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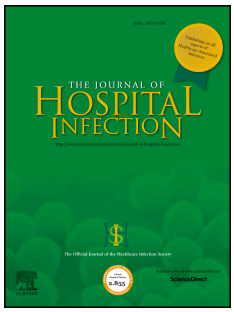

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Invasive device-associated infections caused by *Pseudomonas aeruginosa* in critically ill patients: evolution over 10 years

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Authors' contributions to the study:

F. Álvarez –Lerma: design of the study, drafting of the manuscript, data collection, analysis of results, discussion and supervision of the registry.

P. Olaechea-Astigarraga: collection and analysis of data, critical review of the manuscript, supervision of the registry, and approval of the final draft.

M. Palomar-Martínez: collection of data, supervision of the registry, and approval of the final draft.

M. Catalan: collection of data, supervision of the registry, critical comments, and approval of the final draft.

X. Nuvials: data collection, critical review of the manuscript, supervision of the registry, and approval of the final draft.

R. Gimeno: collection and analysis of data, critical review of the manuscript, supervision of the registry, and approval of the final draft.

M.P. Gracia Arnillas: data collection, supervision of the registry, and approval of the final draft.

I. Seijas Betozala: data collection, supervision of the registry, critical comments, and approval of the final draft.

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Abbreviations

BLEE: extended spectrum ß-lactamases; CAUTI: catheter-associated urinary tract infection; CLSI: Clinical and Laboratory Standards Institute; CRBSI: catheter-related bloodstream infection; ECDC: European Centre for Disease Control and Prevention; ENVIN: National Study

of Surveillance of Nosocomial Infection in Services of Intensive Care Medicine; EUCAST: European Committee on Antimicrobial Susceptibility Testing; HELICS: Hospitals in Europe Link for Infection Control through Surveillance; ICU: intensive care unit; MDR: multidrug-resistant; MIC: minimum inhibitory concentration; PDR: pandrug-resistant; SEMICYUC: Spanish Society of Intensive Care Medicine and Coronary Units; VAP: ventilator-associated pneumonia; XDR: extensively drug-resistant.

Summary (word count 100)

We assessed invasive device-associated infections caused by *Pseudomonas aeruginosa* over 10 years (2007-2016) based on data from the ENVIN-HELICS registry (200 Spanish ICUs). *P. aeruginosa* was the leading pathogen except in the last two years in which there was a slight decrease, with *Escherichia coli* as the leading etiology. The rate of infections caused by *P. aeruginosa* remained between 12.0% and 14.6% throughout the study period. There was a significant increase of isolates resistant to imipenem, meropenem, ceftazidime, cefepime and piperacillin-tazobactam. Multidrug-resistant and the sum of extensively drug- and pandrug-resistant strains also increased. Resistance to anti-pseudomonal antimicrobials remains a matter of concern.

INTRODUCTION

Pseudomonas aeruginosa has become an important cause of invasive device-associated infection in critically ill patients, particularly in mechanically ventilated patients.[1] *P. aeruginosa* infections are of great concern in intensive care units (ICUs) because of common resistance to anti-pseudomonal antimicrobials and current challenges in the management of patients with these infections. The categories of multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria have been proposed to characterize patterns of resistance found in invasive device-associated infections.[2]

In Spain, data collected in the National ICU-Acquired Infection Surveillance Study (ENVIN-HELICS registry) database[3] provide information on ventilator-associated pneumonia (VAP), primary bacteremia related to vascular lines, and catheter-associated urinary tract infection (CAUTI) in ICU patients. The aim of this study was to assess the role of *P. aeruginosa* in invasive device-associated infections diagnosed in patients admitted to Spanish ICUs over the past 10 years (2007-2016) using data of the ENVIN-HELICS registry. The evolution of resistance rates to antimicrobials used for treating these infections, as well as changes of MDR, XDR, and PDR strains were also analyzed.

PATIENTS AND METHODS

Design and study population

This was a prospective observational and multicentre study. All patients admitted for more than 24 hours to the participating ICUs during the months of April 1 to June 30 over 10 consecutive years (2007-2016) were included in the study provided that the diagnosis of invasive device-associated infection caused by *P. aeruginosa* had been established.

