Med Intensiva. 2020;44(7):399–408

medicina intensiva

http://www.medintensiva.org/

ORIGINAL

Changes of resistance rates in *Pseudomonas aeruginosa* strains are unrelated to antimicrobial consumption in ICU populations with invasive device-related infection

F. Álvarez-Lerma[a,b,c,*], P. Olaechea-Astigarraga[d], R. Gimeno[e], M. Catalan[f], X. Nuvials[g], M.P. Gracia-Arnilla[a,c], M. Palomar-Martínez[h], I. Seijas-Betolaza[i], M. Martínez-Alonso[j], ENVIN-HELICS Study Group

[a] *Service of Intensive Care Medicine, Hospital del Mar, Spain*
[b] *Universitat Autònoma de Barcelona, Barcelona, Spain*
[c] *Research Group in Critical Disorders (GREPAC), Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain*
[d] *Service of Intensive Care Medicine, Hospital Galdakao-Usansolo, Bizkaia, Spain*
[e] *Service of Intensive Care Medicine, Hospital Universitario la Fe, Valencia, Spain*
[f] *Service of Intensive Care Medicine, Hospital Universitario 12 de Octubre, Madrid, Spain*
[g] *Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain*
[h] *Intensive Care Unit, Hospital Universitari Arnau de Vilanova, Lleida, Spain*
[i] *Service of Intensive Care Medicine, Hospital de Cruces, Barakaldo, Bizkaia, Spain*
[j] *Unit of Biostatistics, Institut de Recerca Biomèdica de Lleida (IRBLLEIDA) and Department of Basic Medical Sciencies, Universitat de Lleida, Lleida, Spain*

Received 14 June 2019; accepted 22 September 2019

KEYWORDS
Pseudomonas aeruginosa;
Invasive device-related infections (IDRI);
Antibiotic resistance;

Abstract
Objective: To evaluate the relationship between antipseudomonal antibiotic consumption and each individual drug resistance rate in *Pseudomonas aeruginosa* strains causing ICU acquired invasive device-related infections (IDRI).
Design: A post hoc analysis was made of the data collected prospectively from the ENVIN-HELICS registry.
Setting: Intensive Care Units participating in the ENVIN-UCI registry between the years 2007 and 2016 (3-month registry each year).

Abbreviations: CI, confidence interval; CAUTI, catheter-associated urinary tract infection; CRBSI, catheter-related bloodstream infection; DOT, days of treatment; ENVIN, National Study of Surveillance of Nosocomial Infection in Services of Intensive Care Medicine; EUCAST, European Committee on Antimicrobial Susceptibility Testing; GTEIS, Study Group of Infectious Diseases and Sepsis; HELICS, Hospitals in Europe Link for Infection Control through Surveillance; IDRI, invasive device-related infections; ICU, intensive care unit; MRB, multiresistant bacteria; SEMICYUC, Spanish Society of Critical Care Medicine and Coronary Units; VAP, ventilator-associated pneumonia.

* Corresponding author.
E-mail address: Falvarez@parcdesalutmar.cat (F. Álvarez-Lerma).

Critically ill;
ICU;
Antipseudomonal antimicrobials

Patients: Patients admitted for over 24 h.
Main variables: Annual linear and nonlinear trends of resistance rates of *P. aeruginosa* strains identified in IDRI and days of treatment of each antipseudomonal antibiotic family per 1000 occupied ICU bed days (DOT) were calculated.
Results: A total of 15,095 episodes of IDRI were diagnosed in 11,652 patients (6.2% out of a total of 187,100). *Pseudomonas aeruginosa* was identified in 2095 (13.6%) of 15,432 pathogens causing IDRI. Resistance increased significantly over the study period for piperacillin-tazobactam ($P < 0.001$), imipenem ($P = 0.016$), meropenem ($P = 0.004$), ceftazidime ($P = 0.005$) and cefepime ($P = 0.015$), while variations in resistance rates for amikacin, ciprofloxacin, levofloxacin and colistin proved nonsignificant. A significant DOT decrease was observed for aminoglycosides ($P < 0.001$), cephalosporins ($P < 0.001$), quinolones ($P < 0.001$) and carbapenems ($P < 0.001$).
Conclusions: No significant association was observed between consumption of each antipseudomonal antibiotic family and the respective resistance rates for *P. aeruginosa* strains identified in IDRI.

PALABRAS CLAVE
Pseudomonas aeruginosa;
Infecciones relacionadas con dispositivos invasivos;
Resistencia a antibióticos;
Paciente crítico;
Unidad de Cuidados Intensivos;
Antibióticos antipseudomonales

Los cambios en la resistencia de cepas de *Pseudomonas aeruginosa* identificadas en infecciones relacionadas con dispositivos invasores no se relacionan con el consumo de antibióticos en la UCI

Resumen
Objetivo: Evaluar la relación entre el consumo de antibióticos antipseudomonales y la tasa de resistencia de cada fármaco individual en cepas de *Pseudomonas aeruginosa* aisladas en infecciones relacionadas con dispositivos invasivos (IDRI, por sus siglas en inglés) adquiridas en la unidad de cuidados intensivos (UCI).
Diseño: Análisis *post-hoc* de los datos recopilados prospectivamente del registro ENVIN-HELICS.
Ámbito: Las UCI que participaron en el registro ENVIN-UCI entre los años 2007-2016 (registro de 3 meses cada año).
Pacientes: Pacientes ingresados > 24 h.
Variables principales: Se calcularon las tendencias anuales lineales y no lineales de las tasas de resistencia de las cepas de *P. aeruginosa* identificadas en IDRI y los días de tratamiento de cada familia de antibióticos antipseudomonales por 1.000 días de cama ocupada en la UCI (DOT).
Resultados: Se diagnosticaron 15.095 episodios de IDRI en 11.652 pacientes (6,2% de 187.100). Se identificó *P. aeruginosa* en 2.095 (13,6%) de 15.432 patógenos que causaron IDRI. La resistencia aumentó significativamente durante el período de estudio para piperacilina-tazobactam ($p < 0,001$), imipenem ($p = 0,016$), meropenem ($p = 0,004$), ceftazidima ($p = 0,005$) y cefepima ($p = 0,015$), mientras que las variaciones en las tasas de resistencia de amikacina, ciprofloxacina, levofloxacina y colistina no fueron significativas. Se observó una disminución significativa de la DOT para aminoglucósidos ($p < 0,001$), cefalosporinas ($p < 0,001$), quinolonas ($p < 0,001$) y carbapenems ($p < 0,001$).
Conclusiones: No se encontró asociación significativa del consumo de cada familia de antibióticos antipseudomonales con sus respectivas tasas de resistencia para las cepas de *P. aeruginosa* identificadas en IDRI.

