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Impact of a multimodal strategy combining a new standard of care and restriction of carbapenems, fluoroquinolones and cephalosporins on antibiotic consumption and resistance of *Pseudomonas aeruginosa* in a French intensive care unit

Salam Abbara[a], Aurélia Pitsch[b], Sébastien Jochmans[a], Kyann Hodjat[a], Pascale Cherrier[c], Mehran Monchi[a], Christophe Vinsonneau[a,d], Sylvain Diamantis[e,*]

[a] *Service de réanimation, Centre hospitalier Sud Ile-de-France, 77000 Melun, France*
[b] *Laboratoire de microbiologie, Centre hospitalier Sud Ile-de-France, 77000 Melun, France*
[c] *Pharmacie Hospitalière, Centre hospitalier Sud Ile-de-France, 77000 Melun, France*
[d] *Service de réanimation, Centre hospitalier de Béthune, 62660 Beuvry, France*
[e] *Service de maladies infectieuses, Centre hospitalier Sud Ile-de-France, 2 rue Freteau de Peny, 77000 Melun, France*

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ABSTRACT

This study aimed to assess whether post-prescription review and feedback (PPRF) of all antibiotics, with restriction of carbapenems, fluoroquinolones and third-generation cephalosporins (3GCs), along with a change in medical standard of care impacted antibiotic consumption and bacterial antimicrobial resistance in a French medical/surgical intensive care unit (ICU). A 4-year before (2007–2010) and after (2011–2014) retrospective comparative study was performed. Antibiotic consumption was evaluated in defined daily doses per 1000 patient-days. The rates of *Pseudomonas aeruginosa* resistance to piperacillin, ceftazidime, ciprofloxacin, imipenem and amikacin and of AmpC-hyperproducing group 3 Enterobacteriaceae were assessed. Consumption of fluoroquinolones decreased by −85%, carbapenems by −58%, 3GCs by −50% and glycopeptides by −66% ($P \leq 0.0001$). Consumption of penicillins with and without β-lactamase inhibitors increased by +72% and +78%, sulfonamides by +172% and macrolides by +267% ($P < 0.0001$). *Pseudomonas aeruginosa* resistance rates for all antibiotics tested and the proportion of AmpC-hyperproducing group 3 Enterobacteriaceae decreased ($P \leq 0.01$). The median length of stay, use of vasopressors and invasive mechanical ventilation decreased, and the use of renal replacement therapy increased ($P < 0.05$). The initial severity score (SAPS II) increased ($P < 0.01$) due to changes in practice, with no impact on in-hospital mortality ($P = 0.07$). In conclusion, changes in medical care along with PPRF and a restriction of high ecological impact antibiotics were associated with a shift towards the consumption of low ecological impact antibiotics in an ICU. Rates of resistant *P. aeruginosa* and of AmpC-hyperproducing group 3 Enterobacteriaceae decreased simultaneously.

1. Introduction

Antimicrobial-resistant bacteria cause hospital epidemics and are associated with therapeutic failures and increased morbidity and mortality [1,2]. Controlling the consumption of antibiotics is a critical point since the link between antibiotic use and the emergence of antimicrobial resistance has been well established, particularly in intensive care units (ICUs) where broad-spectrum antibiotics are frequently prescribed [3,4]. In particular, quinolones, cephalosporins and carbapenems are believed to have a high 'ecologic impact' by favouring the selection of drug-resistant bacteria, both to the antibiotic used and to other classes of antibiotics, as well as colonisation by drug-resistant organisms [5,6]. Little has been published regarding the impact of antimicrobial stewardship (AMS) in ICUs in a real-life setting [7–11]. In 2015, the French Intensive Care Society (FICS) and the French Society of Anesthesia and Intensive Care Medicine (SFAR) published guidelines to reduce curative antibiotic therapy in ICUs in the fight against antimicrobial resistance [12]. Since 2010, the medical surgical intensive care unit (MSICU) of a hospital in Melun, France, implemented a multimodal AMS programme relying on post-prescription review and feedback (PPRF) of all antibiotic prescriptions and applying

* Corresponding author. Tel.: +33 1 64 71 60 42; fax: +33 1 64 71 63 76.
E-mail address: sylvain.diamantis@ch-melun.fr (S. Diamantis).