Data of the study patients were collected from the ENVIN-HELICS registry, the main characteristics of which have been previously described.[3] Briefly, information on infections related to invasive devices that developed in all patients admitted to participating ICUs from April 1 to June 30 each year are registered in the database. Data are collected using the ENVIN-HELICS software application located in a web-based

server available at http://hws.vhebron.net/ENVIN-helics. Two quality control audits performed in 2008 and 2010 ensured internal validity of the clinical information recorded in the database.[4]

The ENVIN registry was approved by the Ethics Committees of the majority of participating ICUs and was declared a registry of healthcare interest by the Spanish Ministry of Health, Social Services and Equality in 2014. Consent statement is not applicable given the noninterventional nature of the study because data were collected from the ENVIN-HELICS registry.

Definition of invasive device-related infections

Only infections directly associated with invasive devices (VAP, catheter-related bloodstream infection [CRBSI] and CAUTI) were included in the study. Definitions of these infections were those reported in the manual of the ENVIN project following indications of the European Centre for Disease Control and Prevention (ECDC). 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. These intensivists prospectively recorded the infections and verified the diagnosis of controlled infections with attending physicians.

Criteria for antimicrobial resistance

Bacterial identification procedures were based on criteria used in each participating ICU. Susceptibility of *P. aeruginosa* isolates to different antimicrobials was assessed at the Services of Clinical Microbiology of the participating hospitals following specifications (method and breakpoints) of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and/or the Clinical and Laboratory Standards Institute (CLSI). Standardized definitions proposed by Magiorakos et al.[2] were used for classifying *P. aeruginosa* isolates according to resistance to different anti-pseudomonal antimicrobials: MDR as 'resistant to at least one antimicrobial of three anti-pseudomonal antimicrobial categories', XDR as 'resistant to at least one antimicrobial of five anti-pseudomonal categories', and PDR as 'resistant to all antimicrobials from all categories'. Anti-pseudomonal categories and antimicrobials included in each

category were as follows: aminoglycosides (amikacin), cephalosporins (ceftazidime and cefepime), carbapenems (imipenem and meropenem), ureidopenicillins (piperacillin-tazobactam), and quinolones (levofloxacin and ciprofloxacin).

Outcome measures

The rates of VAP, CRBSI, and CAUTI were calculated by dividing the number of episodes by respective device-days and expressed as number of infections per 1,000 days of exposure to device. Rates of CRBSI included bloodstream infection with origin catheter and bloodstream infection with unknown origin. Days of exposure were globally estimated for all patients admitted to the ICU during the surveillance period. Patients on mechanical ventilation, urinary catheter, and central venous catheter (including pulmonary artery catheters, parenteral nutrition, hemodialysis, and catheters with reservoirs) were recorded daily. The utilization ratio was defined as the quotient between the number of days of use of each invasive technique and the days at risk (days of stay). In the case of vascular lines, the simultaneous presence of several central catheters was counted as one day of instrumentalization. The cumulative incidence of *P. aeruginosa* infection was calculated as the percentage in relation to the total number of microorganisms identified in invasive device-associated infections controlled in the ENVIN registry. The proportion of resistance of *P. aeruginosa* isolates to different anti-pseudomonal antimicrobials was estimated as the quotient between the number of resistant strains to one particular antimicrobial and the number of strains for which data on susceptibility/resistance to this antimicrobial were available, per 100. Additionally, the proportion of resistance to colistin was defined as the number of colistin-resistant strains divided by the number of strains of *P. aeruginosa* identified per 100 (independently of whether data on susceptibility to colistin were available).

Statistical analysis

Outcome measures are expressed as descriptive statistics. Monotonic trends of the different indicators were analyzed with the Mann-Kendall test. Statistical significance was set at $P < 0.05$.

RESULTS

During the study period, 187,100 patients admitted to 200 ICUs from 161 hospitals were included. The distribution of number of patients, participating ICUs, and days of exposure to invasive devices is shown in Table I (Supplementary material).

A total of 15,095 episodes of invasive device-associated infection were diagnosed in 11,652 patients (62.3%) of which 6,418 (42.5%) were VAP, 4,977 (33.0%) CAUTI and 3,700 (24.5%) CRBSI. Changes of VAP, CAUTI, and CRBSI rates during the 10-year study period are shown in Table II (Supplementary material).

