Decline of multidrug-resistant Gram negative infections with the routine use of a multiple decontamination regimen in ICU

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Running title: Decline of MDR AGNB infections with decontamination

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ABSTRACT

Objectives: We have shown that the routine use of a multiple decontamination regimen with oropharyngeal and digestive polymyxin/tobramycin/amphotericin B plus mupirocin/chlorhexidine in intubated patients reduced all-cause acquired infections (AIs) in the intensive care unit (ICU). We now assessed the long-term impact of this strategy on AIs involving multidrug-resistant aerobic Gram negative bacilli (AGNB) and acquired episodes of extended-spectrum betalactamase (ESBL)-producing Enterobacteriaceae rectal carriage.

Methods: This was an observational single center study of all patients admitted to an ICU over 5 years (study population). Decontamination was given for the period of intubation and standard care otherwise. AIs and colonization rates were prospectively recorded. AIs rates were compared between the study period and a 1-year pre-intervention period. During study, trends were analyzed by semester using a Poisson regression model.

Results: The incidence rate of multidrug-resistant AGNB AIs was lower during the study (1.59 per 1,000 patient-days, versus pre-intervention: 5.43‰, p<0.001) and declined with time (adjusted OR=0.85, 95 percent confidence interval 0.77-0.93, p<0.001). ESBL-producing Enterobacteriaceae acquired colonization episodes (OR=0.94 [0.88-1.00] P=0.04) and the use of five major antibiotics (P<0.001) also declined.

Conclusion: a multiple decontamination regimen did not favor the emergence of multidrug-resistant AGNB. In contrast, infection and colonization rates declined with time.

Highlights

- We assessed the long-term impact of decontamination on MDR AGNB acquired infections
- AIs and colonization rates were prospectively recorded
- The incidence rate of multidrug-resistant AGNB AIs substantially declined with time
- ESBL-producing Enterobacteriaceae acquired rectal carriage also declined
- Multiple decontamination did not favor the emergence of antimicrobial-resistant AGNB

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Keywords

chlorhexidine; intensive care unit; multidrug-resistant Gram negative bacilli; mupirocin; selective digestive decontamination; topical antibiotics

ABSTRACT

Objectives: We have shown that the routine use of a multiple decontamination regimen with oropharyngeal and digestive polymyxin/tobramycin/amphotericin B plus mupirocin/chlorhexidine in intubated patients reduced all-cause acquired infections (AIs) in the intensive care unit (ICU). We now assessed the long-term impact of this strategy on AIs involving multidrug-resistant aerobic Gram negative bacilli (AGNB) and acquired episodes of extended-spectrum betalactamase (ESBL)-producing Enterobacteriaceae rectal carriage.

Methods: This was an observational single center study of all patients admitted to an ICU over 5 years (study population). Decontamination was given for the period of intubation and standard care otherwise. AIs and colonization rates were prospectively recorded. AIs rates were compared between the study period and a 1-year pre-intervention period. During study, trends were analyzed by semester using a Poisson regression model.

Results: The incidence rate of multidrug-resistant AGNB AIs was lower during the study (1.59 per 1,000 patient-days, versus pre-intervention: 5.43‰, p<0.001) and declined with time (adjusted OR=0.85, 95 percent confidence interval 0.77-0.93, p<0.001). ESBL-producing Enterobacteriaceae acquired colonization episodes (OR=0.94 [0.88-1.00] P=0.04) and the use of five major antibiotics (P<0.001) also declined.

Conclusion: a multiple decontamination regimen did not favor the emergence of multidrug-resistant AGNB. In contrast, infection and colonization rates declined with time.

INTRODUCTION

Infections acquired in the Intensive Care Unit (ICU) account for substantial morbidity and hospital costs (1) and increase the risk of death in ICU (2). Selective decontamination of the digestive tract has been recognized as an effective measure to control infections in the ICU with high-quality evidence (3). Many protocols using various antimicrobial agents or antiseptics have been used for many decades. Selective digestive decontamination (SDD) using oropharyngeal and digestive topical colistin, tobramycin and amphotericin B with 4-day systemic cefotaxime reduced respiratory infections (4), bloodstream infections (5) and, more importantly, the mortality rate (odds ratio [OR] for death at day 28 = 0.83 [95% CI, 0.72 – 0.97]) compared with standard care (5). Selective oropharyngeal decontamination (SOD) using the same topical antibiotics in the oropharynx also reduced bloodstream infections and decreased mortality rate (OR=0.86 [0.74 – 0.99]) (5). A combination of oropharyngeal and digestive colistin/tobramycin with mupirocin and chlorhexidine body wash has been shown to reduce all-cause infections in intubated patients (6).

However, the impact on the emergence of multi-drug resistant bacteria is unclear. A recent meta-analysis detected no relationship between the use of SDD or SOD and the development of antimicrobial resistance in pathogens in ICU patients and noted that this problem was understudied (7). The prevalence of rectal carriage of aminoglycoside-resistant AGNB increased during the use of SOD and SDD, although the consequence on infections was not shown (8). The use of topical polymyxin/tobramycin/amphotericin B plus mupirocin/chlorhexidine in intubated patients was associated with the reduction of all-cause ICU-acquired infections including multidrug-resistant AGNB in all patients (9). In order to detect the emergence of multidrug-resistant organisms, we assessed the rates of acquired infections (AIs) caused by microorganisms resistant to antibiotics and rectal carriage of extended-spectrum β-lactamase (ESBL)-producing AGNB over a 5-year period with this regimen.

