

# Emergence of Colistin Resistance in *Enterobacteriaceae* after the Introduction of Selective Digestive Tract Decontamination in an Intensive Care Unit

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Selective decontamination of the digestive tract (SDD) selectively eradicates aerobic Gram-negative bacteria (AGNB) by the enteric administration of oral nonabsorbable antimicrobial agents, i.e., colistin and tobramycin. We retrospectively investigated the impact of SDD, applied for 5 years as part of an infection control program for the control of an outbreak with extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* in an intensive care unit (ICU), on resistance among AGNB. Colistin MICs were determined on stored ESBL-producing *K. pneumoniae* isolates using the Etest. The occurrence of both tobramycin resistance among pathogens intrinsically resistant to colistin (CIR) and bacteremia caused by ESBL-producing *K. pneumoniae* and CIR were investigated. Of the 134 retested ESBL-producing *K. pneumoniae* isolates, 28 were isolated before SDD was started, and all had MICs of <1.5 mg/liter. For the remaining 106 isolated after starting SDD, MICs ranged between 0.5 and 24 mg/liter. Tobramycin-resistant CIR isolates were found sporadically before the introduction of SDD, but their prevalence increased immediately afterward. Segmented regression analysis showed a highly significant relationship between SDD and resistance to tobramycin. Five patients were identified with bacteremia caused by ESBL-producing *K. pneumoniae* before SDD and 9 patients thereafter. No bacteremia caused by CIR was found before SDD, but its occurrence increased to 26 after the introduction of SDD. In conclusion, colistin resistance among ESBL-producing *K. pneumoniae* isolates emerged rapidly after SDD. In addition, both the occurrence and the proportion of tobramycin resistance among CIR increased under the use of SDD. SDD should not be applied in outbreak settings when resistant bacteria are prevalent.

Colistin, a polypeptide antibiotic belonging to the polymyxin group, was initially used for the treatment of a variety of Gram-negative bacterial infections. However, because of its significant side effects and the introduction into clinical practice of less toxic antibiotics, the intravenous formulations of colistin were gradually abandoned in the early 1980s in most parts of the world (1). Oral nonabsorbable compounds, nebulized formulations, and topical preparations of colistin continue to be used for selective decontamination of the digestive tract (SDD); for treatment of cystic fibrosis patients colonized with *Pseudomonas aeruginosa*; and for therapy of otitis, conjunctivitis, and skin infections (1). With the increasing prevalence of infections caused by multidrug-resistant (MDR) Gram-negative bacteria while the discovery and development of newer, effective antibiotics has declined, colistin has reemerged as the last-resort therapy for many infections. Fortunately, recent clinical data show that the use of colistin is acceptably safe if certain precautions are taken (2). Of great concern, however, is the emergence, all over the world, of colistin resistance in multidrug-resistant clinical strains of *Acinetobacter baumannii* (3) and *P. aeruginosa* (4). This study reports on the impact of long-term use of topical colistin as part of a regimen for SDD started during an outbreak involving extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* in an intensive care unit (ICU) on resistance among aerobic Gram-negative bacteria (AGNB).

## MATERIALS AND METHODS

**Setting.** SDD was applied for 5 years to all patients admitted to the ICU as part of an infection control program for the control of an outbreak in-

volving ESBL-producing *K. pneumoniae* (Fig. 1). SDD was given as a topical mixture of nonabsorbable antibiotics, including tobramycin, colistin, and amphotericin B (doses of 80, 100, and 500 mg, respectively), applied on the buccal mucosa and as a suspension administered via a nasogastric tube in the gastrointestinal tract four times a day (5). The aim of the SDD treatment was to reduce colonization of the digestive tract with resistant bacteria (5).

**Surveillance.** Routine microbiological screening, started in February 2002, was performed for all patients on admission to the ICU and then twice a week. Screening was done by culture of throat and rectal-swab specimens and, in intubated patients, of additional tracheal-fluid samples. When clinically indicated, samples were also obtained from relevant body sites, such as wounds.