Of 15,432 pathogens identified, 2,095 (13.6%) were *P. aeruginosa* (Table III, Supplementary material). *P. aeruginosa* was the most frequent causative microorganisms of invasive device-associated infections except in the last two years (2015 and 2016) in which there was a slight decrease, with *Escherichia coli* as the leading etiology of invasive device-associated infection. Changes in the proportion of invasive device-associated infections caused by *P. aeruginosa* during the study period are shown in Table I. There was a significant increase of VAP episodes due to *P. aeruginosa* infection ($P = 0.032$), which accounted for more than 20% of isolates in the last 4 years. In contrast, changes in CAUTI and CRBSI infections caused by *P. aeruginosa* were not statistically significant ($P = 0.371$ and $P = 1$, respectively).

Resistance patterns of *P. aeruginosa* to different anti-pseudomonal antimicrobials during the study period are shown in Table IV (Supplementary material). An overall increase of resistant strains to all individual antimicrobial agents was observed with statistically significant differences in the percentages of resistances between 2007 and 2016 for imipenem (32% *vs.* 46.1%, $P = 0.049$), meropenem (28.2% *vs.* 46.5%, $P = 0.007$), ceftazidime (27.2% *vs.* 39.1%, $P = 0.012$), cefepime (24.2% *vs.* 37.2%, $P = 0.004$), and piperacillin-tazobactam (18.9% *vs.* 40.2%, $P < 0.001$). *P. aeruginosa* strains classified as MDR increased from 15.3% in 2007 to 21.9% in 2016 ($P = 0.023$), whereas the sum of XDR and PDR strains increased from 3.7% in 2007 to 8.5% in 2016 ($P < 0.001$) (Figure 1). Also, an increase of colistin-resistant strains was found, although differences were not statistically significant (3.2% in 2007 and 4.4% in 2016, $P = 0.530$).

DISCUSSION

This study shows a progressive increase in resistance to all antimicrobials potentially active against *P. aeruginosa* isolated from critically ill patients with invasive device-associated infection admitted to Spanish ICUs, particularly to meropenem, imipenem, ceftazidime, cefepime, and piperacillin-tazobactam as well as MDR, XDR, and PDR strains.

In the ICU setting, *P. aeruginosa* continues to be an important causative pathogen of invasive device-associated infections controlled in the ENVIN-HELICS registry, accounting for around 13% of all isolates recovered from patients with invasive devices-related infections. However, studies assessing the predominant pathogens of ICU-acquired infections carried out at national levels[5] have shown a large variation in the percentage of infections caused by *P. aeruginosa*. In Spain, *P. aeruginosa* ranked first among all nosocomial pathogens related to invasive devices-associated infections, although *Escherichia coli* has been the most common pathogen in the last two years.

P. aeruginosa was the causative pathogen of 20% of VAP with an increasing trend in recent years, whereas the percentage of CAUTIs remained around 12%, with lower and decreasing percentages for CRBSI. *P. aeruginosa* is a common pathogen of VAP and has been the subject of numerous studies,[6] although the predominance of this pathogen is not the same in all European countries.[5] The decrease of *P. aeruginosa* in CRBSI may be explained by implementation of the 'Bacteremia Zero' project, which include among other measures, identification and elimination of environmental reservoirs and cleaning the skin with 2% chlorhexidine, reducing catheter contamination which is the main focus of primary bacteremia.

Carbapenems were the antimicrobial agents with the highest resistance rates (over 40%), followed by ureidopenicillins reaching 40%, and third- and fourth-generation cephalosporins with resistance rates between 35% and 40%; these are in turn the most commonly used antimicrobials in Spanish ICUs. By contrast, the resistance rates for colistin were maintained at around 3%. Resistance rates of individual antimicrobial agents against *P. aeruginosa* have shown a marked increase except for quinolones and colistin. The absence of increased resistance to colistin identifies it as a rescue antimicrobial against multiresistant strains. Of note is the

increase in resistance rates of piperacillin-tazobactam, although the change in the breakpoints recommended by international organisms could have had an influence. The resistance level to *P. aeruginosa* in Spain is similar to that observed by the International Infection Control Consortium (INICC) which includes data of 703 ICUs of 50 countries, but much higher than that reported by the CDC-NHSN in US ICUs.7

The increase in *P. aeruginosa* resistant to individual anti-pseudomonal agents has been accompanied by an increase of resistant strains to a combination of antimicrobials (MDR, XDR, PDR), which accounts for one-third of *P. aeruginosa* isolates in our country. In other studies, resistant isolates reached 47% in pediatrics ICUs from India[8] or 40% in strains recovered from respiratory samples in a hospital in Pakistan.[9] The increase of multiresistant strains in ICU-acquired infections suggests the existence of reservoirs that should be identified and eradicated. The clinical impact of multiresistance to anti-pseudomonal antimicrobial agents includes delay in the administration of appropriate treatment, longer ICU stay, more days on mechanical ventilation, and higher mortality. In some cases, treatment includes combined antimicrobials with colistin, fosfomycin or amikacin some of which with well-known nephrotoxicity associated with the duration of exposure.

