The natural history of colonization with carbapenem-resistant *Enterobacteriaceae*: outcomes related to colonization

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Background

Carbapenem-resistant *Enterobacteriaceae* (CRE) present an increasing challenge for healthcare facilities. In order to limit their spread, public health authorities have recommended improving detection methods and expanding surveillance for CRE. Increased identification of CRE-colonized patients will inevitably result in hospitals having cohorts of chronically colonized patients requiring isolation and other measures to prevent transmission as long as they remain colonized. A few reports describe the natural history of CRE colonization and suggest that colonization persists for months and can be prolonged in association with the continued use of antibiotics and repeated hospitalization.

We monitored the CRE colonization status and clinical outcomes of a cadre of CRE-colonized patients at the NIH Clinical Center, including their co-colonization with other multidrug-resistant organisms, over a two-year period.

Methods

Screening began in June 2011 and continued through August 2013. Patients found to be colonized with CRE were re-screened on return inpatient or outpatient visits. Surveillance cultures consisted of throat, groin, and perirectal swabs and were collected using the BD BBL™ CultureSwab™ collection and transport system. Stool cultures were collected after patients had at least one negative set of surveillance cultures. All cultures were inoculated onto KPC CHROMagar (Hardy Diagnostics) at 35ºC for 18-24 hours. Colonies growing on the KPC CHROMagar were identified using matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry. After identification, organisms were tested with *bla*KPC PCR and modified Hodge test. Two isolates underwent testing with *bla*NDM-1 PCR.

Susceptibility testing was performed using both automated (Phoenix) and manual (E-test) methods. Surveillance swabs for VRE, MDR-*Acinetobacter baumannii*, and MRSA were collected when clinically indicated (not universally) from perirectal, throat/groin, and nasal swabs, respectively. For VRE and MRSA a positive rapid PCR (Cepheid) was followed by culture.

For the purposes of infection control and prior to this analysis, we considered patients decolonized after three sets of negative surveillance cultures obtained on separate visits followed by a negative stool culture, and negative follow-up cultures of any previously positive clinical sites.

Results

Among 26 patients identified with CRE colonization, 19 carried a single nosocomial strain of *Klebsiella pneumoniae*, six patients carried distinct strains of *K. pneumoniae* and *K. oxytoca*, two patients had *Enterobacter cloacae* and two patients carried *E. aerogenes* and *Escherichia coli,* respectively (**Table 1)**. Three patients were colonized with two CRE organisms isolated concurrently, and 15 patients (58%) were also colonized with another multidrug-resistant organism **(Figure 1)**.

Table 1: Underlying conditions, CRE species, and carbapenemase PCR testing of CRE-colonized patients.

Patient	Underlying Condition	Organism	KPC PCR	NDM-1 PCR
1	Organ transplant	*K. pneumoniae*	+	
2	Malignancy	*K. pneumoniae*	+	
3	Stem cell transplant	*K. pneumoniae*	+	
4	Malignancy	*K. pneumoniae*	+	
5	Malignancy	*K. pneumoniae* *E. cloacae*	+ +	
6	Malignancy	*K. pneumoniae*	+	
7	Hematologic disorder	*K. pneumoniae*	+	
8	Stem cell transplant	*K. pneumoniae*	+	
9	Lung disease	*K. pneumoniae*	+	
10	Malignancy	*K. pneumoniae*	+	
11	Stem cell transplant	*K. pneumoniae* *E. aerogenes*	+ +	
12	Malignancy	*K. pneumoniae*	+	
13	Malignancy	*K. pneumoniae*	+	
14	Stem cell transplant	*K. pneumoniae*	+	
15	Lung disease	*K. pneumoniae*	+	
16	Primary Immunodeficiency	*K. pneumoniae*	+	
17	Stem cell transplant	*K. pneumoniae* *E. cloacae*	+ +	
18	Hematologic disorder	*K. pneumoniae*	+	
19	Stem cell transplant	*K. pneumoniae*	+	
20	Stem cell transplant	*K. pneumoniae*	+	
21	Acquired immunodeficiency	*K. pneumoniae*	+	
22	Malignancy	*K. oxytoca*	+	
23	Malignancy	*K. pneumoniae*	+	
24	Malignancy	*K. pneumoniae*	+	
25	Hematologic disorder	*K. pneumoniae*	-	-
26	Primary Immunodeficiency	*E. coli*	-	-