Introduction

The relationship between antimicrobial use and increasing emergence of resistance to specific agents or antimicrobial families has been well documented.[1–11] In the ICU setting, other factors unrelated to pressure of antimicrobial use may account for the alarming rate of colonized or infected patients by multiresistant microoganisms (MRB), such as admission of patients already colonized or infected,[12] spread by cross-transmission from MRB carriers,[13] and especially contaminated hospital reservoirs.[14–17]

Pseudomonas aeruginosa is frequently implicated in invasive device-related infection (IDRI) especially in ICUs.[18,19] The increasing resistance to antipseudomonal antimicrobials and the occurrence of epidemic outbreaks of MDR *P. aeruginosa* has become a challenging clinical problem in ICU populations.[12,17]

In Spain, data of IDRI diagnosed in ICU patient are collected since 1994 in the National ICU-Acquired Infection Surveillance Study (ENVIN-HELICS registry) database. Annual reports of the ENVIN-HELICS surveillance program provide detailed information on etiology of IDRI and antimicrobial consumption. The aim of this study was evaluate the relationship between antipseudomonal antibiotic consumption and each individual drug's resistance rate in *P. aeruginosa* strains causing ICU invasive device-related infections (IDRI). It was hypothesized that there was a relationship between ICU consumption of antipseudomonal antimicrobials and development of *P. aeruginosa* resistant strains.

Methods

Design and study population

This was a retrospective analysis of data collected prospectively from the ENVIN-HELICS registry in the framework of an observational, nationwide, multicenter study. The purpose of ENVIN-HELICS database is to register the frequency, etiology, and presence of MRB in ICU patients with IDRI. Invasive device-related infections include ventilator-associated pneumonia (VAP), catheter-associated urinary tract infection (CAUTI) and primary bacteremia including catheter-related bloodstream infection (CRBSI) and bacteremia of unknown origin. Indications and days of treatment of all antimicrobials used during the patients' ICU stay are also registered. All patients admitted for more than 24 h to the participating ICUs during a 3-month period (between April 1st and June 30th) over 10 consecutive years (2007–2016) were included in the study provided that the diagnosis of IDRI related to invasive devices caused by *P. aeruginosa* had been established during the patient's stay in the ICU.

The ENVIN-HELICS registry was developed by the Study Group of Infectious Diseases and Sepsis (GTEIS) of the Spanish Society of Intensive Care Medicine and Coronary Units (SEMICYUC) in 1994. Data from about 200 ICUS (about 80% of the total ICUs in Spain) are collected using the ENVIN-HELICS software application located in a web-based server available at http://hws.vhebron.net/ENVIN-helics.[19] Participation in the registry is voluntary and data collection is longitudinal and prospective. Quality-control audits ensured internal quality of the clinical information recorded in the database.[20]

The ENVIN registry was approved by the Ethics Committees of the participating ICUs and was declared a registry of healthcare interest by the Spanish Ministry of Health, Social Services and Equality in 2014. A consent statement was not applicable due to the non-interventional nature of the study because data were collected from the ENVIN-HELICS registry.

Study variables

Study variables included the annual rate of *P. aeruginosa* resistance to antipseudomonal antibiotics used in ICU patients and days of treatment per 1000 occupied bed-days (DOT), which were calculated for each antipseudomonal agent and antimicrobial families annually as well as in the same year and the previous year for all ICUs that participated in the registry. All *P. aeruginosa* isolates from VAP, CAUTI, and primary bacteremia (bacteremia of unknown origin and/or [CRBSI]) in patients with an established central venous catheter were recorded. Definitions of these infections were those reported in the manual of the ENVIN project following indications published by the European Centre for Disease Control and Prevention.[21,22] Infections associated with invasive devices were diagnosed by attending physicians and recorded in the patient's medical history. Physicians responsible for surveillance of nosocomial infections were intensivists with special interest in infectious diseases.

Susceptibility of *P. aeruginosa* isolates to different antimicrobials was assessed at the Services of Clinical Microbiology of the participating hospitals, in many of them following specifications (method and breakpoints) of the European Committee on Antimicrobial Susceptibility Testing.[23] Antipseudomonal categories and antimicrobials included in each category were as follows: aminoglycosides (amikacin), carbapenems (imipenem and meropenem), cephalosporins (ceftazidime and cefepime), quinolones (levofloxacin and ciprofloxacin), ureidopenicillins (piperacillin-tazobactam), and colistin.

Frequency measures

The resistance rate to each antipseudomonal agent was expressed in percentages and calculated as the number of resistant strains divided by the total number of *P. aeruginosa* strains identified in each annual period for which antimicrobial susceptibility testing against this agent was available, per 100. DOTs were determined for individual agents and for all antimicrobials of each antipseudomonal families (aminoglycosides, carbapenems, cephalosporins, quinolones, and ureidopenicillins).

Statistical analysis

Statistical analyses included estimated annual linear and non-linear trends of resistance rates and DOT per antimicrobial (period 2007 to 2016). Resistance and DOT relationship was adjusted by family of antipseudomonal antimicrobials of the current year (period 2007 to 2016) and by the family DOT of the current and the previous year (period 2008 to 2016). A Poisson regression model was used for adjustment and the 95% confidence intervals (CIs) were calculated. Statistical significance was set at $P < 0.05$. Data were analyzed with the R program.[24]

Results

During the study period, a total 187,100 patients with 1,440,472 patient-days of ICU stay (mean 7.7 days) were included in the ENVIN-HELICS registry. A total of 15,095 episodes of IDRI were diagnosed in 11,652 patients (6.2% of a total of 187,100). *P. aeruginosa* was identified in 2095 (13.6%) of 15,432 pathogens causing IDRI. Table 1 shows the overall number of IDRI caused by *P. aeruginosa* for each study year, as well as the corresponding numbers of VAP, CAUTI,

Table 1 Evolution of *Pseudomonas aeruginosa* strains identified each year in HCAIs related to invasive devices controlled in the ENVIN-HELICS registry.