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Table 1
Antimicrobial stewardship: weekly meeting with post-prescription review and feedback (PPRF) of antibiotic prescriptions.

- Weekly meeting with an infectious diseases specialist and microbiologist
- All patients from the MSICU were reviewed for:
  detailed microbiological results;
  need for antimicrobial treatment;
  choice of empirical and adapted treatment;
  timing and nature of de-escalation;
  duration of treatment;
  choice of laboratory examinations

MSICU, medical/surgical intensive care unit.

local guidelines restricting the use of carbapenems, third-generation cephalosporins (3GCs) and fluoroquinolones. Along with this AMS programme, a new standard of care was introduced. This study assessed the impact of this intervention on antibiotic consumption and the susceptibility rates and patterns of *Pseudomonas aeruginosa* and AmpC-hyperproducing group 3 Enterobacteriaceae isolates.

2. Materials and methods

2.1. Design and setting

This study retrospectively analysed data before and after the intervention, with a 4-year before period (2007–2010) and a 4-year after period (2011–2014). The intervention was implemented in a single centre in the hospital of Melun, France, a 350-bed tertiary-care hospital. The MSICU consists of 16 beds in an ICU and 8 beds in a continuing care unit.

2.2. Intervention

Since 2010, a multimodal AMS programme relying on PPRF of all antibiotic prescriptions as well as restriction of 3GCs, carbapenems and fluoroquinolones was implemented, along with a new standard of care including protocol-based sedation, favouring non-invasive ventilation over invasive ventilation whenever possible, and an improved ventilation weaning process in mechanical ventilation.

The multimodal AMS programme relied on the interaction of an infectious diseases (ID) specialist and a microbiologist through three interventions: (i) establishment of local guidelines for the use of antibiotics; (ii) a weekly meeting to review the diagnosis and antimicrobial strategy for all patients in the MSICU; and (iii) additional bedside advice for some patients. The detailed local guidelines and the content of the weekly meeting are described in Tables 1 and 2. Adapted treatment favoured penicillins, sulfonamides and macrolides over other possibilities because of an expected lower impact on the emergence of antimicrobial resistance [6,13]. De-escalation was defined as a reduction in the antimicrobial spectrum of the antibiotics prescribed and/or the impact of the antibiotics prescribed on the emergence of resistance in the microbiota, and/or a switch from bitherapy to monotherapy [13].

2.3. Outcomes

The primary outcomes were: (i) the change in consumption of antibiotics, expressed in defined daily doses per 1000 patient-days (DDD/1000PD) between the before and after period; and (ii) the change in the patterns of resistance of *P. aeruginosa* and group 3 Enterobacteriaceae isolates, expressed as the number of resistant isolates for a specific antibiotic out of the total number of isolates, between the before and after period.

2.4. Data collection

Identification of micro-organisms was performed using standard methods. Antimicrobial susceptibility testing was performed by the disk diffusion method according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [14]. Susceptibility rates to piperacillin, ceftazidime, ciprofloxacin, imipenem and amikacin of all isolated *P. aeruginosa* from any site in patients in the ICU were evaluated. The susceptibility rate to norfloxacin and the rate of AmpC-hyperproducing group 3 Enterobacteriaceae from any site in patients in the ICU were also assessed. Group 3 Enterobacteriaceae included the following Enterobacteriaceae with an inducible chromosomal AmpC: *Enterobacter* spp.; *Serratia* spp.; *Hafnia alvei; Morganella morganii; Providencia stuartii*; and *Citrobacter freundii* [14]. An isolate was considered in vitro as hyperproducing an AmpC β-lactamase if it displayed all of the following criteria: (i) resistance to 3GCs; (ii) no synergy between any 3GCs and clavulanic acid; and (iii) restoration of susceptibility to 3GCs on Mueller–Hinton agar with 250 mg/L cloxacillin compared with Mueller–Hinton agar without cloxacillin [15]. Duplicate isolates were excluded from the analysis, defined as isolates from the same patient and of the same species with a similar susceptibility pattern for all antibiotics from the standard list defined by EUCAST for the species. The overall incidences of *P. aeruginosa* and group 3 Enterobacteriaceae isolates were also assessed per period and per 1000 patient-days.

