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ORIGINAL ARTICLE

Clinical Microbiology Costs for Methods of Active Surveillance for *Klebsiella pneumoniae* Carbapenemase–Producing Enterobacteriaceae

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OBJECTIVE. To compare direct laboratory costs of different methods for perirectal screening for carbapenemase-producing Enterobacteriaceae (CPE) colonization.

DESIGN. Cost-benefit analysis.

SETTING. A university hospital and affiliated long-term acute care hospital (LTACH).

PARTICIPANTS. Inpatients from the hospital or LTACH.

METHODS. Perirectal samples were collected from inpatients at risk for exposure to CPE. In 2009, we compared the accuracy of the Centers for Disease Control and Prevention (CDC)–recommended CPE screening method with similar methods incorporating a chromogenic agar (CA). We then performed a cost projection analysis using 2012 screening results for the CA method, the CDC method, and a molecular assay with wholesale pricing based on the 2009 analysis. Comparisons of turnaround and personnel time were also performed.

RESULTS. A total of 185 (2.7%) of 6,860 samples were confirmed as CPE positive during 2012. We previously found that the CDC protocol had a lower sensitivity than the CA method and predicted that the CDC protocol would have missed 92 of the CPE-positive screening results, whereas the modified protocol using CA would have missed 26, assuming similar prevalence and performance. Turnaround time was 3 days using the CDC and CA-modified protocols compared with 1 day for molecular testing. The estimated annual total program cost and total technologist's hours would be the following: CA-modified protocol, \$37,441 and 376 hours; CDC protocol, \$22,818 and 482 hours; and molecular testing, \$224,596 and 343 hours.

CONCLUSIONS. The CDC screening protocol appeared to be the least expensive perirectal screening method. However, expense must be weighed against a lower sensitivity and extra labor needed for additional work-up of non-CPE isolates. The molecular test has the shortest turnaround time but the greatest expense.

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We have witnessed a dramatic increase in infection due to carbapenemase-producing Enterobacteriaceae (CPE) in the past decade with associated poor outcomes for infected patients.¹⁻³ The Centers for Disease Control and Prevention (CDC) recommends perirectal screening and isolation for patients colonized or infected with CPE.⁴ Several studies have demonstrated that perirectal screening to identify silently colonized patients coupled with adherence to contact precautions for those colonized is an effective strategy for reducing transmission of carbapenem-resistant Enterobacteriaceae.⁵⁻⁸ Because of ongoing cases of *Klebsiella pneumoniae* carbapenemase (KPC)–producing Enterobacteriaceae within the University of Virginia Health System (UVaHS), we have performed active surveillance for selected patients since 2009. The laboratory method outlined in the CDC screening pro-

tol, which employs the modified Hodge test (MHT), is validated for only *K. pneumoniae* and *Escherichia coli*. At our institution, however, we have identified more than a dozen species of Enterobacteriaceae that harbor *bla*_{KPC}, including *Enterobacter* species and *Citrobacter* species.⁹ We were therefore compelled to adapt an alternative protocol to fit our experience.¹⁰ Previously, we have demonstrated that the specificity of the indirect carbapenemase test (ICT), used as an alternative phenotypic test, is superior to the MHT for detection of KPC-producing Enterobacteriaceae in clinical samples.¹⁰ Here we assess the accuracy of 3 perirectal screening methods: direct inoculation of a swab to a chromogenic agar (CA), selection in broth with plating on CA, and the CDC method of broth selection with plating on MacConkey agar. We then analyze the financial impact to the microbiology

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laboratory of supporting an annual program of our size where CPE is endemic and compare that impact with the estimated costs of other laboratory screening approaches.

METHODS

Patient Characteristics

Screening was conducted at UVaHS, a 708-bed tertiary care hospital with a 40-bed long-term acute care hospital (LTACH) in central Virginia. The initial performance assessment took place from September 8, 2009, through January 22, 2010 (the assessment period), and the cost analysis took place from January 1, 2012, to December 31, 2012 (the cost-analysis period). Weekly perirectal screening was performed for all patients from selected intensive care units (ICUs) and the LTACH, where a persistently high incidence of CPE was detected. Weekly surveillance also included inpatient units caring for a patient known to be colonized or infected with CPE. All patients newly admitted to the LTACH and patients newly admitted to the hospital with known hospitalization outside of the United States were also screened.

