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Short Communication

Application of new indicators to assess the quality of antimicrobial use in intensive care units

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ABSTRACT

This study explored the feasibility of a bundle of indicators aimed at assessing the quality of antimicrobial use in intensive care units (ICUs) through an observational prospective study spanning 12 quarters (January 2019–December 2021) in a 1290-bed teaching hospital in Spain. Members of the antimicrobial stewardship programme team selected the indicators to analyse the quality of antimicrobial use based on consumption data from a list proposed in a previous study. Antimicrobial use in the ICU was measured as defined daily dose (DDD) per 100 occupied bed-days. Trends and points of change were analysed with segmented regression. The intravenous macrolides/intravenous respiratory fluoroquinolones ratio in the ICU increased progressively, although not significantly, by 11.14% per quarter, likely related to prioritization of the use of macrolides in serious community-acquired pneumonia and the coronavirus disease 2019 pandemic. A remarkable upward trend of 2.5% per quarter was detected in the anti-methicillin-susceptible *Staphylococcus aureus*/anti-methicillin-resistant *S. aureus* agents ratio in the ICU, which could be explained by the low prevalence of methicillin-resistant *S. aureus* at the study centre. Patterns of amoxicillin-clavulanic acid/piperacillin-tazobactam ratio and diversification of anti-pseudomonal beta-lactams showed an increment in use over the study. The use of these novel indicators provides additional information for the current analysis of DDD. Implementation is feasible, and led to the detection of patterns that agree with local guidelines and cumulative antibiogram reports, and foster targeted improvement actions within antimicrobial stewardship programmes.

1. Introduction

In the context of increasing antimicrobial resistance, surveillance of antimicrobial use allows intra- and interfacility comparison, and provides the necessary information for action in support of local, national and global strategies, and antimicrobial stewardship programmes (ASPs) [1].

The defined daily dose (DDD) metric, established by the World Health Organization as the average standard daily dose of a drug used in a 70-kg adult for the most common indication, remains one of the gold standard units of measurement to quantify antimicrobial use in intensive care units (ICUs) [2]. Regarding the quality of antimicrobial prescriptions, audits and point prevalence surveys are the preferred methodologies, although they are infrequent due to difficulties and heterogeneity in their evaluation [3,4].

In 2019, a committee comprised of members of the Spanish Societies of Hospital Pharmacy and Infectious Diseases and Clinical Microbiology published a bundle of indicators aimed to assess

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Table 1
Descriptive data and overall trend of each indicator, numerators and denominators of ratios.

Indicator	Intensive care unit			Hospital		
	Mean (range)	AQPC	95% CI	Mean (range)	AQPC	95% CI
MACR/FQ	0.10 (0.01 to 0.24)	11.14	-4.48 to 29.32	0.30 (0.17 to 0.48)	-3.31	-7.92 to 1.53
MACR	0.92 (0.12 to 2.03)	11.47	-1.80 to 26.52	1.34 (0.73 to 2.10)	-3.61	-8.56 to 1.62
FQ	9.22 (7.24 to 11.79)	1.95	-2.35 to 6.44	4.47 (3.73 to 6.02)	-0.21	-1.86 to 1.48
Anti-MSSA/anti-MRSA	0.91 (0.67 to 1.18)	2.52	-4.92 to 10.54	1.33 (1.05 to 1.70)	-1.41	-3.13 to 0.34
Anti-MSSA	19.86 (9.97 to 28.91)	8.80	4.94 to 12.79	6.62 (5.22 to 8.08)	1.12	-1.18 to 3.47
Anti-MRSA	21.27 (14.23 to 26.67)	4.68	2.72 to 6.68	5.01 (3.66 to 6.06)	2.48	1.41 to 3.57
AC/PTZ	0.91 (0.57 to 1.12)	0.07	-4.22 to 4.55	1.91 (1.45 to 2.99)	-2.71	-7.35 to 2.17
AC	14.79 (12.68 to 17.17)	1.59	-1.67 to 4.96	9.57 (7.94 to 11.97)	-1.05	-6.42 to 4.62
PTZ	16.67 (13.71 to 23.53)	1.45	-1.42 to 4.40	5.12 (3.61 to 5.83)	2.80	0.69 to 4.97
CEPH	10.40 (6.59 to 13.95)	5.85	2.55 to 9.26	3.53 (2.29 to 4.09)	2.62	0.80 to 4.48
CARB	15.42 (8.34 to 20.26)	4.91	0.94 to 9.04	2.81 (1.84 to 3.42)	3.69	1.11 to 6.33
FLUCO/EQ	2.81 (1.29 to 5.05)	-2.99	-15.48 to 11.35	3.61 (2.17 to 6.71)	-3.43	-10.97 to 4.74
FLUCO	7.97 (4.85 to 17.17)	5.24	-9.48 to 22.35	2.52 (2.18 to 2.97)	0.71	-0.36 to 1.79
EQ	3.09 (1.75 to 4.63)	4.82	-5.21 to 15.90	0.75 (0.38 to 1.08)	4.12	-4.58 to 13.62