	Study years										Total
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	
Pathogens isolated in invasive device-associated infections, no.	1625	1805	1633	1589	1601	1430	1351	1491	1369	1538	15,432
P. aeruginosa isolates, no. (%)	217 (13.4)	254 (14.1)	196 (12.0)	209 (13.2)	223 (13.9)	208 (14.6)	196 (14.5)	216 (14.5)	177 (12.9)	199 (12.9)	2095 (13.6)
VAP, no. (%)	146 (67.3)	172 (67.7)	142 (72.4)	139 (66.5)	136 (61.0)	109 (52.4)	104 (53.0)	106 (49.1)	93 (52.5)	112 (56.3)	1259 (60.1)
CAUTI, no. (%)	45 (20.7)	60 (23.6)	41 (20.9)	51 (24.4)	65 (29.1)	74 (35.6)	65 (33.2)	83 (38.4)	63 (35.6)	76 (38.2)	623 (29.7)
Primary bacteremia, no. (%)	26 (12)	22 (8.7)	13 (6.6)	19 (9.1)	22 (9.9)	25 (12.0)	27 (13.8)	27 (12.5)	21 (11.9)	11 (5.5)	213 (10.2)

VAP: ventilator-associated pneumonia; CAUTI: catheter-associated urinary tract infection; no.: number.

and primary bacteremia. *P. aeruginosa* mostly caused VAP, although with a trend to decrease in recent years (from 67.3% in 2007 to 56.3% in 2016), whereas an increase of CAUTI caused by *P. aeruginosa* was observed (from 20.7% in 2007 to 38.2% in 2016).

Resistance rates of *P. aeruginosa* strains to different antipseudomonal antimicrobials during the study period are shown in Fig. 1. There was a progressive increase of resistance to piperacillin-tazobactam (from 18.9% in 2007 to 40.2% in 2016, $P<0.001$), imipenem (from 32.0% to 46.1%, $P=0.016$), meropenem (from 28.2% to 46.5%, $P=0.004$), ceftazidime (from 27.2% to 39.1%, $P=0.005$), cefepime (from 24.2% to 37.2%, $P=0.015$), and to a lower extent for amikacin (from 12.9% to 17.9%, $P=0.084$). Resistance rates to ciprofloxacin (from 35.2% to 35.5%), levofloxacin (from 35.7% to 34.2%), and colistin (from 3.2% to 4.4%) remained stable.

Evolution of consumption of individual antipseudomonal antimicrobials over 10 years is shown in Table 2. Between 2007 and 2016, a significant decrease of DOT for aminoglycosides (from 66.7 to 35.2, $P<0.001$), cephalosporins (from 37.6 to 27.5, $P<0.001$), quinolones (from 127.7 to 87.3, $P<0.001$), and carbapenems (from 150.6 to 138.2, $P<0.001$) was observed. The consumption of ureidopenicillins remained stable (from 116.4 in 2007 to 120.9 in 2016, $P=0.096$). Changes of DOT for each antipseudomonal antibiotic are shown in Fig. 2. There was an important predominance of beta-lactam antibiotic families, with common mechanisms of action and development of resistances.

The adjusted Poisson regression model of the relationship between the resistance rates of *P. aeruginosa* isolates of each antibiotic and the DOT of its antimicrobial family is shown in Table 3. An association between annual resistance rates of *P. aeruginosa* isolates in ICU-acquired IRDI and consumption antipseudomonal antimicrobial families in the current and previous years was not found. The linear trend of the relationship between resistance rate and DOT for individual antipseudomonal agents and for each antimicrobial is shown in Fig. 3. There was a non-significant inverse association of resistance to ceftazidime and cefepime in the DOT (the higher the consumption, the less the resistance) both of the same year and the previous year, whereas resistance to imipenem and levofloxacin showed a non-significant association with DOT of the same year and the previous year (the higher the consumption, the greater the resistance).

Discussion

This study failed to demonstrate a statistically significant relationship between the overall consumption of antipseudomonal antimicrobials in ICU populations, expressed as DOT and resistance of *P. aeruginosa* to individual antimicrobial agent in patients with IDRI related to invasive devices admitted to a large number of Spanish ICUs during a 10-year period. Such negative finding is clinically relevant and in contrast to different studies published in the literature.[1,25–34]

In individual patients, it has been shown that previous exposure to imipenem or fluoroquinolones influences upon the selection of resistant *P. aeruginosa* strains to these agents or the development of multiresistant isolates.[25–31] In

Table 2 Evolution of each antipseudomonal antimicrobial family consumption during the study period (2007–2016) expressed as DOT (days of treatment/days of ICU stay × 1000).

	Study years									
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
ICU stay, days	102,974	107,610	125,804	136,407	142,954	154,625	157,476	162,678	173,949	175,995
Antimicrobials, no./DOT										
Aminoglycosides	6871 66.7	6899 64.1	6766 53.8	6864 50.3	6427 45.0	5842 37.8	5447 34.6	6233 38.3	6295 36.2	6190 35.2
Cephalosporins	3870 37.6	4141 38.5	4552 36.2	4639 34.0	4830 33.8	4574 29.6	3953 25.1	4406 27.1	4093 23.5	4.832 27.5
Quinolones	13,151127.7	12,874119.6	13,867110.2	14,602107.0	15,521108.6	15,253 98.6	15,849100.6	16,084 98.9	16,349 94.0	15,367 87.3
Carbapenems	13,611132.2	16,204150.6	18,718148.8	20,304148.8	22,246155.6	24,175156.3	23,598149.9	23,908147.0	24,204139.1	24,321138.2
Ureidopenicillins	11,988116.4	12,960120.4	15,048119.6	15,358112.6	16,815117.6	18,203117.7	18,757119.1	19,377119.1	20,089115.5	21,271120.9
Polymyxins	2247 21.8	2041 19.0	2452 19.5	2715 19.9	3249 22.7	2846 18.4	2479 15.7	2866 17.6	2307 13.3	2567 14.8