All antibiotic consumption in the MSICU and in the hospital medical ward were recorded in DDD/1000PD. For better data visualisation, penicillin consumption was artificially presented divided by 6 in Fig. 1.

Medical data were collected for all patients by screening the medical reports and/or the 'Programme de Médicalisation des Systèmes d'Information' (PMSI) database. The PMSI is a computerised medical data recording system set by the French Ministry of Health to evaluate medical and cost efficiency [16]. The following information was recorded: age; sex; medical and surgical history; Simplified Acute Physiology Score (SAPS) II; ICU and in-hospital mortality and length of stay; use of catecholamines; need for invasive mechanical ventilation; and need for renal replacement therapy (RRT). The duration of treatment was not collected.

2.5. Statistical analysis

Data were expressed as the median (interquartile range) for continuous variables and as the number (%) for categorical variables. Comparisons were performed by Mann–Whitney test or Kruskal–Wallis test for continuous variables and by χ^2 test or Fisher's exact test for categorical variables, as appropriate. All *P*-values were two-sided, and a *P*-value of <0.05 was considered statistically significant. Parameters tested in the univariate analysis were: age, medical and surgical history; ICU and in-hospital mortality; ICU length of stay; use of catecholamines; need for invasive mechanical ventilation; invasive mechanical ventilation with a positive end-expiratory pressure (PEEP) >6 mmHg or/and an inspiratory oxygen fraction $>60\%$; after period; invasive central venous catheter; RRT for acute renal failure; and infection with *P. aeruginosa* whatever the site of infection. Variables with a *P*-value of <0.157 in the univariate analysis were included in the multivariate analysis, which was performed using multinomial logistic regression. Statistical analyses were carried out using the software Epi Info 7.1 [US Centers for Disease Control and Prevention (CDC), Atlanta, GA] and IBM SPSS Statistics v.20 (IBM Corp., Armonk, NY).

Table 2
Antimicrobial stewardship: local guidelines.

Systematic microbiological sampling prior to initiation of empirical antibiotherapy.
Selection of empirical antibiotherapy according to local bacterial epidemiology and patient's colonisation status.
Tracking of microbiological samples by the medical team of the ICU.
Fast reporting of positive results, including the pattern of resistance of the pathogen, to the medical team by the microbiologist.
Determination of the MIC to antibiotics, if needed.
Carbapenems used in empirical treatment only when the patient had septic shock plus either proof of urinary tract carriage of ESBL-producing micro-organisms in the last 6 months or a history of urinary tract infection with ESBL producing micro-organisms in the last 6 months.
Fluoroquinolones restricted to documented infections only, mainly osteoarticular infections.
Empirical treatment of pulmonary infections in the case of septic shock included a macrolide and a β-lactam with a β-lactamase inhibitor, or piperacillin/tazobactam if *Pseudomonas aeruginosa* was suspected.
Third-generation cephalosporins were restricted as empirical treatment for urinary tract infections in men.
Adapted treatment favoured penicillins, sulfonamides and macrolides over other possibilities.
De-escalation whenever the clinical condition of the patient and microbiological results allowed it.
Duration of antibiotherapy was shortened, following similar rules as later described by Brettonières et al. [12]

ICU, intensive care unit; MIC, minimum inhibitory concentration; ESBL, extended-spectrum β-lactamase.

