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Major article

# Eradication of carbapenem-resistant *Enterobacteriaceae* gastrointestinal colonization with nonabsorbable oral antibiotic treatment: A prospective controlled trial

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***Background:*** Carbapenem-resistant *Enterobacteriaceae* (CRE) are emerging. In attempt to eradicate CRE colonization, we conducted a semirandomized, prospective, controlled trial using oral nonabsorbable antibiotics.

***Methods:*** Consecutive hospitalized CRE carriers were studied. Patients whose rectal isolates were gentamicin sensitive but colistin resistant were treated with gentamicin. Patients whose isolates were colistin sensitive but gentamicin resistant were treated with colistin. Patients whose isolates were sensitive to both drugs were randomized to 3 groups of oral antibiotic treatment: gentamicin, colistin, or both. Patients whose isolates were resistant to both drugs, and those who did not consent, were followed for spontaneous eradication.

***Results:*** One hundred fifty-two patients were included; 102 were followed for spontaneous eradication for a median duration of 140 days (controls), and 50 received 1 of the 3 drug regimens: gentamicin, 26; colistin, 16; both drugs, 8, followed for a median duration of 33 days. Eradication rates in the 3 treatment groups were 42%, 50%, and 37.5%, respectively, each significantly higher than the 7% spontaneous eradication rate in the control group ($P < .001$, $P < .001$, and $P = .004$, respectively) with no difference between the regimens. No significant adverse effects were observed.

***Conclusion:*** Oral antibiotic treatment with nonabsorbable drugs to which CRE is susceptible appears to be an effective and safe for eradication of CRE colonization and, thereby, may reduce patient-to-patient transmission and incidence of clinical infection with this difficult-to-treat organism.



Carbapenem-resistant *Enterobacteriaceae* (CRE) has recently emerged around the world.[1,2] Since 2006, almost all major hospitals in Israel observed a continuous increase in the number of clinical isolates of CRE,[3-5] and this occurrence rapidly became a major ongoing national outbreak. Treatment of infections caused by these highly resistant organisms is obviously problematic, and there are very few therapeutic options available, usually with extremely low success rates.[6-8] To prevent the spread of CRE among inpatients, several infection control measures were instituted early in 2006 in our hospital. These measures, based on Ministry of Health and Centers for Disease Control and Prevention recommendations,[9] included strict contact isolation and cohorting of CRE carriers identified by clinical cultures and surveillance rectal swabs from patients at risk.

Despite the strict infection control measures, in late 2008 we noticed a sharp increase in CRE isolates (from surveillance and from clinical cultures) among hematology-oncology and bone marrow transplant (BMT) inpatients, including cases of persistent bacteremia despite appropriate intravenous antibiotic treatment. We

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Conflicts of interest: None to report.

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hypothesized that continuous bacteremia could have been secondary to repeated bloodstream invasion by the CRE from a reservoir in the gastrointestinal (GI) tract through the damaged mucosa during severe mucositis. Several studies have shown that selective digestive decontamination (SDD) treatment may eradicate carriage of multidrug-resistant bacteria, reduce the incidence of nosocomial infections, and control nosocomial outbreaks caused by these organisms.[10-14] In an attempt to eradicate the GI source of CRE in these patients, to prevent development of associated bacteremia, and to control infection spread to other inpatients, a pilot study of oral treatment with gentamicin, to which CRE was susceptible, was conducted. This study demonstrated a 66% eradication rate of carrier state of CRE among hematology-oncology and BMT recipient patients and resolution of the persistent bacteremia in 62.5% of the patients after eradication of the carrier state.[15]

These results prompted us to conduct a randomized, prospective, controlled trial throughout the hospital, aimed at eradicating GI CRE colonization, using oral nonabsorbable antibiotic treatment with gentamicin (GM), colistin (COL), or both.

## PATIENTS AND METHODS

The study was conducted at the Rambam Health Care Campus, a 1,000-bed, tertiary care center in northern Israel. The hospital admits approximately 80,000 patients a year and includes all major departments and services, with 85 intensive care unit (ICU) beds and 25 hematology-BMT beds. All consecutive hospitalized adult patients identified as CRE carriers by rectal surveillance cultures were included in the study, which was approved by the Institutional Review Board (Approval No. 0004-09) and registered in the ClinicalTrials.gov (ID No. NCT00966810).

Rectal surveillance cultures were obtained in the following situations: on admission to the hospital, from high-risk patients (defined as patients who were hospitalized during the previous 6 months in acute care or long-term health care facilities, about 20 patients per day); on admission and routinely once weekly in selected wards such as ICU, hematology-oncology, and BMT; and from contacts of identified carriers.

