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Major Article

Surveillance-guided selective digestive decontamination of carbapenem-resistant *Enterobacteriaceae* in the intensive care unit: A cost-effectiveness analysis

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drug resistance
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Background: Clinical findings have shown effectiveness and safety of selective digestive decontamination (SDD) for eradication of carbapenem-resistant *Enterobacteriaceae* (CRE) in high-risk carriers. We aimed to evaluate the cost-effectiveness of SDD guided by CRE surveillance in the intensive care unit (ICU).

Methods: Outcomes of surveillance-guided SDD (test-guided SDD) and no screening (control) in the ICU were compared by Markov model simulations. Model outcomes were CRE infection and mortality rates, direct costs, and quality-adjusted life year (QALY) loss. Model inputs were estimated from clinical literature. Sensitivity analyses were conducted to examine the robustness of base case results.

Results: Test-guided SDD reduced infection (4.8% vs 5.0%) and mortality (1.8% vs 2.1%) rates at a higher cost (\$1,102 vs \$1,074) than the control group in base case analysis, respectively. Incremental cost per QALY saved (incremental cost-effectiveness ratio [ICER]) by the test-guided SDD group was \$557 per QALY. Probabilistic sensitivity analysis showed that test-guided SDD was effective in saving QALYs in 100% of 10,000 Monte Carlo simulations, and cost-saving 59.1% of time. The remaining 40.9% of simulations found SDD to be effective at an additional cost, with ICERs accepted as cost-effective per the willingness-to-pay threshold.

Conclusions: Surveillance-guided SDD appears to be cost-effective in reducing CRE infection and mortality with QALYs saved.

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Carbapenem-resistant *Enterobacteriaceae* (CRE) is emerging globally.¹ In Hong Kong, CRE prevalence increased exponentially from 0.05% in 2009 to 0.6% in 2011 in health care institutes.² Antibiotic regimens for treatment of CRE infection are limited, and reported mortality is substantial (50%).³⁻⁶ Patients in the intensive care unit (ICU) setting are at high risk to acquire infection caused by multidrug-resistant organisms and often receive empirical carbapenem therapy. CRE transmission further complicates the treatment of multidrug-resistant bacterial infections in the ICU setting.^{7,8}

Active CRE surveillance is one of the strategies recommended by the Centers for Disease Control and Prevention.⁹ An outcome analysis showed active surveillance of CRE to be cost-effective in preventing CRE infection and mortality in the ICU setting by reduction of noncarriers-to-carriers conversion and early initiation of adequate empirical treatment.¹⁰ Selective digestive decontamination (SDD) is an infection preventive measure, and it has been reported to reduce the mortality rate in the ICU.¹¹ Clinical trials have reported promising results on using nonabsorbable oral antibiotics (gentamicin and colistin) as SDD for CRE eradication. The findings suggest oral administration of gentamicin and colistin to be effective and safe for eradication of CRE in carriers, risk reduction of CRE infection, and risk reduction of patient-to-patient CRE transmission.^{12,13} The potential impact of SDD on the outcomes of CRE infection control has yet to be investigated. Our study aimed to examine the cost-effectiveness of SDD guided by active CRE surveillance in patients admitted to the ICU in Hong Kong.

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Conflicts of interest: None to report.

METHODS

Model design

A Markov model was designed to compare active CRE surveillance plus nonabsorbable oral antibiotics (test-guided SDD group) versus no CRE screening (control group) in adult patients admitted to the ICU (Fig 1). Markov modeling is a form of decision analysis in which hypothetical patients proceed through different Markov health states in every model interval over time, based on probability inputs of the model. The Markov states of this model included CRE carrier, noncarrier of CRE, CRE infection, survived CRE infection, and death. This model used daily cycle as the model interval, and the model time frame was the average length of stay in a medical ICU of Hong Kong (4 days; range, 2-10 days).¹⁴ Outcome measures simulated by the model were CRE infection rate, mortality rate, direct costs, and quality-adjusted life year (QALY) loss.

In the present model, universal precautions were applied to patients in both groups. In the test-guided SDD group, CRE surveillance was conducted by real-time polymerase chain reaction (PCR) testing of rectal swab or stool specimen obtained for all patients on ICU admission and every 3 days thereafter. Patients who tested CRE-positive were triaged to receive care under cohort isolation and to start nonabsorbable oral antibiotics. The oral antibiotic regimen was adopted from 2 prospective clinical trials on SDD for CRE eradication in carriers^{12,13}: gentamicin (80 mg) and colistin (100 mg) 4 times daily, orally or through a nasogastric tube. The antibiotic regimen would be further streamlined to a single-agent regimen (gentamicin or colistin) according to susceptibility findings. It would be discontinued if the isolate was resistant to both gentamicin and colistin.