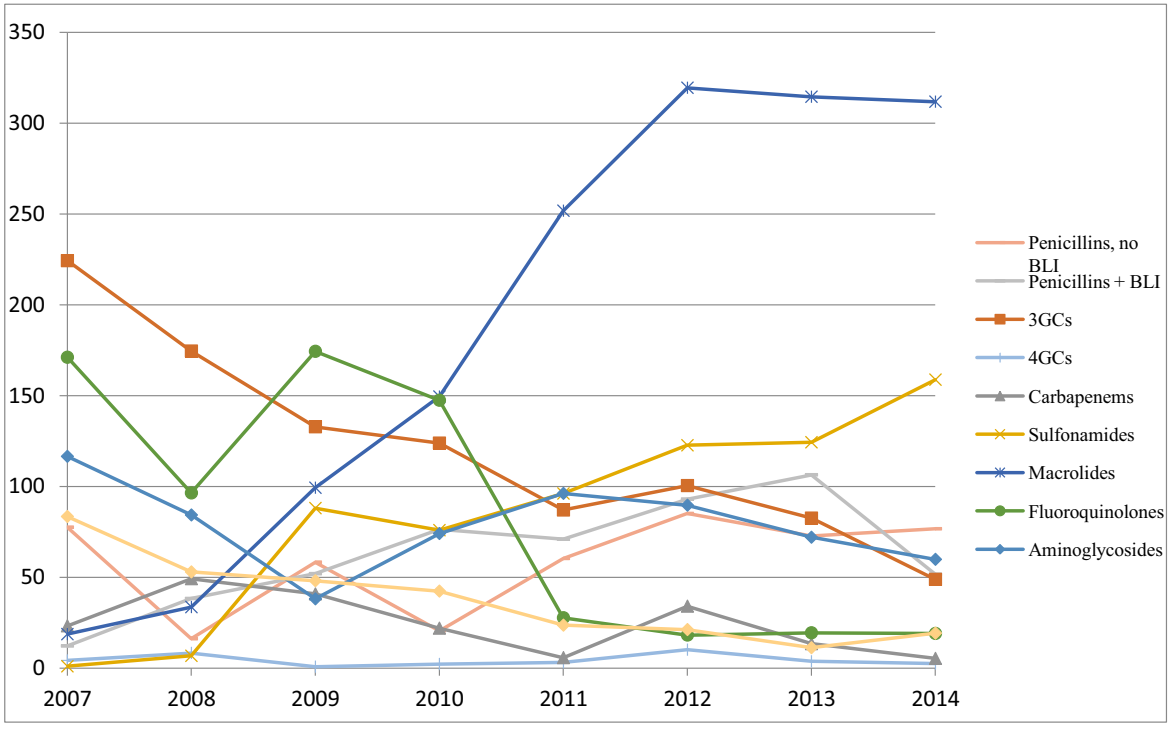

Fig. 1. Evolution of total consumption of different classes of antibiotics as a function of the year. The results are expressed in defined daily doses (DDD) per 1000 patient-days. Standard DDD are presented for all antibiotics, except for penicillins for which DDD divided by 6 are presented. BLI, β-lactamase inhibitor.

3. Results

The clinical and microbiological characteristics of all patients are presented in Table 3. The number of patients admitted increased by 81% during the second period ($P < 0.01$). The percentage male and the percentage of admission for a medical purpose increased in the second period ($P < 0.01$). The median ICU length of stay decreased from 9.9 days to 5.4 days ($P < 0.01$). Use of vasopressors and invasive mechanical ventilation decreased ($P < 0.01$) and use of RRT increased ($P < 0.01$). Whilst the median SAPS II at admission and the mean predictive mortality at admission (calculated on SAPS II) increased between both periods ($P < 0.01$), with an impact on in-ICU mortality (+2.2%; $P = 0.04$), the overall in-hospital mortality did not differ significantly ($P = 0.07$).

Mean annual antibiotic consumption in the ICU increased from 1218 DDD/1000PD to 1637 DDD/1000PD between the two periods (Table 4; Fig. 1). Mean consumption of the following antibiotics decreased: fluoroquinolones, –85%; carbapenems, –58%; 3GCs, –50%; and glycopeptides, –66% (all $P < 0.0001$). In contrast, there was an increase in mean consumption of penicillins with and without β-lactamase inhibitors by +72% and +78%, sulfonamides by +172% and macrolides by +267% (all $P \leq 0.0001$). These evolutions contrast with those in the hospital medical ward where statistical differences concerned only penicillins with and without β-lactamases inhibitors, sulfonamides and fluoroquinolones (Table 5).

Results of the multivariate analyses showing the parameters independently associated with in-hospital mortality, isolation of an AmpC-hyperproducing group 3 Enterobacteriaceae and isolation of a *P. aeruginosa* with resistance to ciprofloxacin are presented in Tables 6 and 7.

4. Discussion

This study, over an 8-year period and in a real-life setting, analysed the impact on antibiotic consumption of an intervention including systematic PPRF of all antibiotic prescriptions, local prescription guidelines restricting the use of high ecological impact antibiotics, along with an improvement of medical care resulting among others in a decrease of median ICU length of stay by approximately one-half and a decrease in invasive

Table 3
Clinical and microbiological characteristics of patients in the before (2007–2010) and after (2011–2014) periods in the medical/surgical intensive care unit (ICU).

