CONCISE COMMUNICATION

The Limits of Serial Surveillance Cultures in Predicting Clearance of Colonization with Carbapenemase-Producing *Enterobacteriaceae*

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An accepted practice for patients colonized with multidrug-resistant organisms is to discontinue contact precautions following 3 consecutive negative surveillance cultures. Our experience with surveillance cultures to detect persistent carbapenemase-producing *Enterobacteriaceae* (CPE) colonization suggests that extrapolation of this practice to CPE-colonized patients may not be appropriate.

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Carbapenemase-producing *Enterobacteriaceae* (CPE) are pathogens of increasing prevalence and worldwide concern.[1] The Centers for Disease Control and Prevention (CDC) recommends that institutions in which CPE is endemic perform active surveillance testing and maintain contact precautions for patients infected or colonized with CPE.[2] However, the CDC does not provide guidance regarding discontinuation of contact precautions for these patients.[2] Through retrospective review of our institution's CPE surveillance program, we sought to determine the utility of serial screening in predicting clearance of CPE colonization.

METHODS

CPE Surveillance and Infection Control Measures

The University of Virginia Health System (UVAHS) is comprised of a 600-bed academic medical center, a 40-bed long-term acute care hospital (LTACH), and numerous primary care and subspecialty ambulatory clinics. In April 2009, in response to CDC guidance,[3] UVAHS initiated CPE surveillance using weekly perirectal cultures for all patients in select intensive care units, at the LTACH, and on all units on which a CPE-positive patient was present. Patients transferred to UVAHS from regions in which CPE is endemic or who were otherwise designated as high-risk for CPE colonization by the hospital epidemiologist were screened on admission. All CPE-colonized or infected patients were maintained on contact precautions, and a long-term indicator was entered in the electronic medical record. To assess for ongoing colonization, follow-up perirectal cultures were collected on known CPE-colonized patients who were not receiving antibacterial medication, no sooner than 8 weeks after the initial positive culture, at an outpatient clinic visit or upon readmission to the hospital.

Subjects

The study period was defined as April 2009, the start of the CPE surveillance program, through August 2013. All UVAHS patients with a positive CPE perirectal culture obtained during the study period were included in this study. Patients with CPE from clinical isolates but without documented perirectal colonization were not included, as negative follow-up perirectal cultures in these patients would incorrectly be interpreted as "cleared" when they in fact had never been perirectally colonized. Recurrence of CPE-positivity was defined as a perirectal or clinical culture positive for carbapenemase production, following at least 1 negative perirectal culture. Patients were counted once and were censored following recurrence. The University of Virginia Institutional Review Board for Health Sciences Research approved this study with waiver of consent.

Microbiology

All clinical *Enterobacteriaceae* isolates meeting criteria for production or possible production of extended spectrum β-lactamase by automated testing (VITEK 2; bioMérieux, Durham, NC) were phenotypically screened for carbapenemase production using the indirect carbapenemase test, performed as previously described.[4] bla_{KPC} polymerase chain reaction testing was performed on all isolates with a positive phenotypic test as previously described.[4] Surveillance cultures were obtained via perirectal swabs and processed as previously described.[5]

RESULTS

During the study period, 142 patients had at least 1 positive CPE perirectal culture. Patient characteristics are listed in Table 1. A total of 95 patients had at least 1 follow-up perirectal culture. Of these, 51 patients (53.7%) were negative for CPE colonization at the first follow-up culture (Table 2). Of the 51 patients with 1 negative follow-up perirectal culture, 31 patients had a second follow-up culture. The cultures of 24 patients (77.4%) remained negative, and positive cultures recurred in 7 patients. A positive urine culture for *Klebsiella pneumoniae*, the same organism that had grown on the initial perirectal culture, was recorded in 1 patient. Recurrently positive perirectal cultures were observed in 6 patients; 4 of these patients had recurrent positive cultures with the same organism as their initial positive perirectal culture (3 with *K. pneumoniae*, 1 with *Citrobacter freundii*). In the other 2 patients, distinct species other than those previously isolated

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TABLE 1. Characteristics of 142 Patients

Mean age, y (range)	57 (1–89)
Male gender (%)	81 (57)
Race, No. (%)	
Asian	2 (1)
Black	12 (8)
Hispanic	3 (2)
White	120 (85)
Other	5 (4)
Comorbidities, No. (%)	
Transplant[a]	25 (18)
Cancer	12 (8)
HIV/AIDS	0 (0)
Kidney disease	66 (46)
Liver disease	46 (32)
Prior CPE clinical isolate	31 (22)

NOTE. HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; CPE, carbapenemase-producing *Enterobacteriaceae*.
[a]Includes 16 liver, 6 kidney, 1 kidney-pancreas, and 2 lung transplant patients.