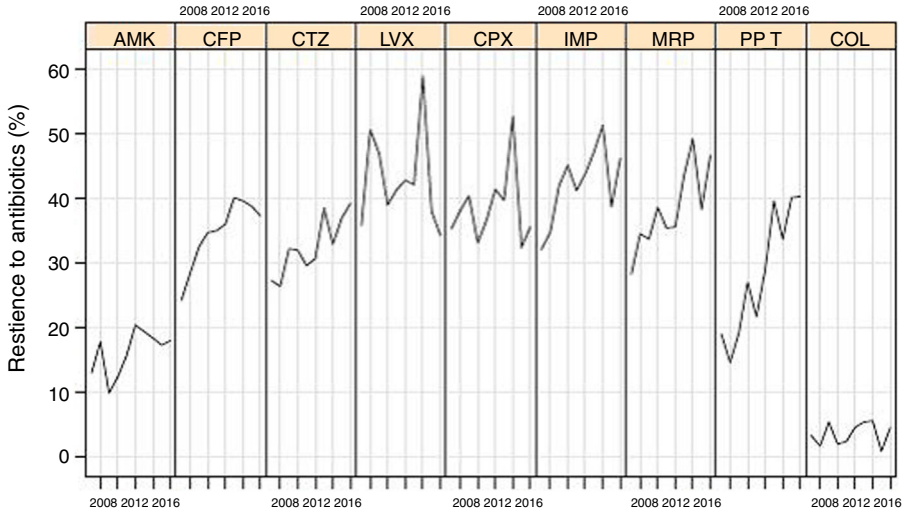

Figure 1 Linear evolution of antipseudomonal antimicrobials resistance rates of *P. aeruginosa* isolated in invasive device-related infections in ICU patients between 2007 and 2016. (AMK: amikacin; CFP: cefepime; CTZ: ceftazidime; LVX: levofloxacin; CPX: ciprofloxacin; IMP: imipenem; MRP: meropenem; PP_T: piperacillin-tazobactam; COL: colistin).

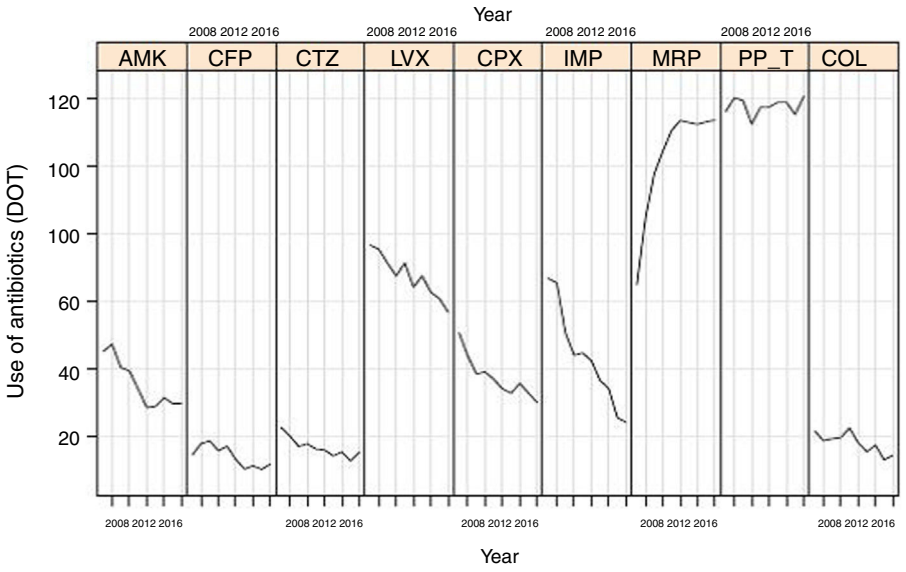

Figure 2 Linear evolution of consumption of antipseudomonal antimicrobials (expressed as DOT) in Spanish ICUs participating in the ENVIN-HELICS registry. (AMK: amikacin; CFP: cefepime; CTZ: ceftazidime; LVX: levofloxacin; CPX: ciprofloxacin; IMP: imipenem; MRP: meropenem; PP_T: piperacillin-tazobactam; COL: colistin).

a national surveillance study of antimicrobial consumption in 203 hospitals from Japan, there was a significant association between consumption of imipenem, meropenem, ciprofloxacin, or amikacin and *P. aeruginosa* resistance to these antimicrobials.[32] Data on antimicrobial usage in Korea from 2002 to 2013 revealed that decreasing consumption of amikacin correlated strongly with a decrease of gentamicin-resistant rates of *P. aeruginosa*.[33] Also, in a tertiary-care hospital in Greenville (North Carolina, USA), introduction of ertapenem and reduction of the use of fluoroquinolones was associated with a significant decrease of *P. aeruginosa* resistant to group 2 carbapenems (imipenem, meropenem, and doripenem).[34] In a recent 2-year prospective study conducted in an ICU of a Romanian university hospital,[35] the incidence of carbapenem-resistant and multiresistant *P. aeruginosa* increased significantly, mirroring the increase in consumption of β-lactam agents with β-lactamase inhibitors (piperacillin-tazobactam) and carbapenems (meropenem). However, cross-correlation coefficients and fitted regression models showed that resistance to antimicrobials during a given quarter depends not only on the consumption of antimicrobials during that quarter, but also on consumption during the previous one combined with the incidence of resistant circulating strains.[35] By contrast, Fihman et al.[36] did not find a correlation between VAP episodes due to *P. aeruginosa* and antimicrobial consumption in the ICU. Our results of *P. aeruginosa* strains isolated in ICU-acquired infections related to the use of invasive

Table 3 Relationship between evolution of annual resistance rates of *P. aeruginosa* isolates in ICU-acquired IDRI and consumption of antipseudomonal antimicrobials family in the current and previous years, expressed as DOT (days of treatment/days of ICU stay × 1000).