Laboratory Isolation and Confirmation of CPE

Perirectal swab samples were collected by nursing staff using BD BBL Culture Swab Collection Transport System (Becton Dickinson) and submitted to the Clinical Microbiology Laboratory for CPE surveillance testing as outlined above. Each collection system contains 2 swabs. During the assessment period, one swab was used to directly inoculate a Ramba-CHROM KPC agar (CA; CHROMagar). The second swab was placed in 4.5 mL of trypticase soy broth (Remel) with a 10- μ g ertapenem disk (TSB/E; Becton Dickinson). Both the inoculated CA and the TSB/E were incubated for 18–24 hours. After incubation of TSB/E culture, 10- μ L loops were used to inoculate MacConkey agar (MAC; Remel) according to the CDC protocol and a CA. The plates were incubated 20–24 hours. MAC was examined for the presence of slow to rapid lactose-fermenting gram-negative bacilli, and the CA (direct and subcultured from TSB/E) were examined for colony growth and color formation at 20–24 hours and again at 44–48 hours for any slower-growing colonies. Blue colonies on CA are associated primarily with carbapenemase-producing *K. pneumoniae*, but other species of Enterobacteriaceae also produced this color. Mauve colonies on CA were associated with carbapenemase-producing *E. coli*. All organisms with suspected carbapenemase production were subcultured onto trypticase soy agar with 5% sheep blood (Remel) before identification, susceptibility testing, and KPC confirmatory testing. All solid media were incubated at 35°–37°C in ambient air.

The ICT was performed as previously described for phenotypic detection of CPE throughout both study periods because of observed poor specificity of the MHT for non-*K. pneumoniae* clinical specimens at UVaHS.¹⁰ Quality control for the ICT was performed weekly using *K. pneumoniae* ATCC

strains 1705 (MHT, ICT, and *bla*_{KPC} positive) and 1706 (MHT, ICT, and *bla*_{KPC} negative; American Type Culture Collection). All isolates that grew on CA with an Enterobacteriaceae appearance and/or had a positive ICT underwent *bla*_{KPC} polymerase chain reaction (PCR) analysis as previously described with KPC-producing *K. pneumoniae* CAV1016 as a positive control.⁹

Cost Analysis

For the 2012 cost analysis period, we used our current screening protocol with TSB/E paired with CA (TSB/E-CA) to detect CPE as outlined above. Cost of each step was in US dollars, based on wholesale charges. Laboratory technologist time was estimated at \$27.60 per hour (Table 1).¹¹ Technologist time was tracked during the assessment period and applied to the cost-analysis period. We estimated the number of isolates requiring additional work-up in the cost-analysis period on the basis of the results of the assessment period. We estimated cost and technologist time of a laboratory-developed molecular test that would detect the following carbapenemase genes: KPC, New Delhi metallo- β -lactamase (NDM), and oxacillinase-48 (OXA-48) using “research use only” reagents available from BD Diagnostics (Becton Dickinson). Technologist time was estimated from a similar molecular screening protocol used in our laboratory for methicillin-resistant *Staphylococcus aureus*. The estimated costs of our current protocol, the CDC protocol with the ICT, and a PCR assay were compared.

Statistics

During the assessment period, the presence of a PCR result positive for a carbapenemase gene was used as the true positive in the evaluation of sensitivity. Sensitivity results from the TSB/E-CA method from the assessment period were applied to the actual positive samples by phenotypic testing from the cost analysis period to predict the number of false-negative results by different methods.