**Bacteriological methods.** Biochemical tests were routinely performed by using the API 20E system (bioMérieux, Marcy l'Étoile, France). Antimicrobial susceptibility was determined by the agar dilution method according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) (6). CLSI did not include criteria for colistin susceptibility testing (6). Colistin susceptibility testing was performed by the disc diffusion method (potency of the disc, 10 µg) as recommended in the package insert, where zone diameter breakpoints of ≥11 mm (susceptible), 9 to 10 mm (intermediate), and ≤8 mm (resistant) were used. ESBL confirma-

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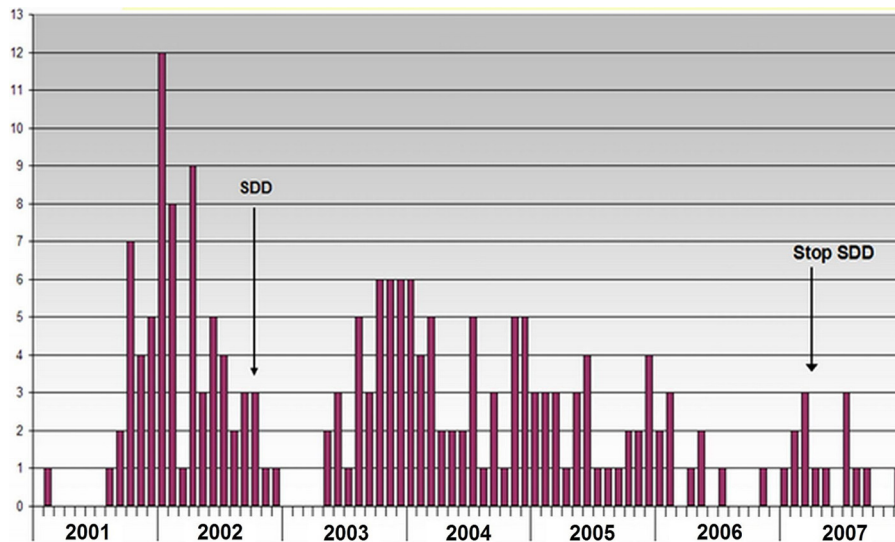


FIG 1 Monthly observed numbers of patients harboring extended-spectrum beta-lactamase-producing *K. pneumoniae* between 2001 and 2008 ( $n = 197$ ). The ICU was closed from January through April 2003.

tion was performed with the double-disc synergy test (7). ESBL-producing *K. pneumoniae* isolates were stored at  $-70^{\circ}\text{C}$ .

**Retrospective analysis.** In 2008, a retrospective study was undertaken on existing databases to determine the exact extent of the ESBL-producing *K. pneumoniae* outbreak, to obtain data on colistin antimicrobial susceptibility among ESBL-producing *K. pneumoniae* isolates, and to determine the occurrence of pathogens intrinsically resistant to colistin (CIR) (*Proteus*, *Morganella*, and *Serratia* spp.) that were tobramycin resistant (CIR-tR) during the use of SDD. The occurrence of bacteremia caused by ESBL-producing *K. pneumoniae* and CIR was also investigated. In addition, isolates stored before and after the start of SDD as ESBL-producing *K. pneumoniae* were retrieved for further analysis. The Vitek 2 Advanced Expert System (bioMérieux, Marcy l'Étoile, France) was used for reidentification of the strains and to determine colistin susceptibility using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints ([http://www.eucast.org/clinical\\_breakpoints](http://www.eucast.org/clinical_breakpoints)). ESBL screening and confirmation were performed according to national guidelines (laboratory detection of highly resistant microorganisms [HRMO]; <http://www.nvmm.nl>). The colistin MIC was determined by the Etest using EUCAST breakpoints ([http://www.eucast.org/clinical\\_breakpoints](http://www.eucast.org/clinical_breakpoints)). DiversiLab (bioMérieux, Marcy l'Étoile, France), a semiautomated repetitive-sequence-based PCR (REP-PCR) (8), was used to investigate the clonality of the ESBL-producing *K. pneumoniae* isolates, using  $>95\%$  similarity as the similarity threshold.