Resistance rates of *P. aeruginosa* isolates to each antibiotic in relation to the DOT of its antimicrobial family	Rate	95% confidence interval	*P* value
Amikacin-DOT aminoglycosides, current year	1.0185	0.9747–1.0639	0.4118
Amikacin-DOT aminoglycosides, previous year	0.9770	0.9391–1.0143	0.2164
Cefepime-DOT cephalosporins, current year	0.9804	0.9478–1.0142	0.2513
Cefepime-DOT cephalosporins, previous year	1.0003	0.9685–1.0340	0.9861
Ceftazidime-DOT cephalosporins, current year	0.9837	0.9529–1.0156	0.3119
Ceftazidime-DOT cephalosporins, previous year	0.9945	0.9650–1.0255	0.7204
Levofloxacin-DOT quinolones, current year	1.0082	0.9825–1.0345	0.5334
Levofloxacin-DOT quinolones, previous year	1.0003	0.9774–1.0239	0.9817
Ciprofloxacin-DOT quinolones, current year	1.0009	0.9802–1.0218	0.9360
Ciprofloxacin-DOT quinolones, previous year	0.9994	0.9812–1.0181	0.9492
Imipenem-DOT carbapenems, current year	0.9928	0.9791–1.0069	0.3140
Imipenem-DOT carbapenems, previous year	1.0109	1.000–1.022	0.0541
Meropenem-DOT carbapenems, current year	0.9863	0.9713–1.0015	0.0762
Meropenem-DOT carbapenems, previous year	1.0054	0.9931–1.0183	0.4035
Piperacillin-tazobactam-DOT ureidopenicillins, current year	0.9901	0.9536–1.0288	0.6070
Piperacillin-tazobactam-DOT ureidopenicillins, previous year	1.0152	0.9738–1.0596	0.4834
Colistin-DOT colistin current year	1.0175	0.8829–1.1707	0.8088
Colistin-DOT colistin previous year	0.9450	0.8216–1.0850	0.4223

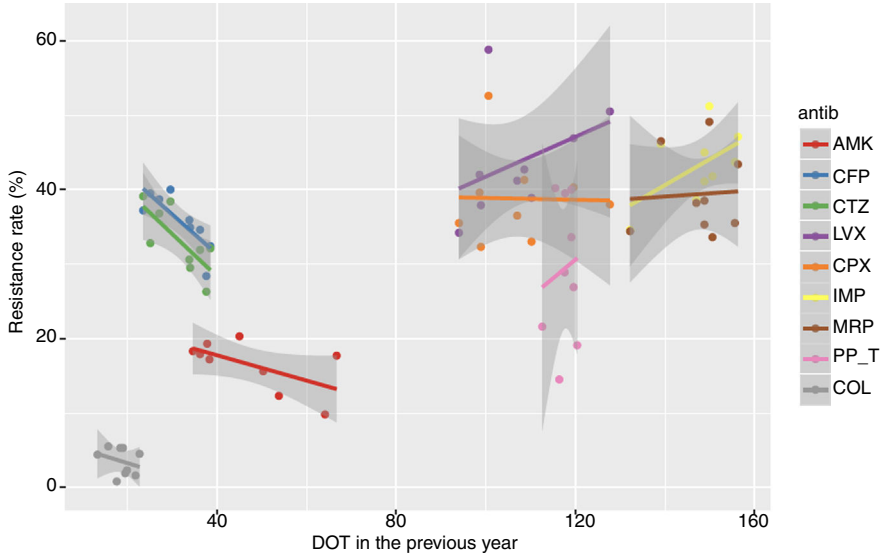

Figure 3 Relationship between resistance rate and DOT of each antipseudomonal antibiotic in the current and the previous year for the period 2008–2016, showing the linear trend for each antibiotic. (AMK: amikacin; CFP: cefepime; CTZ: ceftazidime; LVX: levofloxacin; CPX: ciprofloxacin; IMP: imipenem; MRP: meropenem; PP_T: piperacillin-tazobactam; COL: colistin).

devices and consumption of antipseudomonal agents during the ICU stay are consistent with these data.

To reduce the presence of multiresistant pathogens, national and international organisms have launched campaigns to optimize the use of antimicrobials in all areas (livestock, agriculture, health sciences),[37–39] with emphasis on avoiding the use of antimicrobials in clinical situations where they are not indicated and in reduction of days of treatment.[40] In our country, the ''Resistant Zero'' project developed by the SEMICYUC with the technical support of the Spanish Ministry of Health has been effective to improve antimicrobial use in the ICU setting.[41] Recommendations included designation of at least one intensivist as responsible for the use of antimicrobials in each ICU, prioritizing early antimicrobial discontinuation, and limiting empirical coverage with broad-spectrum agents (piperacillin-tazobactam and carbapenems) to severe infections with systemic response (septic shock or severe sepsis).[41] All these measures have contributed to reduce ICU consumption of most antimicrobial families with

antipseudomonal activity, such as cephalosporins, aminoglycosides, and quinolones except for carbapenems and ureidopenicillins. However, the linear reduction of the use of these antipseudomonal antimicrobials has not been associated with a reduction of the rate of resistance of antipseudomonal antimicrobials in *P. aeruginosa* strains isolated from ICU-acquired infections in the same year or in the previous year. In a previous study of our group based on data of the ENVIN-HELICS registry over the same 10-year period, a progressive increase of multiresistant isolates, particularly of extensively drug- and pandrug-resistant strains was observed.[42] However, in this previous study data on consumption of antipseudomonal antimicrobials was not analyzed.