RESULTS

Assessment of CA Accuracy in a Screening Protocol

For the assessment period, we evaluated the CA with perirectal swab samples from 588 independent samples. The method with the least number of unique isolates requiring additional work-up was direct inoculation of a perirectal swab sample to CA (direct CA), whereas enrichment of perirectal swab samples in TSB/E subcultured to MAC (TSB/E-MAC) resulted in the highest number of unique isolates. When the TSB/E was subcultured onto CA (TSB/E-CA), the number of positive specimens and unique isolates, compared with direct CA, increased by approximately 70% (Figure 1). Potential Enterobacteriaceae from each method then underwent phenotypic testing using the ICT.

There were 15 isolates from 14 specimens positive by ICT

TABLE 1. Cost of Each Individual Component of Our Current Chromogenic Agar (CA) Indirect Carbapenemase Test (ICT) Protocol, the Centers for Disease Control and Prevention MacConkey Agar (MAC) ICT Protocol, and Molecular Protocols

Protocol component	US\$	CA-ICT positive (n = 185)	CA-ICT additional work-up (n = 58)	CA-ICT negative (n = 6,617)	MAC-ICT positive (n = 119)	MAC-ICT additional work-up (n = 1,459)	MAC-ICT negative (n = 5,282)	Molecular (n = 6,860)
Tryptic soy broth	0.68	+	+	+	+	+	+	...
Ertapenem 10- μ g disk	0.13	+	+	+	+	+	+	...
RambaChrom agar	3.00	+	+	+
Blood agar plate	0.26	+	+
Mueller Hinton	0.50	+	+	...	+	+
Tris-EDTA disk	0.45	+	+	...	+	+
Imipenem 10- μ g disk	0.05	+	+	...	+	+
VTK GN ID card	3.50	+	+
MA	0.28	+	+	+	...
Supply total		8.57	4.81	3.81	5.85	2.09	1.09	31.36 ^a
Technologist time ^b	0.46	5.52	3.68	1.38	5.52	3.68	1.38	1.38
Time to perform, min		12	8	3	12	8	3	3
Total cost		14.09	8.49	5.19	11.37	5.7	2.47	32.74
Total cost 2012		2,606.65	492.42	34,342.23	1,353.03	8,418.43	13,046.54	224,596.4
Total min		2,220	464	19,851	1,428	11,672	15,846	20,580

NOTE. The CA-ICT refers to use of incubation of swab in tryptic soy broth with ertapenem disk (TSB/E) followed by CA and subsequent ICT currently used by our institution. The MAC-ICT is a modified Centers for Disease Control and Prevention method of TSB/E incubation followed by MAC and subsequent ICT. Plus sign indicates that the item is involved in the procedure. EDTA, ethylenediaminetetraacetic acid; VTK GN ID card, VITEK2 Gram-Negative Identification card.

^a Estimate.

^b Per minute.

and KPC PCR: 7 *Enterobacter cloacae*, 3 *K. pneumoniae*, 2 *Citrobacter freundii*, 2 *K. oxytoca*, and 1 *Pantoea* species. The rate of *bla*_{KPC} positivity of unique isolates varied, with the direct CA and TSB/E-CA resulting in similar rates (13 [72%] of 18 and 8 [73%] of 11, respectively), whereas TSB/E-MAC was substantially less (7 [5%] of 138; Figure 1). None of the 8 isolates (3 from direct CA and 5 from TSB/E-CA) that grew on CA and were negative by the ICT phenotypic test were positive for *bla*_{KPC} by PCR.

Direct CA and TSB/E-MAC detected KPC-producing organisms in 7 of 14 specimens (sensitivity, 50.0%) and the TSB/E-CA detected isolates in 12 of 14 specimens (sensitivity, 85.7%; Figure 1). Of the isolates that grew on MAC alone, only the 7 with a positive phenotypic test result underwent PCR. Of note, at least 1 isolate recovered by each method was missed by the other 2 methods. One isolate determined to be a *bla*_{KPC}-positive *K. pneumoniae* was identified by inoculation of TSB/E broth onto MAC only and not by either method employing CA. This result was likely attributable to overgrowth of *Pseudomonas aeruginosa* resulting in cream color colonies that may have obscured the appearance of blue colonies. Another isolate was identified by direct CA without TSB/E enrichment. Although the reason for this is not clear, it is conceivable that the second swab lacked organisms due to insufficient sampling. The results are summarized in Figure 1.