METHODS AND PATIENTS

Surveillance of antimicrobial-resistant microorganisms

Surveillance of total AIs was performed prospectively in our ICU as reported previously (9-11). The definitions used were those of the Centers for Disease Control and Prevention (12) modified with the new definitions of the French National Technical Committee for Nosocomial Infection (available at http://www.sante.gouv.fr/IMG/pdf/rapport_complet.pdf). For the purpose of this study, pneumonia was diagnosed on a clinical and radiologic basis and was confirmed by a positive culture of a bronchoalveolar lavage ($>10^3$ CFU/ml) or an endotracheal aspiration ($\geq 10^5$ CFU/ml). Infections were considered to be acquired in the ICU when they were diagnosed after 48 hours and if patients were not incubated at the time of admission. Antibiograms were performed on all clinical samples. Methicillin resistance was determined on all *Staphylococcus aureus* isolates and vancomycin resistance on all *Enterococcus* sp. isolates. Special attention was paid to the resistance to 3rd-generation cephalosporins, aminoglycosides, carbapenems, fluoroquinolones and colistin in AGNB.

Universal ESBL-producing Enterobacteriaceae screening was performed on rectal swabs taken at admission, discharge and once a week during the ICU stay. Samples were directly inoculated onto antibiotic selective agar (chromID BLSE agar®, bioMérieux, Marcy l'Etoile, France) (13). The diffusion method for antimicrobial susceptibility testing was systematically executed on growing oxidase negative colonies. The ESBL resistance mechanism was phenotypically confirmed by the existence of a synergy between a third-generation cephalosporin and clavulanate using the double-disk synergy test or ESBL Etests® (bioMérieux, Marcy l'Etoile, France) (14). Contact precautions were applied to the patients who were screened positive and maintained during the entire ICU stay or until the negative

results of two consecutive weekly samples. An episode of acquired colonization was defined as the acquisition during the ICU stay of a new ESBL-producing AGNB, whether the patient was not colonized or colonized with a different ESBL-producing species on a prior sample. Due to multiple epidemic ESBL-producing AGNB species (mostly *Klebsiella* sp., *Enterobacter* sp. or *Citrobacter* sp.), more than one episode per patient could be recorded. Screening for methicillin-resistant *S aureus* (MRSA) and vancomycin-resistant enterococci (VRE) was not a routine procedure.

Prevention of healthcare-associated infections in the ICU

The Guidelines of the French Society for Hospital Hygiene were applied for the prevention of ICU-acquired infections (available at http://www.sf2h.net/publications-SF2H/SF2H_surveiller-et-prevenir-les-IAS-2010.pdf). Hand rubbing with hydroalcoholic solutions was implemented as standard care. Chlorhexidine was used for skin disinfection. Procedures for the maintenance of indwelling catheters and the management of intubated patients were applied according to institutional care bundles.

Decontamination was applied to intubated patients who were expected to require intubation for 24 hours or more. The protocol has been reported elsewhere (9) and consisted of oral suspension of colistin, tobramycin and amphotericin B administered in the oropharynx and the gastric tube four times daily and one course of nasal mupirocin and chlorhexidine gluconate body washing twice daily during the period of intubation plus 24 hours. The patients who were not intubated received standard care. This protocol was implemented from June 2007 and has continued uninterrupted. In patients who had any sample positive for an AGNB resistant to both tobramycin and colistin, oropharyngeal and digestive topical antimicrobials were discontinued and replaced by oropharyngeal rinse with chlorhexidine 0.12% 5 ml four times daily. The administration of mupirocin and chlorhexidine body washing were maintained.

Study design

We previously reported a strong decline in AIs during a 1-year period following the implementation of our multiple-site decontamination protocol compared to the previous 1-year period without decontamination (9). Because 1-year surveillance may have been too short to detect a significant emergence of resistant bacteria, we continued the surveillance over a longer period of time. The 5,250 patients who were admitted to the ICU from 1 January 2008 to 31 December 2012 were included in the study. The study period was divided into 10 semesters based on the date of admission. Infection and colonization rates, expressed per 1,000 patient-days (‰), were assessed by semester, and trends over time were assessed. The main characteristics of the patients and their ICU stay were extracted from the ICU patients' database. In order to better characterize the level of antimicrobial resistance at our Hospital during this 5-year period, we recorded the proportion of all positive blood cultures growing a resistant strain for the following species: methicillin resistance for *S. aureus*, vancomycin resistance for enterococci, ESBL for Enterobacteriaceae and ceftazidime resistance for *P. aeruginosa*. The study was approved by the Institutional Ethics Committee as part of a prospective surveillance of an ICU-acquired infections program. Written informed consent was waived because decontamination was considered routine care.