Characteristic	All patients ($n = 5442$)	Before period ($n = 1939$)	After period ($n = 3503$)	*P*-value
Age (years) [median (IQR)]	65 (51–78)	66 (51–79)	65 (51.5–78.5)	0.0628
Male sex [*n* (%)]	3103 (57.0)	1054 (54.4)	2049 (58.5)	0.0032
Medical admission [*n* (%)]	3899 (71.6)	1089 (56.2)	2810 (80.2)	<0.0001
ICU length of stay (days) [median (IQR)]	6.2 (5.9–12.3)	9.9 (8.9–12.1)	5.4 (5–6.1)	<0.0001
RRT [*n* (%)]	693 (12.7)	174 (9.0)	519 (14.8)	<0.0001
Invasive mechanical ventilation [*n* (%)]	2449 (45.0)	984 (50.7)	1465 (41.8)	<0.0001
Use of vasopressors [*n* (%)]	2039 (37.5)	782 (40.3)	1257 (35.9)	0.0012
SAPS II score at ICU admission [median (IQR)]	37 (26–51)	35 (25–49)	37 (27–52)	<0.0001
Overall in-ICU mortality [*n* (%)]	919 (16.9)	300 (15.5)	619 (17.7)	0.0381
Mean predictive mortality (SAPS II at admission) (%)		15.3	19.6	<0.0001
Observed to predicted mortality rate		1.27	1.1	
Overall in-hospital mortality [*n* (%)]	1130 (20.8)	377 (19.4)	753 (21.5)	0.0738
Incidence of *Pseudomonas aeruginosa* (per 1000 PD)	5.87	5.81	6.28	0.3590
Incidence of group 3 Enterobacteriaceae (per 1000 PD)	4.23	2.84	5.37	1

IQR, interquartile range; RRT, renal replacement therapy; SAPS, Simplified Acute Physiology Score; PD, patient-days.

Table 4
Mean consumption of antibiotics during the before (2007–2010) and after (2011–2014) periods in the medical surgical intensive care unit[a].

Antibiotic	Before period	After period	Trend in the after period	*P*-value
Penicillins without β-lactamase inhibitor	247.40	439.89	+77.81%	<0.0001
Penicillins with β-lactamase inhibitor	280.38	482.97	+72.26%	0.0001
Third-generation cephalosporins	160.22	80.24	–49.92%	<0.0001
Fourth-generation cephalosporins	3.88	4.87	+25.49%	1
Carbapenems	34.48	14.49	–57.99%	0.0001
Sulfonamides	45.70	124.40	+172.21%	<0.0001
Macrolides	78.88	289.18	+266.62%	<0.0001
Fluoroquinolones	146.06	21.37	–85.37%	<0.0001
Aminoglycosides	75.91	80.16	+5.60%	0.1203
Glycopeptides	55.16	19.01	–65.53%	<0.0001
Total	1218.13	1637.38	+34.42%	–

[a] Results are expressed in defined daily doses (DDD) per 1000 patient-days. Standard DDD are presented for all antibiotics.

Table 5
Mean consumption of antibiotics during the before (2007–2010) and after (2011–2014) periods in the hospital medical ward[a].

Antibiotic	Before period	After period	*P*-value
Penicillins without β-lactamase inhibitor	79.91	199.59	<0.0001
Penicillins with β-lactamase inhibitor	271.89	295.33	0.0027
Third-generation cephalosporins	39.12	61.46	0.3574
Fourth-generation cephalosporins	0.21	4.88	0.0734
Carbapenems	1.02	3.11	0.6379
Sulfonamides	8.59	23.93	0.0494
Macrolides	29.30	53.29	0.14
Fluoroquinolones	88.49	23.19	<0.0001
Aminoglycosides	12.53	13.42	0.6024
Glycopeptides	3.26	6.30	0.7396
Total	1218.13	1637.38	–

[a] Results are expressed in defined daily doses (DDD) per 1000 patient-days. Standard DDD are presented for all antibiotics.

Table 6
Multivariate analysis of risk factors associated with in-hospital mortality.