**Statistical analysis.** Segmented regression analysis was performed to test the regression slopes pre- and post-SDD and to quantify the difference in tobramycin resistance among CIR by comparing the intercepts at the time of the start of SDD. To further investigate the impact of SDD on tobramycin resistance among CIR isolates from surveillance culture and from clinically indicated cultures, a logistic regression model was fitted to the data. The test outcome (1 or 0) of tobramycin resistance was taken as a response variable. The explanatory variables were sampling date (day), SDD (before, during, and after), and culture (surveillance or clinically indicated). The sudden jump in the proportion of resistant isolates after the start of SDD was incorporated in the regression model, as well as the decrease in the proportion of resistant isolates after stopping SDD. No sudden jump was present here. To avoid numerical problems, it was assumed that there was no difference in the proportion of resistant isolates between the two cultures before the start of SDD. Differences in proportions of resistant isolates are reported as absolute risk differences (RD),

while slopes are reported as odds ratios (OR) per year, together with their corresponding 95% confidence intervals (CI) and  $P$  values.

## RESULTS

Between January 2001 and January 2008, 197 ESBL-producing *K. pneumoniae*-positive patients were identified (Fig. 1). Isolates from 134 out of the 197 identified cases (one isolate per patient) were included in the present analysis. Upon retesting, all isolates were confirmed to be ESBL-producing *K. pneumoniae*. Most ESBL-producing *K. pneumoniae* isolates were resistant to tobramycin prior to the introduction of SDD (data not shown). Data on colistin susceptibility, as determined by disc diffusion, could be found for 89 ESBL-producing *K. pneumoniae* isolates and are shown in Table 1. All isolates tested before the introduction of SDD were found susceptible to colistin by this method. Four isolates (4.5%), all isolated after starting SDD, were resistant (Table 1). The results of the antimicrobial susceptibility testing of stored isolates as performed by the Vitek method revealed that of the 134 tested isolates, all 28 isolates obtained before the start of SDD were colistin susceptible. However, of the remaining 106, isolated after starting SDD, 75 (70.75%) were colistin resistant (Table 1). The results of the Vitek susceptibility testing were confirmed by the Etest method (Table 1). All isolates obtained before SDD had

TABLE 1 Susceptibilities of ESBL-producing *K. pneumoniae* isolates to colistin as determined by disc diffusion, Vitek, and Etest

Isolate group <sup>a</sup>	No. of isolates <sup>b</sup>								
	Disc diffusion ( $n = 89$ )			Vitek ( $n = 134$ )			Etest ( $n = 134$ )		
	S	I	R	S	I	R	S	I	R
Before SDD	12	0	0	28	0	0	28	0	0
After SDD	45	28	4	31	0	75	32	0	74

<sup>a</sup> Isolates are grouped according to whether they were identified before or after the introduction of SDD on the ICU in October 2002.

<sup>b</sup> S, susceptible; I, intermediate; R, resistant.

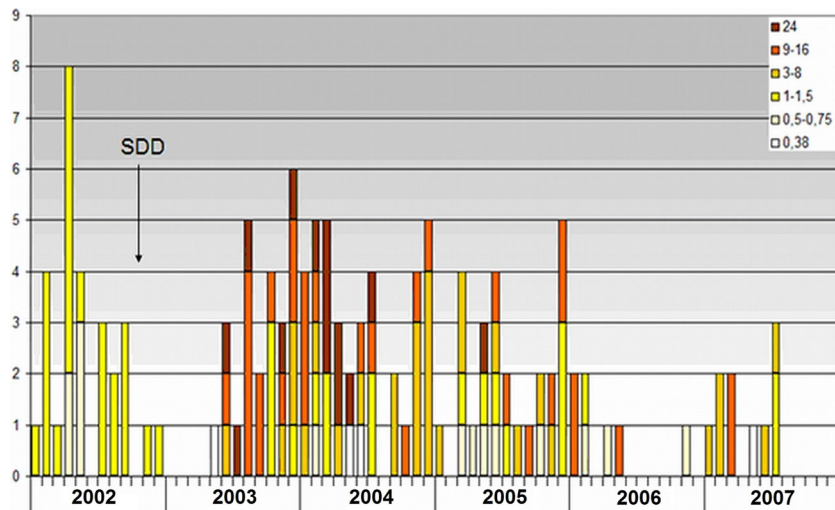


FIG 2 Susceptibility to colistin among 134 extended-spectrum beta-lactamase-producing *K. pneumoniae* isolates, as retrospectively determined by the Etest method. MICs (mg/liter) are shown.

colistin MICs of <1.5 mg/liter, but the MIC values rose to 24 mg/liter in those tested isolates that were obtained after the introduction of SDD (Fig. 2).