Endpoints

The surveillance study focused on the resistance of AGNB to seven antimicrobials: ceftazidime, imipenem, ciprofloxacin, gentamicin, tobramycin, amikacin and colistin. Multidrug resistance in AGNB was defined as the resistance to 2 or more among the following antibiotics: third-generation cephalosporins, imipenem, all three aminoglycosides and ciprofloxacin. Based on positive clinical cultures which were sampled at the time of the patients's admission (from 48 hours before to 24 hours after), we assessed the prevalence of AGNB which were resistant to at least one antibiotic at admission per 100 admissions. The

main endpoint was the incidence rates of ICU-attributable AIs caused by multidrug-resistant AGNB. We also studied the incidence rates of AIs caused by Enterobacteriaceae, *Pseudomonas aeruginosa* and other glucose-nonfermenting GNB resistant to each antibiotic separately, because the detection of increased resistance to one of these antimicrobials would be a relevant finding as well. First, the incidence rates of AIs during the entire study period were compared to those previously reported during a 1-year pre-intervention period without decontamination (9). Then, trends throughout the 10 study semesters were investigated. As secondary endpoints, the acquisition of colonization with ESBL-producing AGNB and with colistin-resistant ESBL-producing AGNB in the ICU was assessed during the study period. Lastly, the incidence rate of total AIs (distinguishing Gram-positive cocci, GNB and fungal AIs) and the consumption of five broad-spectrum antibiotics and hydroalcoholic solutions were also evaluated.

Statistical analysis

Statistical analysis was performed using SAS 9.4 for Windows (SAS Institute, Cary, NC, USA). Quantitative variables are expressed as the median (25^{th} percentile-75^{th} percentile), and comparisons between groups were performed using a Kruskall-Wallis test. Categorical variables were compared with a chi-square test. Incidence rates were analyzed with a Poisson regression model. The trend analysis of multidrug-resistant AGNB infections and total infections was adjusted for the following risk factors: the presence of urinary catheter ≥3 days, intubation ≥3 days, central venous catheter ≥1 day, Simplified Acute Physiology Score II (SAPSII) greater than 25 and diagnosis with a high risk AI (digestive, trauma categories) at admission (9). An odds ratio (OR) greater than 1 indicated an increase with each semester, and an OR lower than 1 indicated a decrease. Trends for categorical variables were analyzed by logistic regression. All tests were two sided, and a *p* value of less than or equal to 0.05 was considered statistically significant.

RESULTS

Report of bacteremia due to resistant microorganisms in our Hospital

The proportion of bacteremia due to resistant organisms was used to assess the general level of antimicrobial resistance in our Institution (Table 1). The proportion of *S. aureus* bacteremia due to MRSA varied between 20% and 26% depending on the year, and did not significantly change with time, especially in the non-ICU wards (p for trend 0.09). For enterococci, the proportion of VRE was lower than 5%, whether in ICU or outside ICU. Ceftazidime resistance rate for *P. aeruginosa* bacteremia averaged 3% in the non ICU wards. In contrast, there was a significant increase with time in the rate of ESBL-producing Enterobacteriaceae outside ICUs from 3% to 7% (p=0.003).

Characteristics of the patients at admission, device exposition and outcome

During the study period, there were some differences in patients' demographic characteristics and diagnosis categories across semesters, reflecting temporal variability in recruitment. The use of a central venous catheter and urinary catheter, but not intubation, tended to increase significantly over time (details in Supplemental digital content, eTable 1 and legend). Although mortality in ICU tended to decrease during the ten semesters of the study (adjusted OR=0.96 [0.93-0.99], p=0.02; adjustment for the Glasgow coma score, SAPSII, the category of diagnosis, the presence of infection at admission and the use of invasive devices), the overall rate (15.0%) did not differ from the ICU mortality rate during the pre-intervention period (14.4%, p=0.61; eTable 1).

Prevalence of antimicrobial resistant AGNB at admission

Based on positive clinical cultures, the prevalence rate at admission of AGNB resistant to at least one of the marker antimicrobials was 3.2 per 100 admissions during the pre-intervention period and 3.5 per 100 admissions during the study period (p=0.71). During the

study semesters, there was no change in the prevalence rate of AGNBs resistant to each antimicrobial, multidrug-resistant or ESBL-producing (p for trend ≥ 0.30 for all analyses, Table 2). By contrast, the overall rate of rectal colonization with ESBL-producing AGNB was 4.5 per 100 admissions and tended to increase with time with a peak at 7.6% during the 8th semester (p for trend =0.03; Supplemental digital content, eTable 1).

Acquired infections caused by multidrug-resistant AGNB

The numbers (incidence rates) of ICU-attributable AIs involving antimicrobial resistant organisms and episodes of acquired rectal colonization with ESBL-producing AGNB are detailed in the Supplemental digital content, eTable 2. Of 206 AIs involving AGNB, 63 (30.6%) were caused by multidrug-resistant AGNB.

Comparison with the pre-intervention period. The incidence rates of AIs involving multidrug-resistant AGNB, by semester, are represented in Figure 1. The incidence rate was 5.43‰ during the 1-year pre-intervention period. It was significantly lower during the entire 5-year study period (1.59‰, p<0.0001) and during each during study year (2.02‰ [2008]: 2.50‰ [2009]; 2.13‰ [2010]; 0.77‰ [2011]; 0.50‰ [2012]; all p<0.01). Incidence rates were also lower for AIs caused by: *Enterobactericae* resistant to ceftazidime and to ciprofloxacin; *Pseudomonas aeruginosa* resistant to ceftazidime, ciprofloxacin, tobramycin and amikacin; and other glucose-nonfermenting AGNB resistant to ceftazidime, ciprofloxacin, tobramycin and amikacin (all p< 0.05, eTable2).