The presence of MBR strains facilitates the development of a progressively complex endemic flora, which is resistant to common antimicrobial agents and responsible for infections that appear in ICU patients independently of the previously administered antimicrobial treatment. The present findings of a lack of relationship between ICU consumption of antipseudomonal antimicrobials and development of *P. aeruginosa* resistant strains identified in IDRI related to invasive devices may be explained by different arguments. Firstly, admission to the ICU of patients already colonized with multidrug resistant *P. aeruginosa*, a status unknown to the medical personnel. These patients can act as a reservoir from which strains are spread through cross-transmission to patients at risk, sometimes without prior mucosal colonization and without prior use of antipseudomonal antimicrobials.[43,44] It is recommended to perform active search of MBR pathogens in all patients on admission to the ICU and application of contact precautions in patients at high risk of MBR carriage are some of the recommendations included in the ''Resistant Zero'' project applied to Spanish ICUs.[41] Secondly, there are numerous evidences of MBR reservoirs in the ICU environment (mattress, drains, nebulizers, taps and sinks, portable equipments, floors, walls, etc.) that favor rapid colonization of patients and development of invasive device-associated infections. Active search of MBR pathogens in environmental samples (at least once a week), cleaning protocols with daily cleaning and final cleaning at patient discharge, protocolization of cleaning and disinfection of portable equipments, and application of dry hygienic measures (disposable chlorhexidine towels) in colonized or infected patients are essential to reduce acquisition rates of MBR pathogens.[41,45]

Limitations of study are its multicenter nature and some design characteristics. Data of identification of *P. aeruginosa* and susceptibility testing were provided by the Services of Microbiology of the participating hospitals, and a single reference laboratory was not used. On the other hand, a regression to the mean bias cannot be excluded. Also, the transversal nature of the study should be taken into account. A selection bias cannot be excluded because data on consumption of antipseudomonal antimicrobials and resistance rates were based on information of patients admitted during three months (April-June) each year. Likewise, the influence of other factors associated with the selection of MBR strains, such as the concomitant use of other antimicrobials, doses, or sequential therapy[45-47] were not assessed since these variables are not registered in the ENVIN database. For this reason, DOT was used instead of daily defined dose (DDD). Finally, different programs aimed to reduce the number ICU-acquired infections due to invasive devices, such ''Bacteremia Zero''[48] and ''Pneumonia Zero''[49] as well as ''Zero Resistance'' program[41] could have influenced the decrease of antimicrobial use, although the impact of these interventions cannot be evaluated with the present data.

Conclusions

In a large number of Spanish ICUs accounting for about 80% of ICUs in the country, a relationship between reduction of consumption of antipseudomonal antimicrobials and resistance rates against most of these agents was not documented. Other factors besides antimicrobial use may account for the increase of resistant *P. aeruginosa* isolates. Any intervention to reduce MBR *P. aeruginosa* in the ICU setting should be accompanied by active search of patients carriers of MBR strains on ICU admission together with active search and destroy of potential MBR reservoirs. We suggest that future studies collect detailed information about concomitant patient carriage with *P. aeruginosa* on admission to intensive care, as well as potential environmental reservoirs.

Consent statement

Not applicable given the non-interventional nature of the study because data were collected from the ENVIN-HELICS registry.

Availability of data and material

Please contact authors for data request.

Authors' contributions

FAL, conception and design of the study, drafting of the manuscript, data collection, analysis of results, discussion and supervision of the registry; POA, collection and analysis of data, critical review of the manuscript and supervision of the registry; MPM, collection of data and critical review of the manuscript; MC, collection of data and supervision of the registry; XN, collection of data and supervision of the registry; RG, collection of data and supervision of the registry; MPGA, collection of data, interpretation of results and supervision of the registry; ISB, collection of data and supervision of the registry; MMA, statistical analysis and interpretation of results and critical review of the manuscript. All authors have seen and approved the final draft.

Funding

None to be declared.

Conflict of interests

The authors declare that they have no competing interests.

Acknowledgments

To all Healthcare professionals, physicians and nurses, who had collaborated in 2007 and 2016 to the ENVIN-HELICS database entering information that has been analyzed in the present study. All of them are coauthors of the study and their names are listed in the annual reports of the ENVIN registry, available at http://hws.vhebron.net/envin-helics/. We are grateful to Sonia Uriona, MD, and Susana Otero, MD, for their contribution in the administration and secretariat of the ENVIN-HELICS registry, and to Marta Pulido, MD, for editing the manuscript and editorial assistance. The fees of medical editing were supported by MSD España. MSD was not involved in the content of the article.