Typing of the 134 isolates by REP-PCR revealed that the majority were clonally related, as 114 were identical by this method, 28 of which were isolated before the start of SDD and 86 after. Of the remaining 20, 1 cluster contained 5 isolates, 4 clusters each contained 2 isolates, and the remaining 7 isolates had different patterns. Colistin MICs among the ESBL-producing *K. pneumoniae* isolates that were obtained after the start of SDD and that belonged to the major clone varied between 0.5 and 24 mg/liter. Of the 74 colistin-resistant ESBL-producing *K. pneumoniae* isolates, 71 belonged to the major clone and 3 had different patterns.

After the ward was reopened in April 2008, ESBL-producing *K. pneumoniae* isolates were sporadically detected in the ICU; all were colistin susceptible and genotypically unrelated to the outbreak, as investigated by DiversiLab.

Between 2001 and 2008, data on 2,572 CIR could be retrieved

(Fig. 3). CIR isolates were found sporadically before the introduction of SDD, but their prevalence increased immediately afterward (Fig. 3). Segmented regression analysis showed a highly significant relationship between the introduction of SDD and resistance to tobramycin, with an RD value for the increase in the proportion of tobramycin-resistant isolates at the start of SDD of 0.41 (95% CI, 0.33 to 0.47;  $P$  value < 0.001) (Fig. 4). Figure 5 shows the proportions of resistant isolates for the surveillance cultures (black dots) and the clinically indicated cultures (gray triangles) between 2001 and 2009. After the start of SDD, the proportion of resistant isolates suddenly increases. The increase for the surveillance cultures (RD = 0.51 [95% CI, 0.42 to 0.57;  $P$  value < 0.001]) is greater than the increase for the clinically indicated cultures (RD = 0.27 [95% CI, 0.18 to 0.34;  $P$  value < 0.001]). The difference between the two is 0.24 (95% CI, 0.15 to 0.32;  $P$  value < 0.001). During the SDD period, the slope, in terms of an odds ratio, for the surveillance cultures is as follows: OR = 1.34 (95% CI, 1.21 to 1.48). For the clinically indicated cultures, the slope is

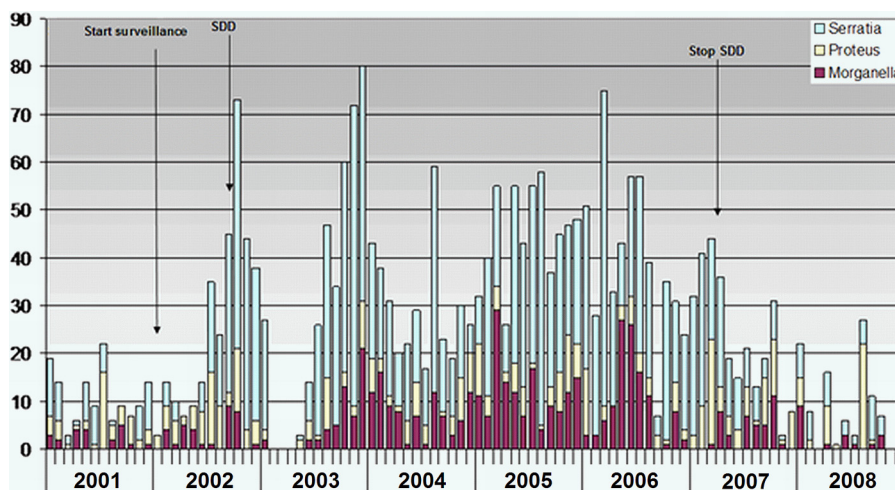


FIG 3 Monthly occurrence of CIR isolates ( $n = 2,572$ ) between 2001 and 2008.