Characteristic	*P*-value	OR (95% CI)
Age	<0.0001	1.03 (1.03–1.03)
Medical admission		
ICU length of stay	<0.0001	0.86 (0.86–0.86)
In-hospital length of stay		
RRT for ARF	<0.0001	2.26 (2.25–2.28)
Invasive mechanical ventilation		
Invasive mechanical ventilation with a PEEP > 6 mmHg or/and an inspiratory oxygen fraction >60%	<0.0001	1.90 (1.90–1.91)
Use of vasopressors	<0.0001	3.45 (3.43–3.47)
Invasive central venous catheter		
Infection with *Pseudomonas aeruginosa*	<0.0001	3.17 (3.13–3.21)
Overall in-ICU mortality		
After period	0.070	1.00 (0.99–1.00)

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; RRT, renal replacement therapy; ARF, acute renal failure; PEEP, positive end-expiratory pressure.

Table 7
Multivariate analysis of risk factors associated with isolation of a fluoroquinolone-resistant (FQ-R) *Pseudomonas aeruginosa* isolate (resistant to ciprofloxacin) and pf AmpC-hyperproducing group 3 Enterobacteriaceae (G3E AmpC).

	G3E AmpC		FQ-R *P. aeruginosa*	
	P-value	OR (95% CI)	*P*-value	OR (95% CI)
Age			0.731	1.00 (0.98–1.01)
Medical admission				
ICU length of stay			0.008	0.96 (0.93–0.99)
In-hospital length of stay	0.393	0.99 (0.98–1.01)	<0.0001	1.01 (1.01–1.02)
RRT for ARF	0.241	1.85 (0.66–5.16)	0.826	1.11 (0.44–2.79)
Invasive mechanical ventilation			0.029	1.95 (1.07–3.55)
Invasive mechanical ventilation with a PEEP > 6 mmHg or/and an inspiratory oxygen fraction >60%	0.048	2.57 (1.01–6.56)	0.021	2.01 (1.11–3.63)
Use of vasopressors			0.054	1.98 (0.99–3.97)
Invasive central venous catheter	0.442	1.72 (0.43–6.86)	0.023	2.96 (1.16–7.50)
Infection with *P. aeruginosa*				
Overall in-ICU mortality				
Overall in-hospital mortality				
After period	0.036	0.40 (0.17–0.94)	<0.0001	0.27 (0.14–0.53)

OR, odds ratio; CO, confidence interval; ICU, intensive care unit; RRT, renal replacement therapy; ARF, acute renal failure; PEEP, positive end-expiratory pressure.

mechanical ventilation. Altogether, this strategy led to a decrease of >50% in the consumption of carbapenems, fluoroquinolones, glycopeptides and 3GCs. On the other hand, prescription of antibiotics with a lower ecological impact increased, namely penicillins, macrolides and sulfonamides. Macrolides were prescribed instead of fluoroquinolones for pulmonary infections as empirical or adapted treatment, in addition to a β-lactam and a β-lactamase inhibitor. Trimethoprim/sulfamethoxazole (SXT) was prescribed as de-escalation therapy, as an adapted treatment, in lung or urinary tract infections in accordance with the pattern of susceptibility of the isolated bacterium. Although not a traditional common treatment of critically ill patients with lung infection, SXT is being used increasingly as an alternative to glycopeptides in methicillin-resistant *Staphylococcus aureus* (MRSA) infections, even in ventilator-associated pneumonia (VAP) [17]. SXT was used effectively in our patients both for community-acquired pneumonia and VAP as an adapted treatment whenever the isolated bacterium was susceptible.

Due to the real-life design of this study, we were unable to analyse the exact relative role of each parameter from the intervention on the modification of antibiotic use. Indeed, the change in standard of care, particularly the decrease in length of ICU stay and use of invasive mechanical ventilation, could have led to a modification of the epidemiology of infections in the ICU, which could have acted along with the AMS to change the way antibiotics are prescribed. For instance, the decrease in invasive mechanical ventilation use could have decreased the occurrence of VAP, which is a major reason for antibiotic use in ICUs [1]. Comparing the evolution of antibiotic consumption in the ICU and in the hospital medical ward eliminated potential hospital-wide confounders.

