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A Trial of Discontinuation of Empiric Vancomycin Therapy in Patients with Suspected Methicillin-Resistant *Staphylococcus aureus* Health Care-Associated Pneumonia

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Healthcare-associated pneumonia (HCAP) guidelines recommend de-escalating initial antibiotic therapy based on results from lower-respiratory-tract cultures. In the absence of adequate lower respiratory cultures, physicians are sometimes reluctant to discontinue empirical vancomycin, which is given for suspected methicillin-resistant *Staphylococcus aureus* (MRSA) HCAP. We evaluated a strategy of discontinuing vancomycin if both nasal and throat cultures were negative for MRSA when lower-respiratory-tract cultures were not available. An antimicrobial stewardship team identified patients receiving empirical vancomycin for suspected or proven HCAP but for whom adequate lower-respiratory-tract cultures were not available. Nasal and throat swab specimens were obtained and plated on MRSA selective media. If both nasal and throat MRSA cultures were negative, the stewardship team recommended discontinuation of empirical vancomycin. Demographic and clinical aspects, a clinical pulmonary infection score (CPIS) on the day of the stewardship recommendation, and mortality of patients for whom vancomycin was discontinued were obtained by retrospective chart review. A convenience sample of 91 patients with nasal and throat cultures negative for MRSA in the absence of adequate respiratory cultures had empirical vancomycin therapy discontinued. A retrospective review revealed that 88 (97%) patients had a CPIS of ≤6 on the day of the stewardship recommendation. In-hospital mortality (7.7%) was similar to that of a previous study of de-escalation of antibiotics in pneumonia patients without adequate cultures. In the absence of adequate lower-respiratory-tract cultures, it is reasonable to discontinue empirical vancomycin HCAP therapy in patients with negative MRSA nasal and throat cultures and a CPIS of <6.

In 2007, the Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America published antimicrobial stewardship guidelines to combat the overuse of antibiotics (1). After establishing an antimicrobial stewardship (AMS) program at the Saint Raphael campus of Yale-New Haven Hospital (Hospital of Saint Raphael at the time of the study), we targeted patients receiving empirical piperacillin-tazobactam for review by the AMS team. During AMS rounds, we noted that many patients with suspected or proven health care-associated pneumonia (HCAP) were treated empirically with piperacillin-tazobactam plus vancomycin. The IDSA Guidelines for the Management of Adults with Hospital-Acquired, Ventilation-Associated, and Health Care-Associated Pneumonia (HCAP guidelines) recommend de-escalation of empirical antibiotic therapy based on microbiologic cultures and the clinical response of the patient (2). The HCAP guidelines did not make recommendations on how to de-escalate antibiotic therapy in the absence of adequate lower-respiratory-tract cultures, a common scenario in older hospitalized patients with pneumonia, many of whom are not intubated (3, 4). We found that physicians were often reluctant to discontinue empirical vancomycin prescribed for patients at risk for HCAP due to methicillin-resistant *Staphylococcus aureus* (MRSA) when appropriate lower-respiratory-tract cultures were not available, a phenomenon which is not unique to our hospital (5). The safety of discontinuing empirical antibiotics in the absence of microbiological data has also been a matter of controversy even among physicians specialized in infectious diseases. A 2008 survey of IDSA members revealed that more than 50% of respondents supported a statement that de-escalation in patients with HCAP should not occur when microbiological data are unavailable (6).

Most patients with HCAP due to multidrug-resistant organisms (including MRSA) develop the infection following aspiration of the organism from the patient's oropharynx, followed by tracheal colonization (2). The fact that the combination of a nasal plus a throat culture negative for MRSA has a negative predictive value (NPV) of 92 to 100% for MRSA colonization (Table 1) (7–11) suggests that MRSA pneumonia is unlikely to be present in patients who do not have MRSA nasal or throat colonization. This concept is supported by a recent study which found that a negative nasal swab using PCR methods had an NPV of 98% for estimating

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TABLE 1 Sensitivity and NPV of nose and throat cultures for MRSA

Study	No. of patients screened	Body sites screened	Sensitivity (%)		NPV (%)	
			Nose	Nose and throat	Nose	Nose and throat
Coello et al. (9)	975	Nose, throat, perineum	78.5	85.6	95.3	96.8
Marshall and Spelman (11)	686	Nose, throat, groin, axilla	69.2	81.7	87	91.3
Bignardi and Lowes (7)	635	Nose, throat, perineum, skin lesions	49.6	69.7	89.6	93.5
Chaberny et al. (8)	509	Nose, throat, skin	77.8	100	98.8	100
Ide et al. (10)	2,060	Nose, throat, perineum	63.6	80	97.4	99.3

the risk of having a clinical respiratory specimen culture positive for MRSA (12).