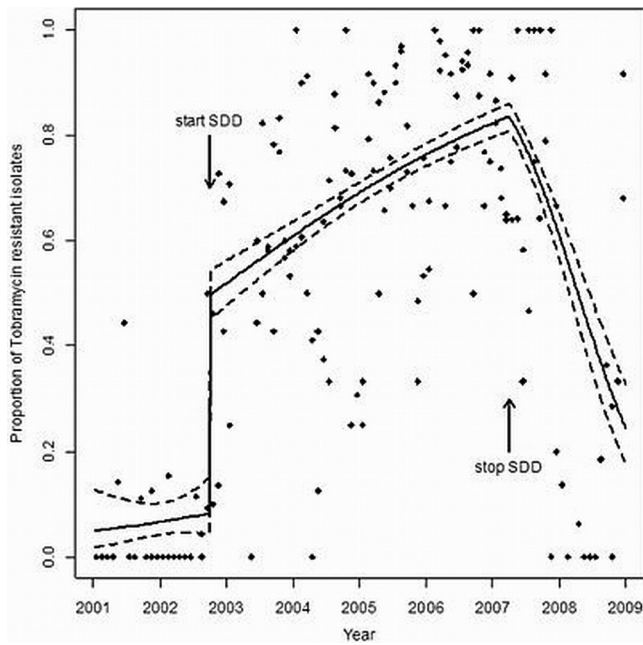


FIG 4 Segmented regression analysis showing the relationship between the introduction of SDD and tobramycin resistance among CIR isolates (black dots). The logistic regression model fit (solid lines) is shown, together with its 95% confidence interval (dashed lines).

steeper (OR = 1.58 [95% CI, 1.43 to 1.76]). The difference is as follows: OR = 0.85 (95% CI, 0.73 to 0.98;  $P$  value = 0.023). After stopping SDD, the proportion of resistant isolates in the clinically indicated cultures sharply decreases, while it does not for the surveillance cultures.

Five patients were identified with bacteremia caused by ESBL-producing *K. pneumoniae* before the introduction of SDD and 9 patients thereafter (Fig. 6). No bacteremia caused by CIR was found before SDD, but its occurrence increased to 26 after the introduction of SDD, 24 of which were caused by *Serratia* spp. and 2 by *Morganella* spp. (Fig. 6).

## DISCUSSION

The main findings of this study are the emergence under SDD of colistin resistance among ESBL-producing *K. pneumoniae* isolates, the increase in both the prevalence and the proportion of tobramycin resistance among CIR, and the increase in occurrence of bacteremia caused by organisms resistant to SDD, which had been introduced in an outbreak setting.

The potential for the emergence of resistance to colistin among sensitive organisms has been found to be low (9). Nonetheless, increase in colistin-resistant aerobic Gram-negative strains during the use of SDD has been observed (10), and with the increasing systemic use of colistin against multidrug-resistant pathogens, development of resistance to the agent has frequently been reported in recent years in nosocomial strains (11), including MDR *K. pneumoniae* (12).

In this study, we retrospectively investigated the impact of long-term use of colistin as part of SDD on resistance among ESBL-producing *K. pneumoniae* and CIR isolates during an outbreak.

