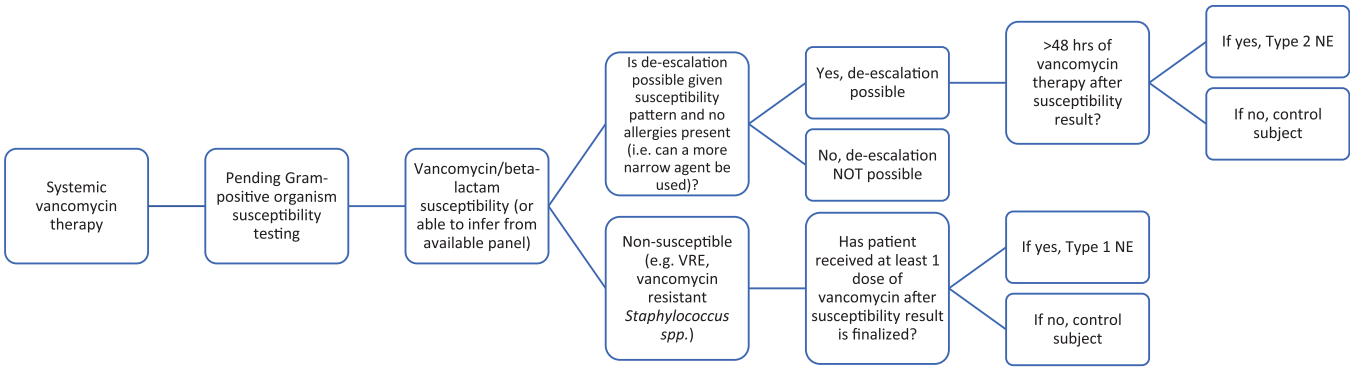


Fig. 1. Schematic of electronic capture of "never events" (NEs). Two types of vancomycin NEs were defined in the electronically applied algorithm: type 1 NE vancomycin use for a vancomycin nonsusceptible organism (after finalization of microbiological data), and type 2 NE vancomycin therapy exceeding 48 hours after de-escalation was possible (based on identification and susceptibility of causative organism) and without any contraindication (eg, allergy).

Table 1. Performance Characteristics of Electronic "Never Events" (NEs) Algorithm for Northwestern Memorial Hospital (NMH) and Henry Ford Hospital (HFH)

			Manual Adjudication							
Sites	NE Type	Sample Size[a]	TP	TN	FP	FN	Sensitivity	Specificity	PPV	NPV
NMH	Type 1	100	18	48	32	2	90.0	60.0	36.0	96.0
	Type 2	100	17	50	33	0	100	60.2	34.0	100.0
HFH	Type 1	117	1	114	1	1	50.0	99.1	50.0	99.1
	Type 2	136	17	114	4	1	94.4	96.6	81.0	99.1

Note. TP, true positive; TN, true negative; FP, false positive; FN, false negative; PPV, positive predictive value; NPV, negative predictive value.
[a]Sample size includes non-NE patients.

documentation (n = 8). Of 100 non-NE cases, 2 were false-negative cases.

At HFH, 23 NEs (2 type 1 and 21 type 2) were identified among 1,034 vancomycin courses (2.2%), which corresponded to ~6 NEs per 1,000 vancomycin therapy days. In total, 138 patients underwent manual review (type 1, n = 2; type 2, n = 21; non-NE, n = 115) and demonstrated sensitivities at 50.0% for type 1 NEs and 94.4% for type 2 NEs, with specificity at 99.1% for both NE categories (Table 1). The PPVs were 50.0% for type 1 NEs and 81.0% for type 2 NEs, whereas the NPV was 99.1% for both NE types. Aggregating both NE types, sensitivity and specificity were achieved at 94.7% and 95.8%, respectively, with 78.3% PPV and 99.1% NPV. One encounter was misclassified as a type 1 NE (ie, a false positive). Among all electronically identified NEs, 17 were confirmed as true positives; false-positive NEs were primarily associated with polymicrobial wound infections. One false-negative NE was identified in each NE category where type 2 NEs occurred.

Discussion

In this study, we demonstrated the application of an objective framework to capture vancomycin "never events" (NEs). The methodology, when applied at separate hospitals using local data capture strategies, resulted in comparable performance characteristics across systems. This approach is important because contemporary tracking methodologies, such as the National Healthcare Safety Network Antimicrobial Use module, provide mechanisms to compare and benchmark hospital- and unit-specific antimicrobial consumption for acute-care centers in the United States; however, they do not classify appropriateness of individual antimicrobial use.[7] Although a PPV of 34% in our study may seem low at first, this methodology is designed to function as a screening test for very low probability events (ie, 0.5%–2.2% of vancomycin courses). Thus, electronic flagging of potential NEs using our methodology would be expected to generate 1 true positive NE for every 3 electronically identified NEs. Furthermore, the excellent NPV objectively ruled out patients not experiencing an NE. Overall, clinicians performing antimicrobial stewardship would only need to review ~15 potential NE instances per 1,000 vancomycin treatment days to find the ~5 true NEs.

Creating guided approaches to safely use antibiotics is important because ~55% of hospitalized patients receive ≥1 dose of antibiotic therapy, and 20% of patients receiving antibiotics for ≥24 hours experience ≥1 adverse drug reaction (ADR).[8,9] We selected vancomycin as a prototype because it is commonly used nosocomially and can cause downstream ADRs.[10] Because much vancomycin use is empiric (~69.9% of vancomycin use at NMH was empiric, data not shown) and understanding the appropriateness of use has traditionally required time-consuming chart reviews, it is important for stewards to efficiently and accurately screen for potential harms. Using our methodology based on readily retrievable clinical data, we were able to comprehensively capture these NEs with relatively high sensitivity and NPV.

Although differences existed in EHR data structures and presented challenges to our initial data acquisition, our analytical framework eventually converged (Supplementary Fig. 2 online). These results demonstrate the flexibility of locally adaptive strategy with broad utility across different EHR platforms. A recent study attempted to quantify inappropriate antibiotic use in the hospital. Denny et al[11] found that 32.7% of antibiotic prescriptions were inappropriate in an emergency room setting. Our study differed in that an electronic data capture strategy was used and we were able to circumvent time-intensive manual chart reviews for all

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patients. Nevertheless, there is an urgent need to address antibiotic inappropriateness globally.

Our study was limited by a single antibiotic and 2 specific types of NEs, which constituted only a proportion of all inappropriate antibiotic use. We did not consider thresholds for antibiotic initiation or durations of therapy. Another limitation was the relatively low PPV (~35%), driven by the low prevalence of NEs; however, NEs are clearly inappropriate uses of vancomycin. If 3 potential NEs required manual chart review to stop 1 NE, this would represent an efficient safety strategy in antimicrobial stewardship efforts. Our methodology has broad implications for future applications and may be automated in real time.

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Conflicts of interest. All authors report no conflicts of interest relevant to this article.

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