References

1. Rice LB, Lakticova V, Helfand MS, Hutton-Thomas RA. In vitro antienterococcal activity explains associations between exposures to antimicrobial agents and risk of colonization by multiresistant enterococci. J Infect Dis. 2004;190:2162–6.
2. Donskey C, Helfand MS, Pultz NJ, Rice LB. Effect of parenteral fluoroquinolone administration on persistence of vancomycin-resistant Enterococcus faecium in the mouse gastrointestinal tract. Antimicrob Agents Chemother. 2004;48:326–8.
3. Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, Quinn JP. Antibiotic resistance among Gram-negative bacilli in US Intensive Care Units Implications for fluoroquinolone use. JAMA. 2003;289:885–8.
4. Kim YA, Park YS, Youk T, Lee H, Lee K. Correlation of aminoglycoside consumption and amikacin- or gentamicin-resistant *Pseudomonas aeruginosa* in long-term nationwide analysis: is antibiotic cycling an effective policy for reducing antimicrobial resistance? Ann Lab Med. 2018;38:176–8.
5. Meyer E, Schwab F, Gastmeier P, Rueden H, Daschner FD, Jonas D. Stenotrophomonas maltophilia and antibiotic use in German intensive care units: data from Project SARI (Surveillance of Antimicrobial Use and Antimicrobial Resistance in German Intensive Care Units. J Hosp Infect. 2006;64:238–43.
6. Graffunder EM, Venecia RA. Risk factors associated with nosocomial methicillin-resistant Staphylococcus aureus (MRSA) infection including previous use of antimicrobials. J Antimicrob Chemother. 2002;49:999–1005.
7. Webber SG, Gold HS, Hopper DC, Karchmer AW, Carmeli Y. Fluoroquinolones and the risk for methicillin-resistant Staphylococcus aureus in hospitalized patients. Emerg Infect Dis. 2003;9:1415–22.
8. Harris AD, Perencevich E, Roghmann MC, Morris G, Kaye KS, Johnson JA. Risks factors for piperacillin-tazobactam-resistant *Pseudomonas aeruginosa* among hospitalized patients. Antimicrob Agents Chemother. 2002;46:854–8.
9. Ozkurt Z, Ertek M, Erol S, Altoparlak U, Akcay MN. The risk factors for acquisition of imipenem-resistant *Pseudomonas aeruginosa* in the burn unit. Burns. 2005;31:870–3.
10. Kang CI, Kim SH, Park WB, Lee KD, Kim HB, Kim EC, et al. Risk factors for antimicrobial resistance and influence of resistance on mortality in patients with bloodstream infection caused by *Pseudomonas aeruginosa*. Microb Drug Resist. 2005;11:68–74.
11. Zavascki AP, Cruz RP, Goldani LZ. Risk factors for imipenem-resistant *Pseudomonas aeruginosa*: a comparative analysis of two case-control studies in hospitalized patients. J Hosp Infect. 2005;59:96–101.
12. DalBen MF, Basso M, Garcia CP, Costa SF, Toscano CM, Jarvis WR, et al. Colonization pressure as a risk factor for colonization by multiresistant *Acinetobacter* spp. and carbapenem-resistant *Pseudomonas aeruginosa* in an intensive care unit. Clinics (Sao Paulo). 2013;68:1128–33.
13. Carpentier M, Appere V, Saliou P, de Tinteniac A, Floch H, Le Gall F, et al. Outbreak of extended spectrum beta-lactamase-producing *Klebsiella pneumoniae* in an intensive care unit (Brest). Med Mal Infect. 2012;42:501–9.
14. Price JR, Cole K, Bexley A, Kostiou V, Eyre DW, Golubchik T, et al. Modernising Medical Microbiology informatics group Transmission of *Staphylococcus aureus* between health-care workers, the environment, and patients in an intensive care unit: a longitudinal cohort study based on whole-genome sequencing. Lancet Infect Dis. 2017;17:207–14.
15. Zhou Z, Hu B, Gao X, Bao R, Chen M, Li H. Sources of sporadic *Pseudomonas aeruginosa* colonizations/infections in surgical ICUs: association with contaminated sink trap. J Infect Chemother. 2016;22:450–5.
16. Lowe C, Willey B, O'Shaughnessy A, Lee W, Lum M, Pike K, et al. Outbreak of extended-spectrum β-lactamase-producing *Klebsiella oxytoca* infections associated with contaminated handwashing sinks(1). Emerg Infect Dis. 2012;18:1242–7.
17. Salm F, Deja M, Gastmeier P, Kola A, Hansen S, Behnke M, et al. Prolonged outbreak of clonal MDR *Pseudomonas aeruginosa* on an intensive care unit: contaminated sinks and contamination of ultra-filtrate bags as possible route of transmission? Antimicrob Resist Infect Control. 2016;5:53, http://dx.doi.org/10.1186/s13756-016-0157
18. Rosenthal VD, Al-Abdely HM, El-Kholy AA, AlKhawaja SAA, Leblebicioglu H, Mehta Y, et al. International Nosocomial Infection Control Consortium report, data summary of 50 countries for 2010–2015: device-associated module. Am J Infect Control. 2016;44:1495–504.
19. Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias. Estudio Nacional de Vigilancia de Infección en Servicios de Medicina Intensiva. Informe del año 2016. Available from: http://www.semicyuc.org/ [accessed 2.04.19].
20. López-Pueyo MJ, Olaechea-Astigarraga P, Palomar-Martínez M, Insausti-Ordeñana J, Alvarez-Lerma F. Quality control of the surveillance programme of ICU-acquired infection (ENVIN-HELICS registry) in Spain. J Hosp Infect. 2013;84:126–31.
21. Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias. Manual de definiciones y términos. Estudio Nacional de Vigilancia de Infección en Servicios de Medicina Intensiva (ENVIN). Available from: http://hws.vhebron.net/envin-helics/Help/Manual_2017.pdf [accessed 2.04.19].
22. Surveil lance of nosocomial infections in Intensive Care Units. Hospital in Europe Link for Infection Control through Surveillance (HELICS) (Version 6.1. September 2004). Available from: http://www.ecdc.europa.eu/IPSE/protocols/icu_protocol.pdf [accessed 2.04.19].
23. European Society of Clinical Microbiology and Infectious Diseases. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Available from: http://www.eucast.org/ [accessed 2.04.19].
24. R core team (2018). R: A language and environment for statistical computing. R foundation for statistical computing, Vienna, Austria. https://www.R-project-org
25. Yusuf E, Van Herendael B, Verbrugghe W, Ieven M, Goovaerts E, Bergs K, et al. Emergence of antimicrobial resistance to *Pseudomonas aeruginosa* in the intensive care unit: association with the duration of antibiotic exposure and mode of administration. Ann Intensive Care. 2017;7:72, http://dx.doi.org/10.1186/s13613-017-0296-z
26. Mladenovic-Antic S, Kocic B, Velickovic-Radovanovic R, Dinic M, Petrovic J, Randjelovic G, et al. Correlation between antimicrobial consumption and antimicrobial resistance of *Pseudomonas*