Our data show that the routinely used disc diffusion method

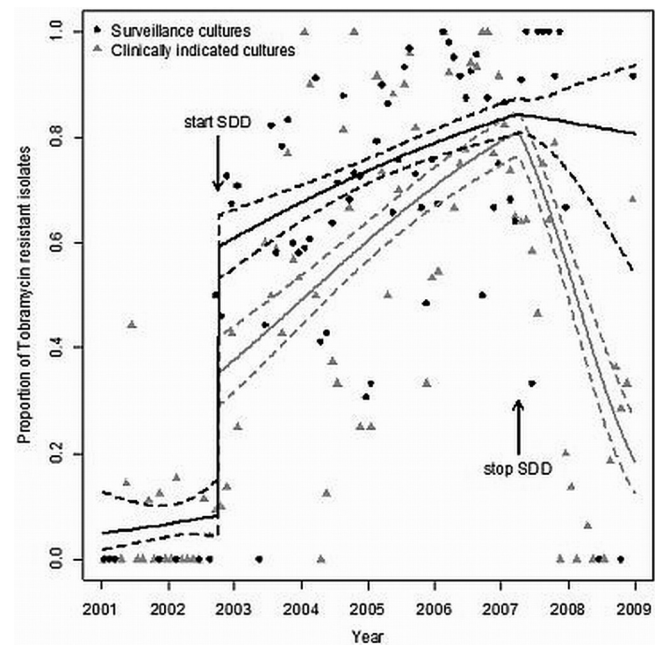


FIG 5 Proportions of tobramycin-resistant isolates from surveillance cultures (black dots) and clinically indicated cultures (gray triangles) between 2001 and 2009. The logistic regression model fit (solid lines) is shown, together with its 95% confidence interval (dashed lines).

failed to detect colistin resistance. As shown in Table 1, most strains that were considered intermediate or susceptible to colistin were found to be resistant when retested by the Vitek method. The Vitek method has been found to be reliable in susceptibility testing for colistin in clinical strains, including *Klebsiella* spp., compared to broth microdilution as the reference method (10). The observed inaccuracy of disc diffusion testing of colistin has also been shown in numerous studies, and therefore, alternative methods should be used (11).

The results of this study demonstrate an association between prolonged use of colistin as part of SDD and the emergence of colistin resistance among ESBL-producing *K. pneumoniae* isolates. The majority of resistant isolates were clonally related, as evidenced by REP-PCR typing, indicating horizontal transmission. All strains isolated before the start of SDD that were colistin susceptible belonged to the same clone as those isolated thereafter that were colistin resistant. In addition, 3 isolates, all obtained after the start of SDD, that were unrelated to the major clone were also colistin resistant, suggesting that resistance emerged through selection pressure. Interestingly, the clonally related strains that were isolated after the start of SDD exhibited a wide range of colistin MIC values, ranging between 0.5 and 24 mg/liter (Fig. 2), a finding that has also been described in a recent study (12) where colistin-resistant *K. pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* strains obtained from patients admitted to the same ward and belonging to the same clone showed different MIC values. This can possibly be explained by the presence of hetero-resistant subpopulations within the colistin-susceptible MDR strains after exposure to colistin, as has recently been shown in clinical strains of *Acinetobacter* (28) and *K. pneumoniae* (13). Combined with the fact that the majority of strains involved in our study were tobramycin resistant, these data suggest a potential role of monotherapy with colistin in the emergence of resistance.

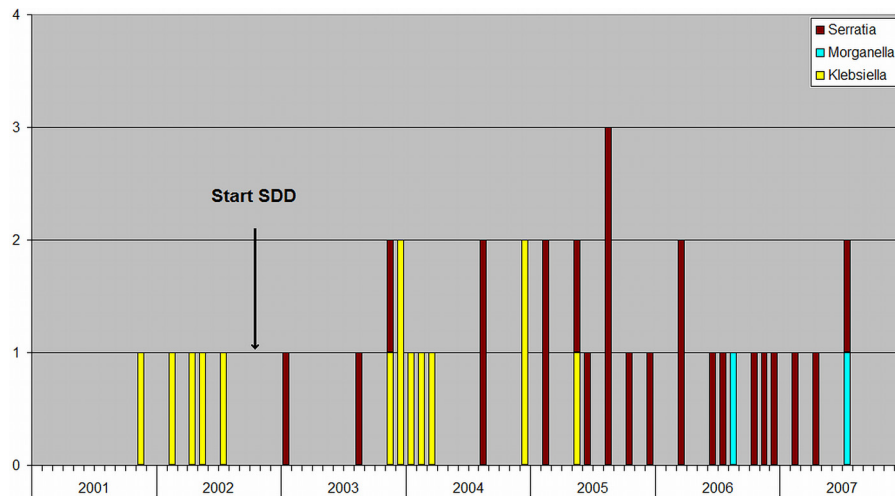


FIG 6 Monthly occurrence of bacteremia caused by CIR (*Proteus*, *Morganella*, and *Serratia* spp.) and extended-spectrum beta-lactamase-producing *K. pneumoniae* between 2001 and 2008.