Trend analysis during the study period. There was a gradual decline in the incidence rates of infections involving multidrug-resistant AGNB (adjusted OR=0.85 [95 percent confidence interval 0.77-0.93], p<0.001; unadjusted OR=0.86 [0.78-0.94], p<0.001) (Table 3). There was also a decline in AIs caused by Enterobacteriaceae resistant to at least one antimicrobial among ceftazidime, ciprofloxacin, aminoglycosides and colistin. During the entire study period, there were only four AIs caused by Enterobacteriaceae resistant to imipenem. The

incidence rates of AIs involving *P aeruginosa* resistant to at least one among imipenem or tobramycin, or any *P aeruginosa* isolate, irrespective of antimicrobial resistance, declined as well. There was no change in AIs involving other glucose-nonfermenting AGNB. AIs involving AGNB resistant to both tobramycin and colistin also substantially declined (OR=0.84 [074-0.96], p=0.009).

Acquired rectal colonization and infection with ESBL-producing AGNB

The incidence rate of ESBL-producing AGNB acquisition episodes significantly declined with time (p=0.04, Table 3). Among the patients who were not carriers of ESBL-producing AGNB at admission (n=5013), the proportion of those who acquired rectal carriage during their days in ICU also gradually declined with time (trend test using the Cox regression model: OR=0.92 [0.86-0.99], P=0.03). Eleven patients (all carriers) developed 12 AIs (*K. pneumoniae* in all), and the incidence rate declined with time, although statistical significance was not reached (OR=0.82 [0.66-1.02], p=0.08).

Twenty-six patients (0.5%) were found to be colonized with colistin-resistant ESBL-producing AGNB (*K. pneumoniae* 24, *E. coli* 1, *E. cloacae* 1; all isolates resistant to tobramycin). The number of positive samples per patient was 2 (1-3, range 1 to 12), and the total number of samples performed was 8 (6-9, range 2 to 17). Four patients were colonized at admission, and 22 acquired colonization in the ICU. Among these patients, the delay to the first positive result was 29 days (7-37, range 6 to 85), and the duration of prior decontamination administration was 26 days (7-38, range 4 to 73). Conversion from colistin-susceptible to colistin-resistant colonization was observed in 7 cases (median delay of 7 days), but genotyping of the isolates was not performed. Colonization with colistin-resistant ESBL-producing AGNB was considered to be transient (a single positive screening sample, n=10), intermittent (n=5) or persistent (n=11). The acquisition of colistin-resistant ESBL-producing

AGNB (OR=0.85 [0.72-0.99], P=0.04) and the presence of colonization at ICU discharge (OR=0.75 [0.57-0.97], p=0.03) both declined with time (Table 4).

Total AIs, use of antibiotics and hydroalcoholic solution

There was a significant trend towards a decline in total AIs and AIs involving AGNB, irrespective of antimicrobial resistance over the study period (Table 5). In contrast, AIs involving Gram-positive cocci remained stable. There was no infection caused by vancomycin-resistant *Enterococcus*. The consumption of five broad-spectrum antibiotics mostly used for the treatment of healthcare-associated infections was studied for each study semester (Figure 2). There was a gradual increase in the use of piperacillin/tazobactam (trend: $p<0.0001$), stability in the use of vancomycin, ($p=0.7783$) and a significant decrease in the use of ciprofloxacin, amikacin, carbapenems, and the five antimicrobials taken altogether (all p-values<0.0001). On average, the use of hydroalcoholic solution for hand disinfection was 116 liters per 1,000 patient-days and did not significantly vary over 5 years ($p=0.07$, supplemental digital content, eFigure 1).

DISCUSSION

We performed a longitudinal study over 5 years to detect the emergence of multidrug-resistant organisms. The main result was the strong decline in the incidence rate of multidrug resistant AGNB, which was observed with time in our ICU, with the lowest rates in the last four semesters. This could not be explained by a simultaneous decline in the prevalence of resistant AGNB at admission not over the same time period.

No consensus has yet been reached on the definition of "multidrug resistance". The interim definitions proposed were non-susceptibility to at least one agent in three or more antimicrobial categories, including penicillins (15). Resistance to all agents of the same category did not change the classification. We used the same definitions of multiresistance as

in a previous publication (9). In AGNB clinical isolates, we observed that the resistance to either third-generation cephalosporins or imipenem was always associated with the resistance to either one broad-spectrum penicillin or one aminoglycoside, and the resistance to both ciprofloxacin and aminoglycosides was also associated to non-susceptibility to at least one broad-spectrum penicillin. Thus, our definition of multidrug resistance was close to the definitions proposed by the international expert panel, except for the resistance to all aminoglycosides in our criteria.

We also studied AIs caused by organisms resistant to any of 7 antimicrobials separately. Regarding AIs involving resistant Enterobacteriaceae, a similar trend was uniformly observed with any antimicrobial except for imipenem resistant organisms due to the low number of AIs (only 4 during the first four semesters). For AIs involving *P. aeruginosa*, the declining trend was observed for the resistance to imipenem and tobramycin. AIs involving *P aeruginosa* resistant to ceftazidime, amikacin or colistin were rare. Similarly, AIs caused by other glucose-nonfermenting AGNB were infrequent and did not vary throughout the study period.