To confront this scenario, it is necessary to rationalize the use of active antimicrobials against *P. aeruginosa*, optimizing their use at appropriate doses and intervals, and to investigate new molecules capable of avoiding the usual mechanisms of resistance. Recently, a new cephalosporin joined to a β-lactamase inhibitor (ceftolozane/tazobactam) has been made available to clinicians which has the necessary characteristics for use as a first-line treatment in patients with severe sepsis or septic shock with a reasonable risk of *P aeruginosa* infection, in an environment where the presence of MDR strains is known.[10]

The multicentre characteristic of the study is a main limitation, since information was collected from more than 200 hospitals in which there are different microbiological procedures, both in the identification of *P. aeruginosa* and in the assessment of susceptibility to different antimicrobials. This has contributed to the lack of data regarding susceptibility patterns of some strains included in the registry. Also, susceptibility of *P. aeruginosa* to some antimicrobials (gentamicin, tobramycin, doripenem, ticarcillin/clavulanic acid, fosfomycin) was not recorded in the registry,

which forced to adapt definitions of multiresistant isolates. Resistances rates may have been affected by differences in the breakpoints recommended by regulatory agencies during the study period.

This observational study showed an important increase of resistance to antimicrobials used for treating invasive device-associated infections caused by *P. aeruginosa* in critically ill patients admitted to Spanish ICUs. The need for new antimicrobials active against this pathogen capable of overcoming the mechanisms of resistance described so far is confirmed.

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Legends

Figure 1. Evolution of *Pseudomonas aeruginosa* strains classified as MDR, XDR, and PDR recovered in critically ill patients with invasive device-associated infections during the 10-year study period (MDR: resistant to at least one antimicrobial of three anti-pseudomonal antimicrobial categories; XDR: resistant to at least one antimicrobial of five anti-pseudomonal categories; PDR: resistant to all antimicrobials from all categories). Evolution of MDR strains, $P = 0.023$ and sum of XDR and PDR, $P < 0.001$).

Table I. Annual changes of the proportion of *Pseudomonas aeruginosa* as causative pathogens of invasive device-associated infections over the 10-year study period

Study year	VAP* *P. aeruginosa*/total pathogens in VAP no. (%)	CAUTI** *P. aeruginosa*/total pathogens in CAUTI no. (%)	CRBSI*** *P. aeruginosa*/total pathogens in CRBSI no. (%)	Invasive device-associated infections *P. aeruginosa*/total pathogens in invasive device-associated infections no. (%)
2007	146/832 (17.6)	45/389 (11.6)	26/404 (6.4)	217/1,625 (13.4)
2008	172/923 (18.6)	60/436 (13.8)	22/446 (4.9)	254/1,805 (14.1)
2009	142/797 (17.8)	41/433 (9.5)	13/403 (3.2)	196/1,633 (12.0)
2010	139/805 (17.3)	51/469 (10.9)	19/315 (6.0)	209/1,589 (13.2)
2011	139/696 (19.5)	65/523 (12.4)	22/382 (5.8)	223/1,601 (13.9)
2012	109/566 (19.3)	74/519 (14.3)	25/345 (7.3)	208/1,430 (14.6)
2013	104/493 (21.1)	65/540 (12.0)	27/318 (8.5)	196/1,351 (14.5)
2014	106/500 (21.2)	83/570 (14.6)	27/414 (6.5)	216/1,491 (14.5)
2015	93/441 (21.1)	63/561 (11.2)	21/367 (5.7)	177/1,369 (12.9)
2016	112/547 (20.5)	76/605 (12.6)	11/379 (2.9)	199/1,538 (12.9)
Total	1,259/6,600 (19.3)	623/5,045 (12.3)	213/3,776 (5.6)	2,095/15,432 (13.6)

*P = 0.032; **P = 0.371; ***P = 1.

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