Cost Analysis

We did not estimate the cost of direct CA, although it was evaluated during the assessment period, because we considered the sensitivity too low to make this a usable test. We assessed the cost of the TSB/E-MAC, because this method is comparable to the current method recommended by the CDC, although initial analysis demonstrated similar issues with low sensitivity as with direct CA. There were 3 possible cost stages of results for the methods that use TSB/E selection followed by plating onto selective agar (either MAC or CA): (1) no growth on agar from broth, (2) growth of Enterobacteriaceae requiring phenotypic testing, and (3) positive phenotypic test requiring subsequent organism identification by Vitek2. Of the 6,860 perirectal screens in 2012 performed using the TSB/E-CA, 185 specimens (2.7%) representing 79 unique patients were positive for CPE by phenotype. The majority of positive results were for *K. pneumoniae* (97; 52%), *E. cloacae* (39; 21%), and *C. freundii* (24; 13%). Applying the results from the assessment period (Figure 1) to the results of the cost analysis period, we were able to calculate the theoretical number of each outcome for the TSB/E-MAC method and by molecular testing (Figure 2).

Laboratory technologist time averaged 3 minutes for set up and labeling of all perirectal specimens. The TSB/E-MAC was longer than the TSB/E-CA because of the additional work required for assessing multiple isolates on MAC and sub-

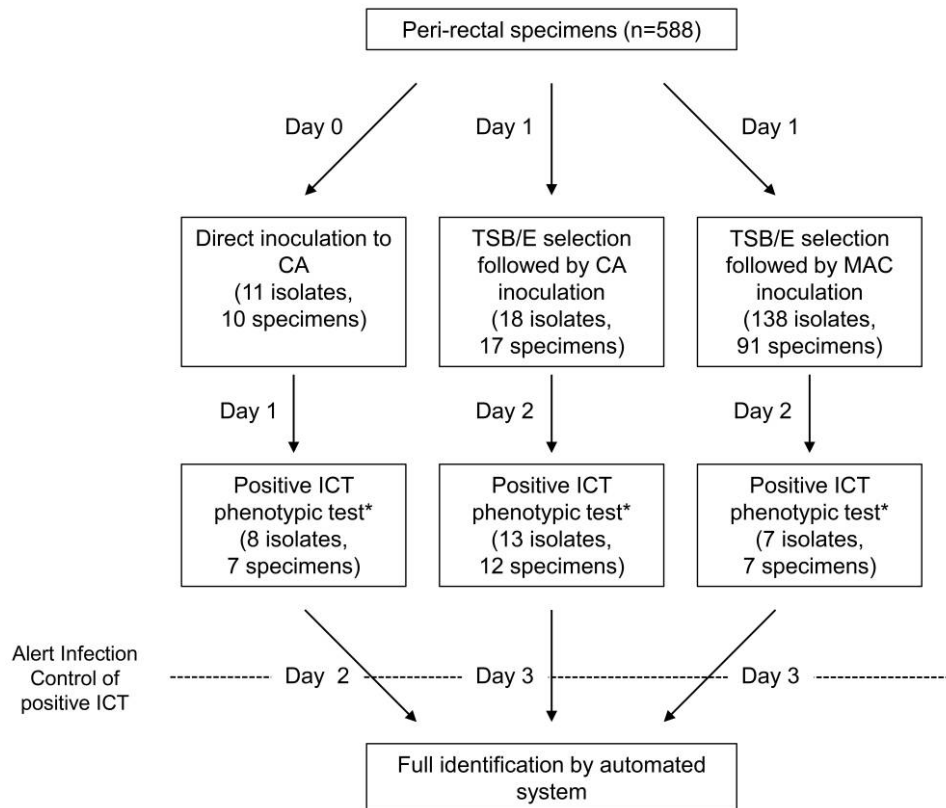


FIGURE 1. Assessment period comparing accuracy and timing of different methods of screening. Asterisk indicates confirmed as positive for *bla_{KPC}* by polymerase chain reaction. CA, chromogenic agar; ICT, indirect carbapenemase test; MAC, MacConkey agar; TSB/E, tryptic soy broth with ertapenem disk.