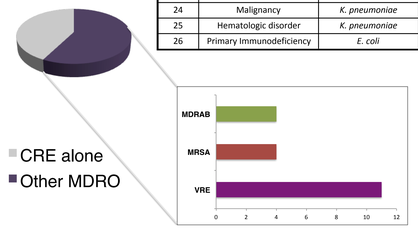

Figure 1: Concurrent co-colonization. 11 patients were colonized with vancomycin-resistant *Enterococcus* (VRE), four with methicillin-resistant *Staphylococcus aureus (*MRSA), and four with multidrug-resistant *Acinetobacter baumannii* (MDRAB).

Ten highly immunocompromised patients developed bacteremia with KPC-carrying *Klebsiella* a median of 11 days (range 2-37) after colonization was first detected. Seven patients (70%) died of CRE bacteremia; two patients survived CRE bacteremia but died of underlying illnesses. One out of these 10 patients survived CRE bacteremia and remains hospitalized.

Results

Among 16 patients with CRE in a clinical site culture (not all clinical cultures represented an infection) including the bacteremic patients, 11 (68.8%) are now deceased, two have had negative surveillance cultures, two have not returned for follow-up and one remains hospitalized. Among 10 colonized patients who did not have a positive clinical culture, four (40%) died of underlying conditions including one who had a negative surveillance culture prior to death. Four of the 10 colonized patients have had negative surveillance cultures, one remains hospitalized and one has not returned for follow-up.

Of 11 surviving patients, 9 patients have undergone serial surveillance cultures. Six patients have had negative perirectal surveillance cultures after a median of six sets of surveillance cultures over a median of 296 days (range 127-649). The other three were more recently recognized and have had one or fewer surveillance cultures. For patients whose surveillance cultures became negative, no active decolonization strategies were employed. One patient had three negative perirectal cultures and one negative stool culture obtained over 44 days, followed 103 days later by a perirectal swab that grew her original CRE isolate. In these 103 days she was hospitalized and received broad spectrum antibiotics.

Three out of the 26 patients met our original decolonization definition but remain on contact isolation for other multidrug-resistant organisms.

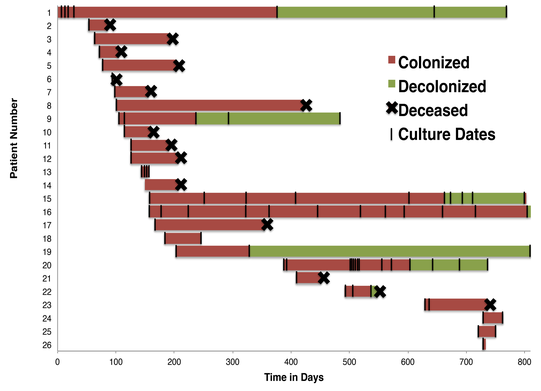

Figure 2: CRE colonization status over time. Patients are shown as colonized when the first culture (surveillance or clinical) grew CRE. "Decolonization" is depicted following the first negative set of surveillance cultures.

Conclusions

- CRE colonization portends a poor prognosis among immunocompromised patients. Infection in these patients can be devastating. In our cohort, CRE bacteremia had a 70% mortality rate.
- Patients can have prolonged CRE colonization; over time surveillance cultures may become negative.
- Persistent, low-level colonization may be missed by surveillance cultures. Further studies are needed to determine the significance, optimal timing, and ideal number of surveillance cultures to ascertain clearance of CRE colonization.
- Antibiotic challenge after apparent decolonization may unmask "silent" CRE colonization in subsequent surveillance cultures.
- Colonization with other multidrug-resistant organisms is common and may prevent discontinuation of isolation for some patients. Immunosuppression, antibiotic exposure, and host characteristics may drive an increased susceptibility to colonization in these patients.
- Until more data are available, we believe a conservative approach to discontinuing isolation for CRE is warranted.

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