As part of our AMS program, we requested that nasal and throat MRSA surveillance cultures be obtained from patients who were receiving empirical intravenous vancomycin for suspected MRSA HCAP and had no adequate lower-respiratory-tract cultures on which to base antibiotic de-escalation. Since vancomycin has been shown to have little, if any, effect on *S. aureus* nasal colonization (13–15) and seldom eradicates MRSA from the lower respiratory tract during the first few days of therapy (16), we did not attribute negative surveillance cultures to ongoing vancomycin therapy. When both nasal and throat MRSA surveillance cultures were negative, the AMS team recommended that empirical vancomycin administered for suspected MRSA pneumonia be discontinued. The purpose of the present study was to evaluate the effects of this evidence-based strategy for discontinuing empirical vancomycin therapy in the absence of adequate lower-respiratory-tract cultures.

MATERIALS AND METHODS

During AMS rounds conducted in the period October 2009 to August 2011 by the codirector of the AMS program (J. M. Boyce), a convenience sample of 139 patients who were receiving empirical vancomycin for suspected HCAP and from whom no adequate lower-respiratory-tract cultures were available was identified. Patients were included regardless of their location in the hospital (in intensive care units [ICU] or on general medical or surgical wards) or their level of acuity. This included (i) patients whose sputum specimen was interpreted by the clinical microbiology laboratory as not representative of lower-respiratory-tract secretions based on the number of epithelial cells present on Gram stain and (ii) patients for whom no sputum specimens were obtained. Patients with lower-respiratory-tract specimens that revealed many neutrophils and few epithelial cells on Gram stain (a good-quality specimen) were excluded, including those that grew only normal flora. To be included in the study, patients had to have a physician diagnosis of suspected or proven HCAP. Risks for HCAP included those listed in the HCAP guideline (2).

Upon identifying patients without an adequate lower-respiratory-tract culture who were receiving empirical vancomycin for suspected MRSA HCAP, the AMS team placed in the patient's chart an AMS recommendation sheet which noted the absence of adequate respiratory cultures and requested that nasal and throat MRSA surveillance cultures be obtained by nursing staff. Nurses used a single swab to sample both anterior nares and a second swab to obtain a specimen from the posterior pharynx. Nasal and throat swabs were subsequently inoculated onto either CHROMagar MRSA (Becton, Dickinson, Sparks, MD) or Chrom ID MRSA plates (bioMérieux, Durham, NC) and incubated for 24 to 48 h according to the manufacturer's directions. Colonies consistent with MRSA morphology on the respective selective media were confirmed as *S. aureus* using a Staphaurex test (Remel, Lenexa, KS). If both nasal and throat surveillance cultures were negative and no clinical cultures were positive for MRSA or other resistant Gram-positive pathogens, the AMS team recommended that empirical vancomycin be discontinued. The medical records of patients were monitored over the next few days to determine if vancomycin was discontinued as recommended.

As a follow-up to this vancomycin de-escalation strategy, a retrospective medical record review was conducted to determine if any of the patients whose vancomycin was discontinued within 48 h of negative nasal and throat culture results expired during their admission, developed culture-proven MRSA pneumonia at any time during the remainder of their hospitalization, or were readmitted to the hospital within 30 days with culture-proven MRSA pneumonia. Variables recorded included the patient's age, gender, location in an ICU or medical ward, whether a sputum sample was of poor quality or was not obtained, the type of pulmonary infiltrate identified by chest X-ray or computerized tomographic scan of the chest on or about the date of the AMS recommendation, maximum temperature and peripheral white blood cell count in the 24 h prior to the AMS recommendation, the number of days the patient received vancomycin, the total length of the patient's hospital stay, the patient's condition at discharge, and the presence or absence of readmission within 30 days.