culturing for purity before phenotypic testing. Data from the assessment period demonstrated that there was an additional 11.5 hours of technologist time on the initial 588 when using the TSB/E-MAC technique compared with an additional 1.5 hours of technologist time with the TSB/E-CA. A total of 1,578 isolates would have needed additional testing with the TSB/E-MAC method, resulting in an estimated 134 additional hours of technologist time versus 243 additional isolates with 17.5 hours of technologist time for the TSB/E-CA method. Due largely to the cost of the CA, supply costs per isolate of TSB/E-CA protocol were higher than those for TSB/E-MAC (Table 1). For molecular analysis, estimated costs were \$32.74 per test with no difference between positive and negative results. On the basis of our 2012 surveillance data, the annual cost of each method, including technologist time, would be \$37,441 for the TSB/E-CA protocol, \$22,818 for TSB/E-MAC protocol, and \$224,596 for molecular testing.

Time from specimen receipt to detection also differs among these approaches. Both the TSB/E-CA and the TSB/E-MAC require 3 days until reporting that a patient has a CPE and 4 days until the culture is complete with identification of the organism. Molecular testing may give a result on the same

day, although it likely would not give a bacterial species identification.

The last issue to consider in the cost analysis is the predicted number of false-negative results from the method used. On the basis of the lack of sensitivity from the assessment period and similar prevalence, we predict that there would have been 211 true positive samples. We estimate 92 CPE isolates would have been missed by the CDC method compared with 26 by our current method. There are insufficient data to speculate about the accuracy and the sensitivity of direct molecular testing, but both would presumably be quite high.

DISCUSSION

Surveillance and isolation have demonstrated effectiveness in reducing nosocomial acquisition of CPE elsewhere.⁵⁻⁸ It is critical to control the dissemination of CPE, and the CDC has stated that it is not too late to contain the spread of these organisms in many places before they become endemic.¹²⁻¹⁴ Cost is a major challenge to achieving prevention in the real-world functioning of a hospital system. Although we appreciate the critical nature of controlling CPE spread, we have

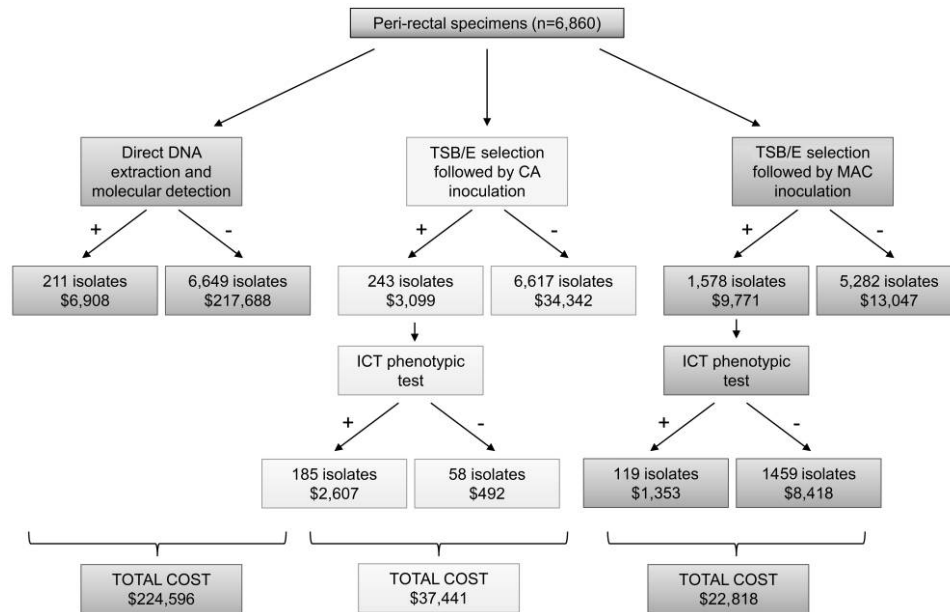


FIGURE 2. Cost-analysis period comparing component and total cost for each method. Estimates were made on the basis of molecular test performance with a presumptive 100% sensitivity, tryptic soy broth with ertapenem disk (TSB/E) selection with chromogenic agar (CA) performing with 85.7% sensitivity, and the TSB/E selection with MacConkey agar (MAC) performing with a 50.0% sensitivity (the latter 2 based on results from the assessment period). ICT, indirect carbapenemase test.