The level of antimicrobial resistance of AGNB was not particularly low during this 5-year period. The proportion of patients colonized with ESBL-producing AGNB, when colonization at admission and acquisition in ICU were combined, was 6.6% (3.9 to 8.8% depending on semesters), consistent with other reports in Europe (16-18) and in the USA (19). Colistin-resistant ESBL-producing *K. pneumoniae* isolates were identified mostly in rectal samples, as reported in the Dutch experience (20, 21), but no epidemic diffusion was observed. In contrast, the incidence rates of AIs caused by ESBL-producing Enterobacteriaceae were low and declining. Third-generation cephalosporins-resistant Enterobacteriaceae isolates were mostly *Enterobacter*, *Citrobacter*, *Serratia* spp., which

exhibited a cephalosporinase hyperproduction phenotype. Overall, the incidence of AIs involving third-generation cephalosporin-resistant Enterobacteriaceae declined steadily.

The reduction in the use of antimicrobials was in accordance with previous studies. Compared with standard care, a substantial decrease in the consumption of carbapenems and quinolones (mostly ciprofloxacin) was shown (5, 22). In our study, the increased use of piperacillin/tazobactam did not compensate the important decrease in the use of carbapenems, ciprofloxacin and amikacin. A reduction in the use of carbapenems and quinolones was encouraged by the antibiotic stewardship bundle in our hospital. The development of antibiotic resistance in AGNB respiratory isolates has been shown to be mostly associated with systemically administered antibiotics, especially carbapenem use, but similar between selective decontamination and standard care (23).

The decline in the incidence of colonization or infection with antibiotic resistant AGNB is in accordance with other data reporting the use of SDD, SOD or derived decontamination protocols. A meta-analysis of 64 studies failed to demonstrate that SDD or SOD was associated with more infections or higher carriage rates with multidrug-resistant organisms in patients who received these interventions. Interestingly, there was a reduction in polymyxin-resistant AGNB (OR=0·58, 0·46–0·72; p<0.0001), third-generation cephalosporin-resistant AGNB (0·33, 0·20–0·52; p<0.0001) and a trend toward reduction of aminoglycoside-resistance (0·73, 0·51–1·05; P=0.09) in recipients of selective decontamination compared with those without intervention (7). Similarly, longitudinal analysis of the antibiotic susceptibilities of respiratory tract isolates from 38 Dutch ICUs revealed a significant decline in antibiotic resistance in those ICUs that introduced SDD or SOD, as well as a trend toward decreasing resistance during its use (24).

These reductions during selective decontamination might result – directly – from the bactericidal effects exerted by the topical antibiotics, even for multidrug-resistant organisms

or, – indirectly – from the observed reduction in systemic antibiotic use, alleviating selective antibiotic pressure (25). First, our decontamination regimen using topical antibiotics in the intestine, similar to SDD, was effective in decontaminating the gut and reducing AGNB bloodstream infections (26). Second, the absence of intravenous cefotaxime may have reduced the risk of the emergence of 3rd-generation cephalosporin-resistant Enterobacteriaceae (21, 27). Third, the use of our regimen was limited to intubated patients for the duration of intubation and not than to all patients with an expected ICU stay greater than 48 hours, thereby reducing the overall antibiotic prescription compared with typical SDD. The contribution of chlorhexidine body wash remains controversial. It has been advocated to reduce the acquisition of multidrug resistant Gram-positive cocci and hospital acquired bloodstream infections (28, 29), but not overall health care–associated infections (30). Mupirocin/chlorhexidine decontamination was able to reduce MSSA (31) and even MRSA (11) infections. Moreover, the use of mupirocin/chlorhexidine combined with topical polymyxin/tobramycin has resulted in fewer AGNB AIs than the use of polymyxin/tobramycin alone compared with all placebos, reflecting an unexpected synergistic effect on the prevention of AIs (6). Data on the effect of chlorhexidine body wash on the incidence of AIs due to antibiotic-resistant AGNB are scarce. However, a decrease in the isolation of *Acinetobacter baumannii* from respiratory samples (32) and a reduction in hospital-acquired infections caused by AGNB (33) were reported.

The absence of a contemporary control group is a limitation of the study. Whereas decontamination is exceptionally used is in France, we were not aware of other French ICUs reporting long-term surveillance of all-cause AIs involving multidrug-resistant AGNB for comparison. This could be due to large differences in AIs surveillance strategies across French ICUs (34) mostly targeting specific MDR organisms. Of note, the French surveillance network of device-associated infections in the ICUs 2008-2012 reported annual incidence

trends for MDR AGNB AIs only for ESBL-producing Enterobacteriaceae (approximately 50% increase; Réseau REA-Raisin, France, results 2012, available at http://www.invs.sante.fr/Publications-et-outils/Rapports-et-syntheses/Maladies-infectieuses/2013/Surveillance-des-infections-nosocomiales-en-reanimation-adulte2). On the opposite, the reduction in AIs due to resistant AGNB was substantial in our study, reaching a ten-fold reduction in 2012 compared with the pre-intervention period.