Because a modified clinical pulmonary infection score (CPIS) of ≤ 6 for 3 days is an objective criterion to select patients at low risk for early discontinuation of empirical treatment of HCAP (2, 17), we also retrospectively calculated a CPIS for each patient based on results in the patient's medical record at the time of the AMS recommendation. For calculating the CPIS, the patient's chest X-ray and/or chest computed tomography scan findings were classified as none, diffuse, or localized by a staff radiologist accompanied by a radiology resident, both of whom were without knowledge of other clinical or laboratory values.

Statistical analysis. Continuous data were compared using an unpaired *t* test, and differences in proportions were compared using Fisher's exact test or chi-square test.

RESULTS

All 139 patients had risk factors for HCAP. Cultures from 12 (8.6%) patients yielded MRSA from either the nose or throat (or both). Vancomycin was often continued in such patients by the attending physician. For 26 (18.7%) patients, an MRSA surveillance culture was performed on only one body site (nose or throat). Seven (5%) patients had vancomycin discontinued before any results of the MRSA surveillance cultures were reported. Three (2.2%) patients had nose and throat cultures negative for MRSA, but physicians caring for the patients refused to discontinue vancomycin as recommended by the AMS team. The remaining 91 (65.5%) patients, who had negative nose and throat cultures and had vancomycin discontinued within 48 h, were included in the remaining analyses. We found that for 77 of the 91 patients (group 1), empirical vancomycin was discontinued within 48 h of both the nasal and throat surveillance cultures returning negative. For another 14 patients (group 2), empirical vancomycin was discontinued after one of the two cultures (either nasal or throat) returned negative but before the results of the

TABLE 2 Demographic and clinical characteristics of 91 patients for whom empirical vancomycin was discontinued based on negative nasal and throat MRSA surveillance cultures

Characteristic	Finding for group:		
	1 ($n = 77$)	2 ($n = 14$)	1 and 2 ($n = 91$)
Median age (yr; range)	84 (40–99)	84.5 (48–101)	84 (40–101)
Gender (no. [%])			
Male	38 (49)	6 (43)	44 (48)
Female	39 (51)	8 (57)	47 (52)
Location at the time of AMS recommendation (no. [%])			
ICU	14 (18)	0	14 (15)
Subacute unit	21 (27)	6 (43)	27 (30)
General medical/surgical ward	42 (55)	8 (57)	50 (55)
Sputum specimen (no. [%])			
Not obtained	56 (73)	12 (86)	68 (75)
Poor quality	21 (27)	2 (14)	23 (25)
Pulmonary infiltrate (no. [%])			
No infiltrate	2 (2.6)	0	2 (2)
Diffuse/patchy	9 (11.7)	3 (21)	12 (13)
Localized	66 (85.7)	11 (79)	77 (85)
Median maximum temp (°C; range) during 24 h before recommendation	98.4 (95.5–101.6)	98.2 (97.5–98.9)	98.3 (95.5–101.6)
Median maximum WBC ($\times 10^3$; range) during 24 h before recommendation	9.9 (3.0–29.9)	8.75 (1.6–30.7)	9.7 (1.6–30.7)
CPIS on day of AMS recommendation (no. [%])			
1	1 (1.3)	0	1 (1.1)
2	32 (41.6)	7 (50)	39 (42.9)
3	11(14.3)	3 (21.4)	14 (15.4)
4	13 (16.9)	3 (21.4)	16 (17.6)
5	12 (15.6)	1 (7.1)	13 (14.3)
6	5 (6.5)	0	5 (5.5)
7	3 (3.9)	0	3 (3.3)
Median	3	2.5	3
Died during admission (no. [%])	7 (9.1)		(7.7)
Died during readmission within 30 days (no. [%])	2	0	2 (2.2)
Total deaths (no. [%])	9 (11.7)	0	9 (9.9)

other culture had returned negative. Demographic and clinical characteristics of group 1 and 2 patients are shown in Table 2.

Group 1. For 70 (91%) of the 77 patients, vancomycin was discontinued within 24 h of the results of surveillance cultures, while for 6 (8%) of patients, it was discontinued within 48 h. In one case (1%) where culture results became available on a Friday afternoon, vancomycin was discontinued on the following Monday morning, which was likely 48 h after care providers became aware of the results. Group 1 patients received empirical vancomycin for a median of 4 days (range, 1 to 30 days). Patients had a median overall length of stay of 10 days (range, 3 to 33), with a median length of stay of 4 days (range, 0 to 27) after vancomycin was discontinued.