This study covered an 8-year period, with the 4-year after period showing long-term compliance of the medical team. Few studies describing the long-term effects of AMS in ICUs have been published so far, especially with restrictive strategies [7–11,18–24]. Rimawi et al. reported a significant reduction in the use of antibiotics, mechanical ventilation days, mean length of stay and hospital mortality following interaction with an ID specialist in an ICU, but the before and after periods only lasted for 3 months [7]. Ntagiopoulos et al. restricted the use of quinolones and ceftazidime in an ICU and showed an overall decrease in antibiotic consumption over 6 months [19]. Sistanizad et al. restricted the use of carbapenems in an ICU and described over 9 months an increase in the susceptibility of *P. aeruginosa* isolates to imipenem [20]. Aubert et al. restricted the use of quinolones in an ICU over 12 months and showed an increase in susceptibility of *P. aeruginosa* to ciprofloxacin and a decrease in the number of cases of VAP due to ciprofloxacin-resistant *P. aeruginosa* [21]. Rahal et al. restricted the use of cephalosporins in a hospital and reported over 12 months a reduction in the incidence of colonisation or infection with ceftazidime-resistant *Klebsiella* in all ICUs. However, the restriction of cephalosporins was accompanied by a doubling in the consumption of imipenem in the medical centre as well as an increase in the incidence of imipenem-resistant *P. aeruginosa* in all ICUs [22]. Gruson et al. restricted the use of ceftazidime and ciprofloxacin for empirical and therapeutic use and performed antibiotic rotation without favouring any use in an ICU [23]. Over 2 years they described a statistical increase in the susceptibility of *P. aeruginosa* isolates to aminoglycosides and cefepime, with a nearly significant value for ciprofloxacin [23]. Brahmi et al. reported the longest follow-up period of 3 years [24]. They applied ceftazidime restriction in favour of piperacillin/tazobactam (TZP) over 3 years in an ICU and described a decrease in the resistance of *P. aeruginosa* isolates to TZP during the 3 years and to imipenem during 1 year. The resistance of *Acinetobacter baumannii* isolates to ceftazidime and imipenem decreased during two years [24].

Table 8
Evolution of the resistance pattern of all *Pseudomonas aeruginosa* isolates in the medical/surgical intensive care unit between the before (2007–2010) and after (2011–2014) periods.

Antibiotic	Antibiotic resistance of *P. aeruginosa* [*n* (%)]		*P*-value
	Before period ($n = 110$)	After period ($n = 119$)	
Piperacillin	44 (40.0)	16 (13.4)	<0.0001
Ceftazidime	39 (35.5)	13 (10.9)	<0.0001
Imipenem	31 (28.2)	8 (6.7)	<0.0001
Ciprofloxacin	66 (60.0)	19 (16.0)	<0.0001
Amikacin	34 (30.9)	1 (0.8)	<0.0001

In the ICU in the current study, resistance of *P. aeruginosa* isolates decreased to all tested antibiotics, including piperacillin, ceftazidime, imipenem, ciprofloxacin and amikacin (Table 8), whilst the incidence density of *P. aeruginosa* isolates did not change. Resistance of group 3 Enterobacteriaceae to norfloxacin and the proportion of AmpC-hyperproducing strains with an overproduced AmpC β-lactamase decreased almost to one-half between the two periods ($P = 0.01$) (Table 9).

Although we could not include antibiotic use in the multivariate analysis, modification in antibiotic consumption likely impacted re-

Table 9
Evolution of the resistance pattern of all group 3 Enterobacteriaceae isolates in the medical/surgical intensive care unit between the before (2007–2010) and after (2011–2014) periods.

Antibiotic	Antibiotic resistance pattern of group 3 Enterobacteriaceae [*n* (%)]		*P*-value
	Before period ($n = 57$)	After period ($n = 108$)	
Resistance to norfloxacin	18 (31.6)	16 (14.8)	0.0114
AmpC hyperproduction	24 (42.1)	25 (23.1)	0.0113

sistance. Many studies have shown a strong correlation between selective antibiotic pressure, especially by carbapenems and fluoroquinolones, and the emergence of resistance among *P. aeruginosa* strains [23–29]. Moreover, a direct link between the use of 3GCs, especially ceftazidime and ceftriaxone, and the selection of AmpC-hyperproducing Enterobacteriaceae has been described previously [6,30].