CONCLUSION

The targeted use of a multiple decontamination regimen with polymyxin/tobramycin/amphotericin B plus mupirocin/chlorhexidine in intubated patients did not favor the emergence of multidrug-resistant bacteria infections in our ICU with a low-to-intermediate level of antimicrobial resistance. On the contrary, a gradual decrease in antimicrobial-resistant AGNB infections and colonization with ESBL-producing Enterobacteriaceae and the reduction in the use of key antibiotics for the treatment of acquired infections have been recorded over five years. Surveillance of antimicrobial resistance remains mandatory.

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Table

Table 1. Report of bacteremias at the Rennes University Hospital and resistance rate for the microorganisms under surveillance, 2008-2012.

	2008			2009			2010			2011			2012		
	Total reported	ICU	non ICU	Total reported	ICU	non ICU	Total reported	ICU	non ICU	Total reported	ICU	non ICU	Total reported	ICU	non ICU
S. aureus – no.	200	50	150	191	50	141	152	29	123	183	42	141	251	55	196
MRSA – no. (%)	40 (20)	7 (14)	33 (22)	39 (20)	9 (18)	30 (21)	32 (21)	7 (24)	25 (20)	47 (26)	5 (12)	42 (30)	61 (24)	8 (15)	53 (27)
Enterococci – no.	60	10	50	54	16	38	77	12	65	71	9	62	88	13	65
VRE – no. (%)	0			0			3 (4)	0	3 (5)	2 (3)	1 (11)	1 (2)	1 (1)	1 (8)	0
Pseudomonas aeruginosa – no.	46	7	39	43	18	25	39	14	25	49	15	34	52	11	41
Ceftazidime resistant – no (%)	2 (4)	1 (14)	1 (3)	2 (5)	1 (6)	1 (4)	1 (3)	0	1 (4)	1 (2)	1 (7)	0	4 (8)	2 (18)	2 (5)
Enterobacteriaceae – no.	422	49	373	416	69	347	444	42	402	481	52	429	460	51	409
ESBL – no. (%)	16 (4)	7 (14)	9 (3)	25 (6)	10 (14)	15 (4)	24 (5)	6 (14)	18 (4)	39 (8)	11 (21)	28 (7)	36 (8)	9 (18)	27 (7)

Table

Table 2. Prevalence of antimicrobial-resistant aerobic Gram negative bacilli at admission based on clinical cultures, per 100 admissions.

	Pre-intervention	Study period									
	N=925	S1 N=527	S2 N=509	S3 N=480	S4 N=542	S5 N=537	S6 N=546	S7 N=597	S8 N=501	S9 N=508	S10 N=503	P-value for trend
Specific antimicrobial-resistance												
Ceftazidime	1.3	1.3	1.8	2.1	2.0	2.4	0.9	1.3	1.6	1.8	1.8	0.85
Imipenem	1.2	0.6	1.2	1.5	0.2	0.6	0.2	1.2	0.2	0.6	1.0	0.61
Ciprofloxacin	1.5	1.5	1.4	2.7	1.5	2.0	1.1	1.7	2.0	1.4	1.4	0.65
Gentamicin	1.4	0.9	1.0	1.5	1.1	1.9	0.5	2.2	1.4	1.0	1.4	0.50
Tobramycin	1.6	1.3	1.0	2.1	1.3	2.0	0.5	2.3	1.6	0.8	1.2	0.78
Amikacin	1.0	0.6	0.4	0.8	0.4	0.2	0.2	0.7	0.2	0.4	0.2	0.30
Colistin	0.4	0.9	1.4	0.2	0.6	0.7	1.3	0.8	0.6	1.2	0.2	0.51
Multidrug resistance	1.2	1.1	1.6	1.7	1.3	1.1	0.5	1.2	0.7	1.0	1.6	0.47
ESBL	0.1	0.8	0.2	0.4	0.7	0.6	0.2	0.3	0.4	0.4	0.4	0.48

Note. S1, S2, ….., S10 denote semesters 1 to 10. N is the number of admissions for the corresponding time period. ESBL: extended spectrum beta-lactamase.

Table

Table 3. Trends in incidence rates of acquired infections involving resistant organisms and of acquired episodes of rectal colonization with ESBL-producing* aerobic Gram-negative bacilli.

Variables	OR	95% confidence interval	P-value
Acquired infection caused by multidrug-resistant AGNB**	0.85[§]	0.77–0.9	<0.001
Acquired infection caused by			
Enterobacteriaceae			
Resistant to ceftazidime	0.85	0.76–0.95	0.004
Resistant to imipenem	0.65	0.40–1.07	0.09
Resistant to ciprofloxacin	0.81	0.72–0.90	< 0.001
Resistant to gentamicin	0.86	0.77–0.96	0.008
Resistant to tobramycin	0.84	0.77–0.93	0.001
Resistant to amikacin resistant	0.86	0.73–1.00	0.05
Resistant to colistin	0.88	0.79–0.98	0.02
ESBL-producing	0.82	0.66–1.02	0.08
Pseudomonas aeruginosa			
Resistant to ceftazidime	0.91	0.71–1.17	0.47
Resistant to imipenem	0.84	0.74–0.95	0.005
Resistant to ciprofloxacin	0.87	0.76–1.01	0.07
Resistant to gentamicin	0.89	0.79–1.01	0.07
Resistant to tobramycin	0.85	0.73–0.99	0.03
Resistant to amikacin	0.97	0.69–1.37	0.86
Resistant to colistin	0.82	0.39–1.74	0.61
Irrespective of antimicrobial resistance	0.91	0.84–0.98	0.02
Other glucose-nonfermenting AGNB			
Resistant to ceftazidime	1.02	0.85–1.24	0.81
Resistant to imipenem	0.98	0.82–1.16	0.80
Resistant to ciprofloxacin	0.81	0.63–1.04	0.11
Resistant to gentamicin	0.92	0.77–1.11	0.41
Resistant to tobramycin	0.97	0.80–1.16	0.71
Resistant to amikacin	0.94	0.78–1.14	0.54
Resistant to colistin	0.94	0.63–1.40	0.77
AGNB resistant to both colistin and tobramycin	0.84	0.74–0.96	0.009
Acquired colonization with ESBL-producing AGNB	0.94	0.88–1.00	0.04