This study also shows an increase in both the occurrence of CIR and resistance to tobramycin among these isolates during SDD use (Fig. 3 and 4). This may represent selection pressure under SDD. Horizontal spread, however, cannot be excluded, since no genotypic analysis of these isolates has been performed. CIR-tR consisted mainly of *Serratia* spp., which can be explained by the fact that these species are known to produce aminoglycoside-modifying enzymes that may affect the activity of tobramycin ([http://www.eucast.org/expert\\_rules](http://www.eucast.org/expert_rules)), rendering them resistant to both SDD components.

As in other studies, detection of antibiotic-resistant nosocomial pathogens was more frequently achieved by surveillance cultures than by clinical cultures alone (14–16). Figure 5 shows that the increase in the proportion of tobramycin-resistant CIR isolates was greater for the surveillance cultures than for the clinically indicated cultures (an increase in RD of 0.24;  $P$  value < 0.001). The figure also shows, in accordance with other studies (17, 18), that the increasing rates of tobramycin resistance were not, at least during the study period, returned to baseline by cessation of SDD.

SDD has been used as a method designed to prevent infection in critically ill patients. In settings with low levels of circulating antibiotic-resistant organisms, SDD has been found not to be associated with increased selection or induction of antibiotic resistance (19, 20). However, in settings with high levels of endemic, multidrug-resistant Gram-negative bacteria, SDD was associated with increased selection of such pathogens (19). In the present study, SDD had been started in an outbreak setting, when enhanced infection control measures were found insufficient to control the outbreak. The aim of SDD was to reduce colonization of the digestive tract with resistant bacteria (5), which, in theory, could have a synergistic effect with infection control measures (20). Reductions of bacterial loads at places frequently contacted by nursing staff would reduce the likelihood of cross-transmission (20). Only a few studies have investigated SDD in such settings (5). The results of studies of SDD in outbreak situations when SDD was introduced in our hospital were conflicting. Some had shown that the outbreak with multiresistant Gram-negative bacilli, including *Klebsiella* spp., could be controlled (21, 22), while in others, SDD alone failed to reduce the incidence of acquisition of

outbreak strains (23). In a recent study assessing the effectiveness of SDD for eradicating carbapenem-resistant *K. pneumoniae* oropharyngeal and gastrointestinal carriage, it was concluded that in outbreaks caused by carbapenem-resistant *K. pneumoniae* infections that are uncontrolled by routine infection control measures, SDD could provide additional infection containment (24). SDD was also found beneficial in decreasing the intestinal reservoir in ICU patients with *A. baumannii* colonization, and no development of resistance to colistin was detected in the strains isolated in the course of SDD (25). In another recent study, however, oral colistin did not prevent colonization with extended-spectrum beta-lactamase-producing *Enterobacteriaceae* and appeared to select for colistin-resistant strains or to induce colistin resistance (26). The results from the present study provide arguments against the use of SDD in outbreak settings when resistant bacteria are prevalent. Not only did SDD fail to control the ESBL-producing *K. pneumoniae* outbreak, it also led to a dramatic increase in resistance, and its introduction was associated with an increase in the occurrence of bacteremia caused by organisms resistant to SDD.

A possible explanation is the selection under SDD for resistant bacteria, which became predominant in the ICU environment, enhancing their likelihood for cross-transmission. This has previously been shown for vancomycin-resistant enterococci (VRE) when their colonization pressure, once high, became the major variable affecting VRE acquisition (27).

In conclusion, our study adds evidence to existing data showing the emergence of colistin resistance in ESBL-producing *K. pneumoniae* strains exposed to prolonged treatment with colistin. The strains were resistant to tobramycin, which was combined with colistin in the SDD regimen, suggesting a potential role for monotherapy in resistance and emphasizing the need for further studies to determine whether combination therapy of colistin with other agents prevents the emergence of resistance (11). This study further provides evidence against the use of SDD in outbreak settings and supports the rational use of colistin, combined with a monitoring surveillance program for colistin resistance and the strict and timely implementation of infection control rules, as a main factor in avoiding the emergence and spread of resistance.

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