Multivariate analysis showed that invasive mechanical ventilation was independently associated with the isolation of a ciprofloxacin-resistant *P. aeruginosa* [odds ratio (OR) = 1.95; 95% confidence interval (CI) 1.07–3.55], and that the need for invasive mechanical ventilation (with a PEEP > 6 mmHg or/and an inspiratory oxygen fraction >60%) and the after period were independently associated with the isolation of an AmpC-hyperproducing group 3 Enterobacteriaceae [OR = 2.57 (95% CI 1.01–6.57) and OR = 0.40 (95% CI 0.17–0.94), respectively] (Table 7).

Thus, the decrease in the rate of AmpC-hyperproducing group 3 Enterobacteriaceae (Table 9) and in resistance of *P. aeruginosa* isolates (Table 8) could both be the result of modifications in antibiotic use and a decrease in the use of invasive ventilation in the after period. Less high ecological impact antibiotics, less resistant bacteria and less invasive mechanical ventilation were three factors that probably acted in synergy and had a positive effect on one another to contribute to the results described.

The mean predicted in-hospital mortality estimated using the SAPS II at admission significantly increased in the second period. This suggests an increase in the initial severity of patients at admission, which could partly explain the increase in in-ICU mortality by +2.2% ($P = 0.04$). However, the observed to predicted mortality rate appeared lower (1.27 vs. 1.1) and the final in-hospital mortality did not statistically change between both periods ($P = 0.07$). Multivariate analysis showed that among the parameters independently associated with in-hospital mortality (Table 6) were RRT for acute renal failure (OR = 2.26; 95% CI 2.25–2.28), invasive mechanical ventilation with a PEEP > 6 mmHg or/and an inspiratory oxygen fraction >60% (OR = 1.90; 95% CI 1.90–1.91), catecholamine use (OR = 3.45; 95% CI 3.43–3.47) and in-ICU length of stay (OR = 0.86; 95% CI 0.86–0.86) (Table 6). Because all these parameters decreased in the after period, except for RRT which increased, they could explain why in-hospital mortality did not change while patients' illness severity increased. Because we did not record individual antibiotic consumption for each patient, it was not possible to test this parameter in the multivariate analysis and we could not assert its impact on the prognosis.

These real-life data confirm the long-lasting effectiveness over 4 years of an AMS programme relying on the application of local guidelines to restrict the use of carbapenems, cephalosporins and fluoroquinolones as well as a systematic PPRF of all antibiotic prescriptions with an ID specialist and a microbiologist in a MSICU. Along with the protocolisation of sedation and the ventilation weaning process as well as the decrease in use of vasopressors and invasive mechanical ventilation, these strategies showed a progressive and durable compliance of the medical team. These results suggest that ICU teams would benefit from fighting antimicrobial resistance on three fronts: medical practices, restriction of broad-spectrum antibiotic use through local guidelines, and the establishment of a dynamic and regular collaboration with ID specialists and microbiologists. In the ICU described here, these three factors probably potentialised each other, which led to real changes in antibiotic prescription strategies and in local bacterial epidemiology. Also not shown here, the epidemiology of infections in the ICU was also likely impacted by these strategies. The resulting situation allowed a progressive and durable switch towards the use of antibiotics with less ecological impact. These results also interestingly suggest that macrolide use in the empirical treatment of pulmonary infections instead of fluoroquinolones, and of sulfonamides in the adapted treatment of pulmonary and urinary tract infections, would be safe and effective in ICU patients.

5. Conclusions

A multimodal strategy including PPRF of all antibiotic prescriptions by an ID specialist and microbiologist, restriction of 3GCs, carbapenems and fluoroquinolones, and a new standard of care decreasing the mean length of ICU stay and the use of invasive mechanical ventilation was successfully implemented in a MSICU. All factors acted in synergy and led to a decrease by ≥50% in the consumption of fluoroquinolones, carbapenems, 3GCs and glycopeptides, a decrease in the resistance of *P. aeruginosa* isolates for all antibiotics tested, and a decrease in the rate of AmpC-hyperproducing group 3 Enterobacteriaceae. A progressive and durable switch towards lower ecological impact antibiotics was observed, such as macrolides and sulfonamides, and in-hospital mortality was not affected.

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Competing interests

None declared.

Ethical approval

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