TABLE 2. Predictive Value of Negative Cultures

Previous Sequential Negative Cultures	Next Culture Negative / No. at Risk (%)
0 (first culture)	51 of 95 (53.7)
1	24 of 31 (77.4)
2	17 of 20 (85.0)
≥3	6 of 8 (75.0)

were detected: *K. pneumoniae* then *K. oxytoca* in one case and *Enterobacter aerogenes* then *C. freundii* in the other.

Of the 24 patients with 2 consecutive negative follow-up perirectal cultures, 20 patients had a third follow-up culture; 17 of these patients (85.0%) remained negative. In 1 patient, a urine culture grew *K. pneumoniae*, which had grown on the initial perirectal culture. Positive perirectal cultures growing species distinct from those with which they were initially colonized occurred in 2 patients: *C. freundii* then *Serratia marcescens* in one case and *E. aerogenes* then *E. cloacae* in the other.

Of the 17 patients with 3 consecutive negative follow-up perirectal cultures, additional culture data were available for 8 patients. Of these, 6 patients (75.0%) remained CPE-negative on all subsequent cultures (ranging from 1 to 9 additional cultures) for the duration of the study. In 1 patient, bla_{KPC}-positive *Citrobacter,* which we were unable to speciate by 16S rRNA sequencing, recurred on perirectal culture nearly 8 months after an initial perirectal culture positive for *E. cloacae* and 7.5 months after the first of 3 negative CPE perirectal cultures. In a second patient, CPE recurred after 5 consecutive negative screens. Although this patient was initially perirectally colonized with *K. oxytoca*, *K. pneumoniae* recurred on perirectal culture in this patient 4 months later and 6 weeks after the first of 5 negative perirectal cultures.

DISCUSSION

The CDC supports discontinuation of contact precautions for patients colonized or infected with methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant *Enterococcus* (VRE) following 3 consecutive negative surveillance cultures obtained while the patient is not receiving antimicrobial therapy,[6] and data validating this practice exists. For example, Byers et al[7] demonstrated that, in patients previously documented to be colonized with VRE, 95% of patients with 3 consecutive negative surveillance cultures and 100% of patients with 4 consecutive negative surveillance cultures remained negative at their next follow-up screening culture.

Few data are available on the natural history of CPE colonization and the predictive utility of CPE surveillance cultures. In a prospective study from Israel, relapse of CPE carriage occurred in 5 of 50 prior CPE carriers (10%) after 3 consecutive negative surveillance cultures.[8] In another recent study, despite treatment with oral gentamicin and/or colistin, 8 of 50 patients (16%) had recurrence of CPE colonization after achieving eradication, defined as 3 consecutive negative perirectal swabs.[9] Similar to the findings of these groups,[8,9] we found a 25% recurrence rate of CPE colonization after 3 or more consecutive negative perirectal cultures.

Our study has several limitations. First, this study was not adequately powered to delineate the risk factors for persistent colonization. Second, we cannot definitively state whether positive CPE surveillance cultures after prior negative perirectal cultures were due to variation in specimen collection techniques, true recurrence caused by re-exposure to a CPE-colonized patient or environment, or persistent colonization at a burden below the limit of detection of our assay that emerged following antibiotic exposure. Notably, we have previously observed co-colonization with multiple species of CPE in the same patient.[10] In some cases, both strains of CPE have been found to carry the same bla_{KPC}-positive plasmid.[10] Thus, recurrence of CPE-positivity with a species distinct from that with which the patient was initially colonized is not necessarily indicative of reinfection but may be secondary to relapse, as a consequence of horizontal transmission of a bla_{KPC}-positive plasmid between different species of *Enterobacteriaceae*. Given the limited sample size of our study and its retrospective nature, larger prospective studies are needed to reach more definitive conclusions about the natural history of CPE colonization and the utility of surveillance cultures to predict clearance of colonization. Our study suggests that the extrapolation of data used to support discontinuation of contact precautions for patients colonized with MRSA or VRE is not sufficient to determine when contact precautions can safely be discontinued for CPE-colonized patients, as this practice may be associated with an unacceptably high risk of relapse and exposure of other patients to these highly resistant pathogens.

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