Non-CRE carriers in both groups might be converted to carriers, and spontaneous eradication might occur in CRE carriers without antibiotics. Both carriers and noncarriers might acquire CRE infection. Infected patients with unknown CRE status or negative CRE test were treated with standard empirical broad-spectrum regimens for ICU-acquired infections (β -lactams with β -lactamase inhibitors, cephalosporins, or carbapenems).¹⁵ Infected patients with known CRE-positive status were started on empirical therapy for CRE infection (triple therapy using colistin, tigecycline, and

meropenem).¹⁶ Patients might die or survive the episode of CRE infection.

Clinical inputs

The clinical inputs were retrieved by literature search on MEDLINE via OvidSP over 2007-2017. The search key words included "carbapenem," "drug resistance," "*Enterobacteriaceae*," "selective digestive decontamination," "non-absorbable antibiotic," "surveillance," "intensive care unit," "prevalence," "transmission," and "mortality." Clinical studies on treatment or prevention of CRE infection written in English with the following findings were selected: (1) CRE prevalence in ICUs, (2) CRE eradication rate with oral gentamicin or colistin, (3) CRE infection rate in carriers or noncarriers, or (4) mortality rate of CRE infections. Case reports were excluded. A publication would be included if it had data relevant to the model inputs. The preferred types of studies were meta-analyses and randomized controlled trials. When a variable was reported by multiple studies, the base case value of this variable would be estimated using the pooled average weighted against the number of patients in each study. When both randomized and observational trials provide data for a model input, the base case value would be derived from randomized trials. Data from both randomized and observational trials would provide the range for sensitivity analysis of this variable.

All model inputs are listed in Table 1. The CRE prevalence in Hong Kong was found to be 0.6%, and a broad range of CRE prevalence (0.3%-12.8%) reported globally was used for sensitivity analysis.^{2,7,8,17-19} Sensitivity and specificity of PCR testing for CRE were reported to be 100%.²⁷ The daily spontaneous decolonization rate in CRE carriers (0.23%; range, 0.05%-1.15%) and the relative increment in the decolonization rate with oral antibiotics (14.6-fold; range, 5.0-16.6) was estimated from 2 randomized controlled trials examining the eradication rate of CRE colonization with daily nonabsorbable oral antibiotics (gentamicin and colistin) in 192 patients.^{12,13} No adverse events were observed in these 2 clinical studies, and the present model therefore did not include adverse outcomes of oral gentamicin and colistin.

The daily conversion rate from noncarriers to CRE carriers under surveillance (1.91%; range, 1.22%-4.37%), daily CRE infection rate in noncarriers (0.87%; range, 0.56%-1.98%), and odds ratio of CRE

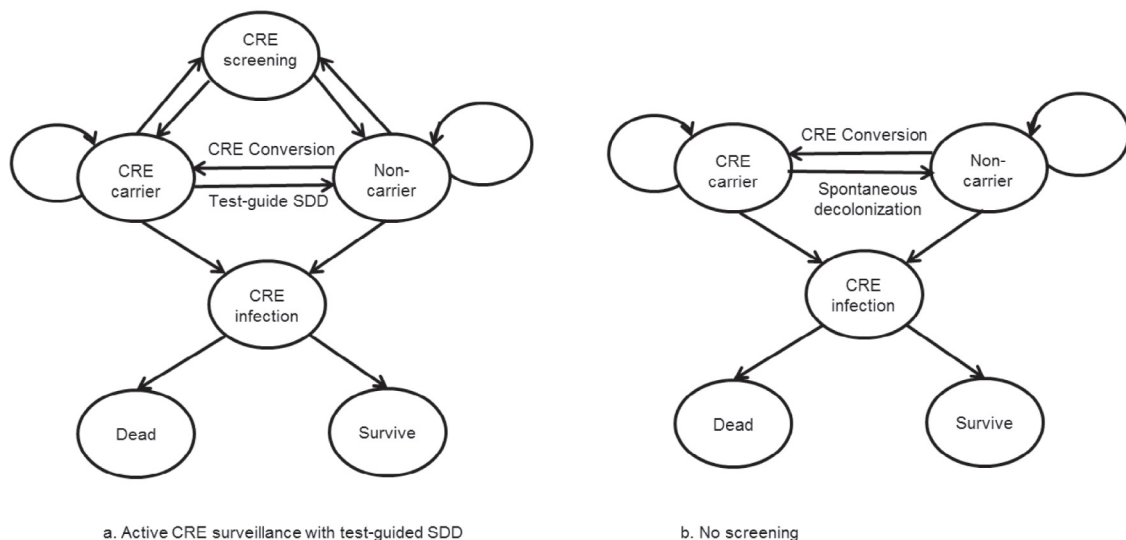


Fig 1. Simplified Markov model on outcomes of CRE carriers and noncarriers in the medical intensive care unit: (A) active surveillance with test-guided SDD and (B) no screening. CRE, carbapenem-resistant *Enterobacteriaceae*; SDD, selective digestive decontamination.

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