Data obtained for the study patients included demographics, underlying diagnosis, duration and eradication of CRE colonization, GM blood levels, adverse events, clinical CRE infection, survival status at study completion, and CRE-related mortality.

### *Microbiologic studies*

Rectal swab screening samples were cultured on PD420 CHROMagar *Klebsiella pneumoniae* carbapenemase (KPC) plates (Hy Laboratories Ltd, Rehovot, Israel). DNA was extracted from suspected KPC-possessing blue colonies using the Qiamp DNA mini kit (QIAgen, Hilden, Germany) in accordance with the manufacturer's instructions. KPC was detected using polymerase chain reaction (PCR)-based assays specific for bla*KPC* gene, as described.[16] Other CRE were detected using the Hodge test according to the Clinical Laboratory Standards Institute (CLSI) methods[17] whenever PCR was negative. Susceptibility to GM was determined by the disk diffusion test. The minimal inhibitory concentration (MIC) for COL was determined by the E-test (AB Biodisk, Salone, Sweden). Isolates were considered COL-susceptible if the MIC was less than or equal to 2 mg/L in accordance with the European Committee on Antimicrobial Susceptibility Testing breakpoints.[18]

### *Preparation of study drugs*

GM 80-mg capsules were prepared using GM sulphate powder (Lot No. 08A24-NO7) mixed with lactose diluents filled into gel capsules size No. 3. COL 100 mg (2,000,000 units) capsules were prepared using COL sulphate powder (Lot No. 20090101) mixed with lactose diluents filled into gel capsules size No. 1.[19] COL sulphate was used to achieve acid and soluble preparation. The capsules were filled using an extemporaneous filling method by a manual filling machine (Feton automatic capsule filling machine).

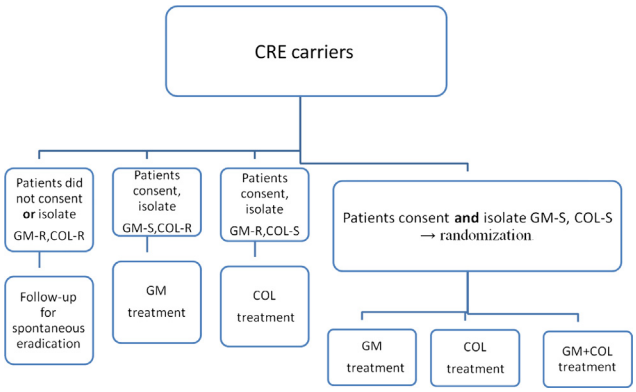


**Fig 1.** Study design. GM, gentamicin; COL, colistin; S, susceptible; R, resistant.

### *Study design*

Patients who did not consent or whose isolates were resistant to both drugs were followed with repeated rectal swabs to assess spontaneous eradication rate (control group). Patients whose rectal isolates were GM susceptible but COL resistant were treated with oral capsules of GM sulphate 80 mg 4 times daily. Patients whose isolates were COL susceptible but GM resistant were treated with oral capsules of COL sulphate 100 mg 4 times daily. Patients whose isolates were sensitive to both drugs were randomized by balanced randomization of total set of subjects to 3 groups of oral antibiotic treatment: GM, COL, or both (Fig 1).

Oral drug treatment was given until eradication, or for a maximum of 60 days, whichever came first. Patients were followed by repeated rectal swabs to determine eradication (minimum interval between 2 samples was 3 days). Blood and other relevant clinical cultures were obtained as clinically indicated. Patients with CRE-associated clinical infection were additionally treated with intravenous GM or COL or tigecyclin (based on in vitro susceptibility) or a combination of those drugs.

### *Definitions*

"Colonization (carrier state)" was defined as the presence of at least 1 positive rectal swab for CRE. "Eradication" was defined when 3 consecutive rectal swabs were negative for CRE, including PCR testing of the third negative sample. "Failure of eradication for the treatment group" was defined when (1) CRE carriage persisted after 60 days of oral antibiotic treatment, (2) CRE relapsed after presumed eradication, (3) isolate turned resistant to the administered drug, and (4) premature discontinuation of drug treatment (death, loss to follow-up, unwilling to continue participation in the study). "Failure of eradication for the control group" was defined when CRE colonization persisted through the end of the study. Patients were excluded from the control arm if the interval between first and last rectal swabs was $< 20$ days (when duration of follow-up was shorter than 20 days. Overall, 34 patients died or were lost for follow-up).