adhered to the CDC guidelines for patient selection and have attempted to strike a balance between sensitivity and expense for detection in clinical microbiology.⁴ Although direct molecular detection has several advantages over more traditional methods (rapid turnaround, identifying carbapenemases with variable phenotypes, and potential for increased sensitivity and specificity), it may be cost prohibitive. In addition, the expertise to adopt new molecular tests may not also be available in smaller hospital system laboratories.

More expensive molecular testing may be most appropriate when there are few specimens. One cost factor influencing implementation of a molecular screening assay is the relative prevalence of CPE. As shown here, more traditional methods are relatively inexpensive for screening negative specimens resulting in cost efficiency compared with a molecular assay. Lack of species identification is another potential drawback to molecular CPE testing, because this information can be helpful for epidemiologic work-up. Although we did not have data to assess the accuracy of a molecular test in this study, we postulate maximum sensitivity at 100% for the cost analysis, although this would likely be an overestimation of the true test performance.

We demonstrate increased technologist time associated with the CDC method compared with the use of TSB/E-CA method (134 vs 17.5 hours). Additional technologist's time resulted from the increased number of non-CPE organisms, by phenotypic testing, which grew on MacConkey agar. The TSB/E-MAC method also provides much lower sensitivity compared with CA (sensitivity of 50.0%, compared with

85.7% with the TSB/E-CA protocol) for detection of CPE. Because technologist hours are a very limited resource at most institutions, we felt that these may be important factors to consider in discussions between clinical microbiology and infection prevention and control departments at other institutions.

One potential limitation to the broad application of accuracy determination was the use of the ICT as our phenotypic test rather than the MHT. Because carbapenemase genes are most often carried on readily disseminated plasmids, we have focused our screening resources to detection of CPE and distinguishing between CPE and other potentially less transmissible mechanisms of carbapenem resistance.¹⁵ Within our health-system, we had already determined that the ICT had superior specificity to the MHT for detection of KPC-producing Enterobacteriaceae for clinical isolates that were nonsusceptible to ertapenem; the MHT had a false-positive result rate of 20.4% when compared with molecular detection of the *bla*_{KPC} gene. This finding was especially pronounced in non-*K. pneumoniae* KPC-producing isolates.¹⁰ If the predicted 1,578 isolates that grew on MAC from the CDC screening protocol were paired with the MHT, as is recommended, 323 additional isolates would have been considered positive and required patient isolation at our institution. If the MHT were paired with TSB/E-CA, then we predict 50 additional isolates considered positive by the MHT but negative for KPC by molecular methods. It should be noted that the ICT would not detect a metallo- β -lactamase. Because of the variable or unknown performance at institutions where

there is a different species profile and/or potential presence of other carbapenemase genes, the sensitivity and specificity results are not generalizable to all outbreaks. For this reason, we would advocate that individual institutions take into account all of these important differences when planning a surveillance program. However, on the basis of our experience, we do feel the accuracy can be applied to detection of multispecies KPC-producing Enterobacteriaceae. These differing screening methods have similar costs, and we therefore believe these data with a cost focus remain valid.

As CPE continues to increase in many parts of the world, the need for assessment of colonization and subsequent isolation in a nosocomial setting for at-risk patients will likely grow.¹⁶ There is no perfect test for colonization with a CPE. However, several factors should be considered when selecting the best screening methods for an individual institution; test performance, result time, prevalence, organism type, mechanism of resistance, laboratory capabilities, and cost. In a world of finite resources, understanding the difference in cost is critical to the decision process and must be considered by hospital leadership, infection preventionists, and clinical microbiologists when developing a collaborative plan to control the dissemination of these devastating pathogens.

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