* ESBL: extended-spectrum β-lactamase. **AGNB: aerobic Gram negative bacilli. [§]Adjusted odds ratio.

Table

Table 4. Number (percent) of patients who acquired rectal colonization with colistin-resistant ESBL-producing aerobic Gram negative bacilli.

1rst semester N=527	2nd semester N=509	3rd semester N=480	4th semester N=542	5th semester N=567	6th semester N=546	7th semester N=597	8th semester N=501	9th semester N=508	10th semester N=503
Number with ICU-attributable colonization episodes									
3 (0.6)	4 (0.8)	1 (0.2)	6 (1.1)	4 (0.7)	0	1 (0.2)	1 (0.2)	0	2 (0.4)
Number with positive rectal colonization at ICU discharge									
2 (0.4)	2 (0.4)	1 (0.2)	2 (0.4)	2 (0.4)	0	1 (0.2)	0	0	0

Table

Table 5. Trends in incidence rates of total acquired infections.

Variables	OR	95% confidence interval	P-value
Acquired infection (any bacterial or fungal)	0.93*	[0.90–0.97]	p = 0.0003
Acquired infection caused by aerobic Gram negative bacilli (any species)	0.92	[0.87–0.96]	p = 0.0005
Acquired infection caused by Gram positive cocci			
Methicillin resistant *Staphylococcus aureus*	0.99	[0.83–1.17]	p = 0.8666
Coagulase negative staphylococcus	0.99	[0.86–1.13]	p = 0.8678
Methicillin susceptible *Staphylococcus aureus*	1.19	[0.92–1.54]	p = 0.1854
Enterococcus	0.95	[0.85–1.05]	p = 0.3135
Gram positive cocci (any species)	0.96	[0.89–1.02]	p = 0.1955
Acquired fungal infection (*Aspergillus*/*Candida*)	1.02	[0.89–1.17]	p = 0.7485

* Adjusted odds ratio.

Figure 1

Figure 1. Incidence rate of acquired infections involving multidrug-resistant Gram-negative bacilli

