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# Inappropriate Dose of Enteral Antimicrobials Promotes Resistance

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We read with interest the South African study based on a collection of separate case reports (1). The authors hypothesized that selective digestive decontamination (SDD) using enteral colistin (i.e., polymyxin E) and tobramycin probably contributed to the selection and carriage of a colistin-resistant OXA-181-producing *Klebsiella pneumoniae* strain. We argue that the use of an inappropriate protocol of enteral decontamination is more likely responsible for both the failure to eliminate intestinal carriage of *K. pneumoniae* and the selection of colistin-resistant *K. pneumoniae*.

Interestingly, the authors used their own decontaminating regimen that included a 2% colistin-tobramycin paste applied three times a day into the oropharynx, combined with a solution of 1 million IU colistin and 80 mg tobramycin administered three times a day into the gut via a nasogastric tube. Three main points should be addressed on this decontaminating protocol.

First, the dosage of the oropharyngeal paste is not specified. Generally, half a gram of 2% polymyxin E-tobramycin paste or gel four times a day has been shown to clear aerobic Gram-negative bacilli (AGNB) from the oropharynx (2).

Second, and most importantly, the enteral dose of 1 million IU colistin three times a day might be too low to achieve successful decontamination, i.e., eradication of the OXA-181-producing *K. pneumoniae* from the gut. Remarkably, the original SDD protocol uses 100 mg colistin sulfate four times a day (2). One milligram of colistin sulfate is equivalent to about 0.670 mg of pure colistin base (Fagron; colistin sulfate certificate of analysis, 2011), which has been assigned a potency of 30,000 IU per mg (3). Therefore, the original SDD protocol consists of about 2 million IU colistin four times a day. This daily dose is approximately three times higher than that used by the South African researchers. Early studies on SDD have shown that high doses of enteral colistin are required to suppress AGNB because colistin is moderately inactivated by fecal and food compounds (4, 5).

Third, although the investigators do not report it explicitly, the OXA-181-producing *K. pneumoniae* strain was almost certainly resistant to tobramycin, the second component of SDD. For successful decontamination, AGNB should ideally be sensitive to both decontaminating agents (2).

The failure to decontaminate the gut from AGNB may cause gut overgrowth, which is the ideal condition for the *de novo* development of new clones following increased spontaneous mutation, resulting in polyclonality (6). The low colistin levels in the gut will kill sensitive clones but allow mutating ones to become resistant to colistin.

Interestingly, in a recent large Dutch study of about 6,000 patients using the original protocol of SDD (7), the acquisition rates of colistin-resistant AGNB in the respiratory tract were low and comparable during SDD and standard care (8).

We believe that this study provides a basis for the conclusion that colistin resistance may be caused by the administration of an inappropriately low enteral dose of colistin. This is the decontamination regimen which should be strongly discouraged.

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