The patients ranged in age from 40 to 99 years old. Thirty-nine (51%) were female. No lower-respiratory-tract specimen was obtained from approximately three-fourths of patients, while poor-quality specimens were obtained from the remaining patients (Table 2). None had evidence of MRSA bacteremia. Seventy-one (92%) patients had a maximum temperature of less than 100.4°C in the 24 h before the AMS recommendation was made. Review of chest imaging studies revealed that all but two patients had either localized or diffuse infiltrates (Table 2). Seventy-four (96%) of the patients had a CPIS of ≤6 on the day the AMS recommendation was made, with a majority having a CPIS of ≤3. At the time of the AMS recommendation to discontinue vancomycin, 35 (46%) patients were located in either ICUs or subacute units, while the remaining patients were located on general medical/surgical wards.

In-hospital all-cause mortality among group 1 patients was 9.1% (7/77) and was 14.3% (2/14) in ICU patients, 9.5% (2/21) in patients on subacute units, and 7.1% (3/42) among patients on general medical/surgical wards. Two additional patients expired after being readmitted 1 and 12 days, respectively, after being discharged, yielding an overall mortality of 11.7% (9/77). The 9 patients, who ranged in age from 66 to 97 years old (5 were >90 years old), expired 1 to 17 days after vancomycin was discontinued. Two patients still had therapeutic vancomycin levels when they expired. Two other patients were on comfort measures only and were receiving morphine when they expired. Five patients had repeat nasal and/or throat cultures obtained <1 to 3 days before they expired that were negative for MRSA. None of the nine patients had evidence of MRSA infection at the time they expired.

One patient, who was discharged and subsequently readmitted expired 12 days after vancomycin was discontinued, had no evidence of pneumonia on autopsy.

Group 2. Fourteen additional patients had both nasal and throat MRSA surveillance cultures that were negative, but only one of the two cultures had returned negative when vancomycin was discontinued, with the other culture returning as negative 1 to 2 days after vancomycin was discontinued. None had evidence of MRSA bacteremia. Demographic and clinical characteristics of group 2 patients are shown in Table 2. All 14 patients had maximum temperatures of <100.4°C during the 24 h before the AMS recommendation was made and a CPIS of ≤6 on the day the AMS recommendation was made. The median length of stay (10.5 days), length of stay after vancomycin was discontinued (5.5 days), and number of days on vancomycin (3.5 days) were similar to values observed in group 1 patients. We found no significant differences between group 1 and group 2 patients with respect to the variables examined ($P > 0.05$ in each case). Inclusion of these 14 patients in the analysis along with the 77 group 1 patients resulted in no substantive changes in the results (Table 2).

DISCUSSION

As part of a unique AMS program, empirical vancomycin was discontinued in patients for whom respiratory cultures were not obtained or were deemed inadequate but who had both nasal and throat surveillance cultures negative for MRSA. We requested that care givers screen patients for both throat and nasal MRSA colonization, because previous studies have found that from 5 to 20% of patients may be colonized in the throat but not the nose (7, 9–11, 18–25). In various studies, the sensitivity of an anterior nares culture for MRSA nasal colonization ranged from 41 to 93% (7–11, 19, 21–24, 26–30), while the sensitivity of combined nose and throat cultures ranged from 80 to 100% (8, 9, 11, 19, 22, 23, 26). The NPV of a nasal culture alone varied from 87 to 98.8%, while the NPV of nasal plus throat cultures ranged from 92 to 100% (Table 1) (7–11). Given the fact that aspiration of pathogens from the oropharynx is the primary route of bacteria entering the lower respiratory tract (2), the data described above provide strong evidence that MRSA pneumonia is unlikely in patients who are not colonized in the nose and throat and have no evidence of MRSA bacteremia.

On the day the AMS recommendation was made to discontinue vancomycin, retrospective chart review revealed that 96.7% of the 91 patients had a CPIS of ≤6, with more than half having a CPIS of ≤3. Previous studies have shown that patients with MRSA pneumonia often have a CPIS of ≥7 at the time the diagnosis is made, and that the CPIS is often still ≥6 following 3 or 4 days of vancomycin therapy (31–34). We believe the combination of negative nasal and throat MRSA surveillance cultures plus a CPIS of ≤6 provides physicians with additional assurance that it is reasonable to discontinue empirical vancomycin in such patients.