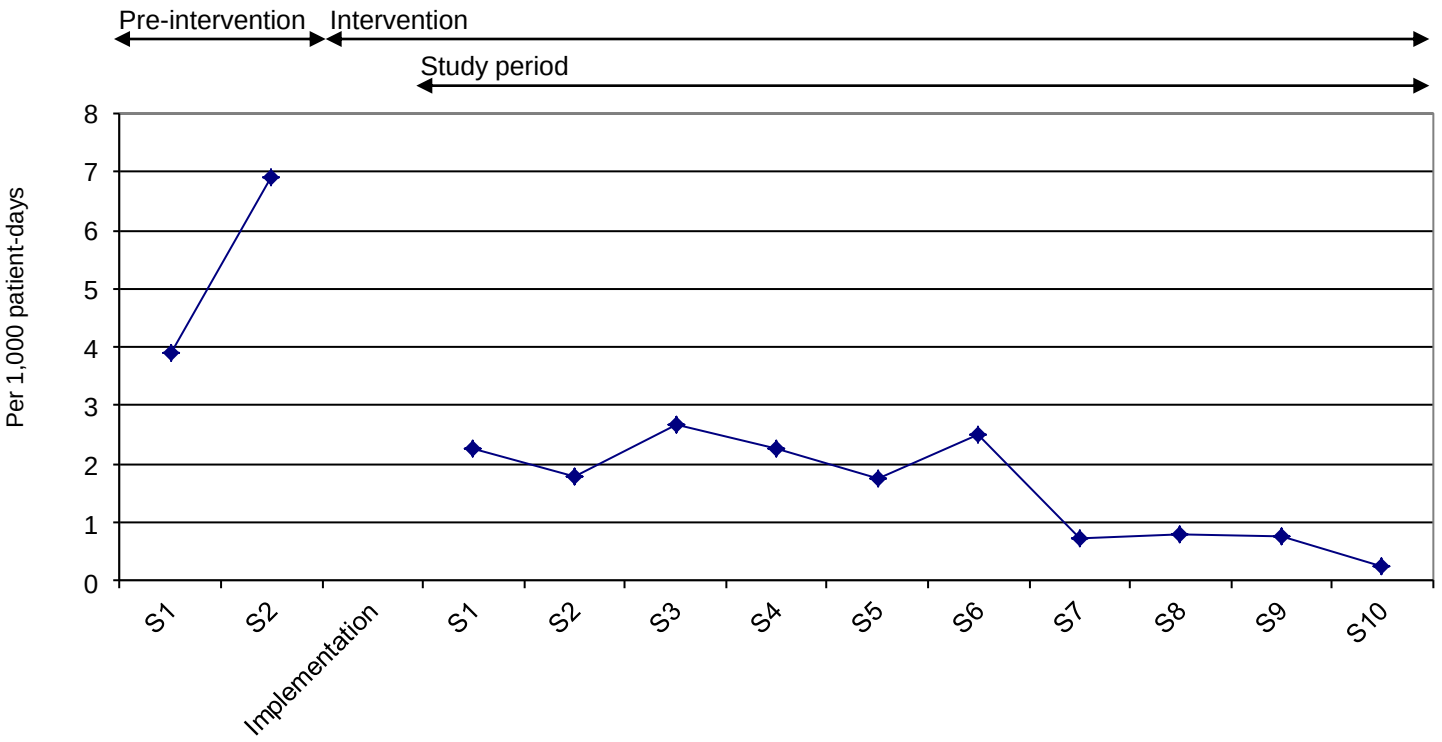
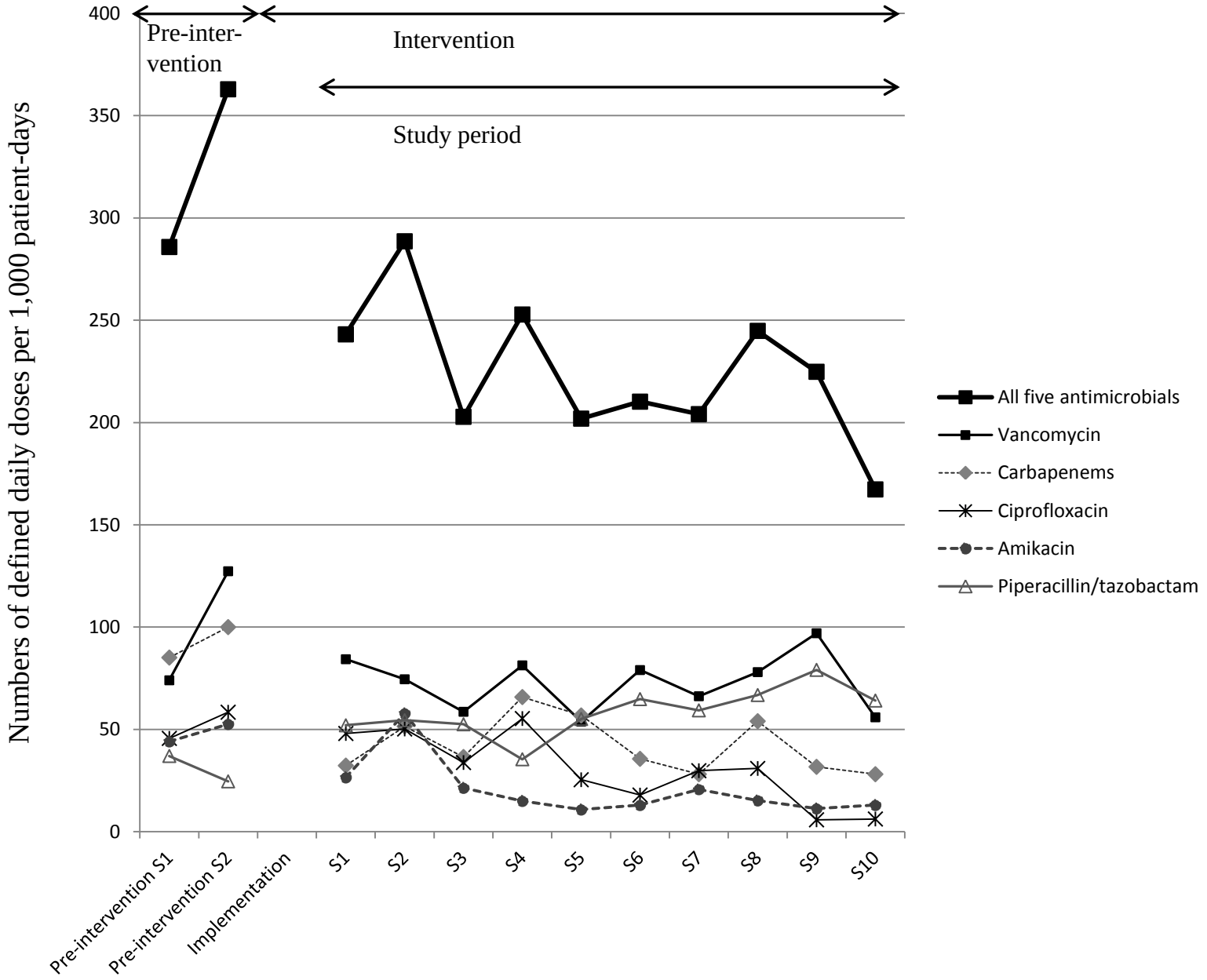


Figure 2

Figure 2. Use of broad spectrum antimicrobials



Legends of figures.

Legend of Figure 1

The two pre-intervention semesters represented group A in a previous study (9). The implementation period was from June to December 2007. S1, S2,… to S10 denote 1st semester, 2nd semester, … to 10th semester.

Legend of Figure 2.

S1, S2,…,S10 denote 1st semester, 2nd semester,…, 10th semester.