aeruginosa in a hospital setting: a 10-year study. J Clin Pharm Ther. 2016;41:532–7.
27. Cobos-Trigueros N, Solé M, Castro P, Torres JL, Hernández C, Rinaudo M, et al. Acquisition of *Pseudomonas aeruginosa* and its resistance phenotypes in critically ill medical patients: role of colonization pressure and antibiotic exposure. Crit Care. 2015;19:218, http://dx.doi.org/10.1186/s13054-015-0916-7
28. Solé M, Fàbrega A, Cobos-Trigueros N, Zamorano L, Ferrer-Navarro M, Ballesté-Delpierre C, et al. In vivo evolution of resistance of *Pseudomonas aeruginosa* strains isolated from patients admitted to an intensive care unit: mechanisms of resistance and antimicrobial exposure. J Antimicrob Chemother. 2015;70:3004–13.
29. Nakamura A, Miyake K, Misawa S, Kuno Y, Horii T, Kondo S, et al. Meropenem as predictive risk factor for isolation of multidrug-resistant *Pseudomonas aeruginosa*. J Hosp Infect. 2013;83:153–5.
30. Ong DS, Jongerden IP, Buiting AG, Leverstein-van Hall MA, Speelberg B, Kesecioglu J, et al. Antibiotic exposure and resistance development in *Pseudomonas aeruginosa* and Enterobacter species in intensive care units. Crit Care Med. 2011; 39:2458–63.
31. Székely E, Bucur G, Vass L, Butiurca M, Bilca D, Foldes A, et al. Antimicrobial use and its correlations with the frequency of carbapenem-resistant *Pseudomonas aeruginosa* strains in a hospital setting. Bacteriol Virusol Parazitol Epidemiol. 2010;55:179–86.
32. Muraki Y, Kitamura M, Maeda Y, Kitahara T, Mori T, Ikeue H, et al. Nationwide surveillance of antimicrobial consumption and resistance to *Pseudomonas aeruginosa* isolates at 203 Japanese hospitals in 2010. Infection. 2013;41:415–23.
33. Fujimura S, Nakano Y, Sato T, Shirahata K, Watanabe A. Relationship between the usage of carbapenem antibiotics and the incidence of imipenem-resistant *Pseudomonas aeruginosa*. J Infect Chemother. 2007;13:147–50.
34. Cook PP, Gooch M, Rizzo S. Reduction in fluoroquinolone use following introduction of ertapenem into a hospital formulary is associated with improvement in susceptibility of *Pseudomonas aeruginosa* to group 2 carbapenems: a 10-year study. Antimicrob Agents Chemother. 2011;55:5597–601.
35. Baditoiu L, Axente C, Lungeanu D, Muntean D, Horhat F, Moldovan R, et al. Intensive care antibiotic consumption and resistance patterns: a cross-correlation analysis. Ann Clin Microbiol Antimicrob. 2017;16:71, http://dx.doi.org/10.1186/s12941-017-0251-8
36. Fihman V, Messika J, Hajage D, Tournier V, Gaudry S, Magdoud F, et al. Five-year trends for ventilator-associated pneumonia: correlation between microbiological findings and antimicrobial drug consumption. Int J Antimicrob Agents. 2015;46:518–25.
37. WHO. Global Strategy for Containment of Antimicrobial Resistance. World Hearth Organization, 2001. Available from: http://www.who.int/drugresistance/WHO_Global_Strategy.htm/en/index.html [accessed 2.04.19].
38. European Centre for Disease Prevention and Control. Risk assessment on the spread of carbapenemase-producing Enterobacteriaceae (CPE) through patient transfer between healthcare facilities, with special emphasis on cross-border transfer. Stockholm: ECDC; 2011.
39. Kessel AS, Sharland M. The new UK antimicrobial resistance strategy and action plan. BMJ. 2013;346:f1601, http://dx.doi.org/10.1136/bmj.f1601
40. Agencia Española del Medicamente y Productos Sanitarios (AEMyPS). Ministerio de Sanidad, Servicios Sociales e Igualdad (MSSSI). Plan Nacional Resistencia Antibióticos. Plan estratégico y de acción para reducir la selección y diseminación de la resistencia a los antibióticos. Noviembre 2014. Available from: https://www.aemps.gob.es/publicaciones/publica/plan-estrategico-antibioticos/v2/docs/plan-estrategico-antimicrobianos-AEMPS.pdf [accessed 2.04.19].
41. Garnacho Montero J, Alvarez-Lerma F, Ramirez Galleymore P, et al. Combatting resistance in intensive care: the multimodal approach of the Spanish ICU ''Zero Resistance'' program. Crit Care. 2015;19:114–22.
42. Alvarez-Lerma F, Olaechea-Astigarraga P, Palomar-Martinez M, Catalan M, Nuvials X, Gimeno R, et al. Invasive device-associated infections caused by *Pseudomonas aeruginosa* in critically ill patients: evolution over 10 years. J Hosp Infect. 2018;100:e204–8.
43. Wójkowska-Mach J, Chmielarczyk A, Borszewska-Kornacka M, Domańska J, Gadzinowski J, Gulczyńska E, et al. Enterobacteriaceae infections of very low birth weight infants in Polish neonatal intensive care units: resistance and cross-transmission. Pediatr Infect Dis J. 2013;32:594–8.
44. Pelat C, Kardaś-Słoma L, Birgand G, Ruppé E, Schwarzinger M, Andremont A, et al. Hand hygiene, cohorting, or antibiotic restriction to control outbreaks of multidrug-resistant Enterobacteriaceae. Infect Control Hosp Epidemiol. 2016;37: 272–80.
45. Hernández-Tejedor A, Peñuelas O, Sirgo Rodríguez G, Llompart-Pou JA, Palencia Herrejón E, Estella A, et al. Recommendations of the Working Groups from the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC) for the management of adult critically ill patients. Med Intensiva. 2017;41:285–305.
46. Rees VE, Bulitta JB, Oliver A, Tsuji BT, Rayner CR, Nation RL, et al. Resistance suppression by high-intensity, short-duration aminoglycoside exposure against hypermutable and non-hypermutable *Pseudomonas aeruginosa*. J Antimicrob Chemother. 2016;71:67–3157.
47. Landersdorfer CB, Rees VE, Yadav R, Rogers KE, Kim TH, Bergen PJ, et al. Optimization of a meropenem-tobramycin combination dosage regimen against hypermutable and nonhypermutable *Pseudomonas aeruginosa* via mechanism-based modeling and the hollow-fiber infection model. Antimicrob Agents Chemother. 2018;62:e02055–2117, http://dx.doi.org/10.1128/AAC.5-170205
48. Palomar M, Álvarez-Lerma F, Riera A, Díaz MT, Torres F, Agra Y, et al. Impact of a national multimodal intervention to prevent catheter-related bloodstream infection in the ICU: the Spanish experience. Crit Care Med. 2013;41:72–2364.
49. Álvarez-Lerma F, Palomar-Martínez M, Sánchez-García M, Martínez-Alonso M, Álvarez-Rodríguez J, Lorente L, et al. Prevention of ventilator-associated pneumonia: the multimodal approach of the Spanish ICU ''Pneumonia Zero'' program. Crit Care Med. 2018;46:181–8.