To make care givers aware that our suggestion to stop vancomycin therapy was based on principles outlined in an evidence-based guideline, we sometimes placed in the patient's chart a copy of a page from the IDSA HCAP guidelines that describes the use of CPIS for establishing when it is safe to de-escalate antibiotics (2). The extent to which this practice was useful was not determined, as our initiative was not designed to assess the effectiveness of this strategy.

Our study differs from several earlier reports dealing with de-escalation of antibiotics in hospitalized patients with pneumonia (3, 35–38). Our study included patients with no respiratory cultures obtained or with sputum cultures classified as inadequate by the laboratory; patients with good-quality sputum specimens that yielded either respiratory pathogens or only normal oral flora were excluded. In contrast, in several previous studies that required pneumonia patients to have respiratory and/or blood cultures performed, de-escalation was performed on 30 to 75% of patients who were classified as culture negative, which was defined as no respiratory pathogen recovered from cultures (35, 36, 38). However, Labelle et al. included 290 pneumonia patients for whom no respiratory culture was obtained plus 149 patients whose respiratory cultures yielded no growth or normal oral flora (the two groups combined were classified as culture negative) (3). De-escalation of antibiotics was performed on 20% of the culture-negative group. The in-hospital mortality in our study (7.7%) was similar to a mortality rate of 10.7% in a previous study of pneumonia patients who underwent de-escalation of antibiotics when respiratory cultures were not obtained (38).

Our study has several limitations. This was a nonrandomized, uncontrolled observational study involving a convenience sample of a relatively small number of patients seen during AMS rounds at a single community teaching hospital. Therefore, our results may not be generalizable to all types of acute-care hospitals. Not all patients on empirical vancomycin therapy for suspected MRSA HCAP were included in the study due to limited personnel resources devoted to the AMS program. Also, two patients who received empirical vancomycin for suspected HCAP had no appreciable pulmonary infiltrates and may not have had definite pneumonia. This is not an unexpected finding. In several previous studies, only 30 to 70% of patients who received broad-spectrum empirical antibiotic therapy for suspected HCAP or had ventilator-associated pneumonia had documented pneumonia (39, 40). Such patients would be expected to do well despite de-escalation. Follow-up of patients after discontinuation of vancomycin was limited to the remainder of their hospitalization and to those who were readmitted within 30 days. We did not test the efficacy of recommending discontinuation of empirical vancomycin based on a negative nasal culture alone. In facilities with access to PCR assays for MRSA nasal carriage, it may be reasonable to evaluate discontinuation of empirical vancomycin HCAP therapy based on a negative nasal PCR result alone, given the high NPV of this test for predicting the presence of MRSA in clinical respiratory cultures (12). None of our patients were intravenous drug users, who are at increased risk of MRSA bacteremia and bacteremic spread to the lungs. Furthermore, our AMS team is comprised of both clinical pharmacists and infectious disease physicians, which may not be true for AMS programs in some other hospitals. Therefore, the willingness of patient care providers to comply with AMS team recommendations to discontinue vancomycin in this study may differ from what might be achieved in other types of facilities. It might be argued that if CPIS values had been calculated in real time, antibiotic therapy of patients with a CPIS of <6 could have been de-escalated without obtaining MRSA screening cultures. However, some physicians may be reluctant to de-escalate antibiotics based on CPIS alone due to concerns about the interobserver variability of the CPIS and lack of evidence of its utility in certain patient populations (e.g., severe pneumonia and trauma patients) (41–44). Previous experience in our hospital revealed that some of our physicians, like those reported elsewhere, were reluctant to

de-escalate antibiotics in the absence of any lower-respiratory-tract cultures (5, 6). A combination of a CPIS of <6 plus negative nose and throat MRSA cultures may provide such individuals with greater assurance of the safety of discontinuing empirical vancomycin therapy.

In conclusion, our preliminary findings suggest that it is reasonable to discontinue empirical vancomycin in patients without adequate respiratory cultures who are receiving this agent for suspected MRSA HCAP but have both nose and throat surveillance cultures negative for MRSA and a CPIS of ≤6. Given the limitations of this study, further evaluation of this strategy in different acute-care hospitals, ideally by using a controlled study design or by comparison to other strategies, such as the use of CPIS alone, is needed.

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