AQPC, average quarterly percentage change; CI, confidence interval; MACR/FQ, intravenous macrolides/intravenous respiratory fluoroquinolones ratio; anti-MSSA/anti-MRSA, anti-methicillin-susceptible *Staphylococcus aureus*/anti-methicillin-resistant *S. aureus* ratio; AC/PTZ, amoxicillin-clavulanic acid/piperacillin-tazobactam ratio; PTZ, and piperacillin-tazobactam; CEPH, anti-pseudomonal cephalosporins; CARB, anti-pseudomonal carbapenems; FLUCO/EQ, fluconazole/echinocandins ratio.
Data are expressed as defined daily dose per 100 occupied bed-days.

the quality of antimicrobial use based exclusively on consumption data. Selection of the 13 indicators was performed by a panel of 21 experts through a modified Delphi method. Seven of these indicators were novel as they attempt to assess strategic drug use, as in the case of ratio-based indicators, and heterogeneity of anti-pseudomonal beta-lactams. The indicators were based on prioritizing the prescription of agents of choice described in guidelines for treatment of the main infectious syndromes to reduce global consumption, particularly broad-spectrum antibiotics, and prevention of the emergence and spread of multidrug-resistant organisms [5].

This article presents a proof of concept of the feasibility of these indicators as a standardized metric to monitor antimicrobial use in ICUs and its implications in ASPs.

2. Materials and methods

2.1. Setting

This study was performed at the University Hospital Virgen del Rocío, Seville, Spain, a tertiary-care teaching hospital with 1290 beds, including 96 adult ICU beds, serving 556,921 people. At this centre, an education-based institutionally supported ASP that includes infectious diseases specialists, clinical pharmacists, intensive care specialists, preventive medicine specialists, paediatricians and microbiologists in the multi-disciplinary team has been in force uninterrupted since 2011 [6,7].

2.2. Study design and period

We conducted an observational study in which data on antimicrobial use, for the ICU and the entire hospital including the ICU, were recorded prospectively from January 2019 to December 2021, spanning 12 quarters.

2.3. Study measures

At the study centre, a team of intensive care physicians and hospital pharmacists – members of the ASP – selected the indicators for application in the ICU from the seven indicators of strategic drug use proposed by Gutierrez-Urbon et al. [5]. Selection was based on ICU consumption data, and antimicrobials with a mean numerator and denominator <1 DDD/100 occupied bed-days (OBD) during the study period were excluded. The selected indicators are detailed in Table S1 (see online supplementary material): (i) intravenous macrolides/intravenous respiratory fluoroquinolones ratio (MACR/FQ); (ii) anti-methicillin-susceptible *Staphylococcus aureus*/anti-methicillin-resistant *S. aureus* agents ratio (anti-MSSA/anti-MRSA); (iii) amoxicillin-clavulanic acid/piperacillin-tazobactam ratio (AC/PTZ); (iv) fluconazole/echinocandins ratio (FLUCO/EQ); and (v) diversification of anti-pseudomonal beta-lactams.

To obtain each indicator, the DDD of antibacterials and antimycotics for systemic use were collected automatically from the computerized pharmacy database of dispensed drugs and expressed as DDD/100 OBD.

2.4. Statistical analysis

A joinpoint segmented regression was performed to characterize the trends over time, and to identify any significant changes that occurred in the linear slope of the trend for each variable using the Joinpoint Regression Program v. 4.9.0.1 [8]. Regression models were fitted using the weighted Bayesian Information Criterion selection method, accounting for autocorrelation. The significance of any point of change in trend was determined using a Monte Carlo permutation method [9]. Results from trend analyses have been presented as average quarterly percentage change (AQPC) and 95% confidence interval (CI) or *P*-values to show significance at alpha of 0.05. Quantitative data have been presented as mean (range).

3. Results

Mean global antimicrobial consumption in the ICU was 161.10 (128.74–193.93) DDD/100 OBD, and increased by an average of 3.71% (95% CI 2.28–5.17) per quarter (Fig. S1, see online supplementary material).

Quantitative data and trend analysis of indicators (numerators, denominators and ratios) of antimicrobial use in the ICU are presented in Table 1, Figs 1 and 2, and Figs S2–S6 (see online supplementary material) (see green lines for ICU data). For a better understanding of the framework, data from the entire hospital, including the ICU, were also included (see blue lines).

Regarding antimicrobial use in the ICU, the MACR/FQ ratio presented a steady trend during the study period, although a non-significant progressive increase (AQPC 11.14%, 95% CI -4.48 to

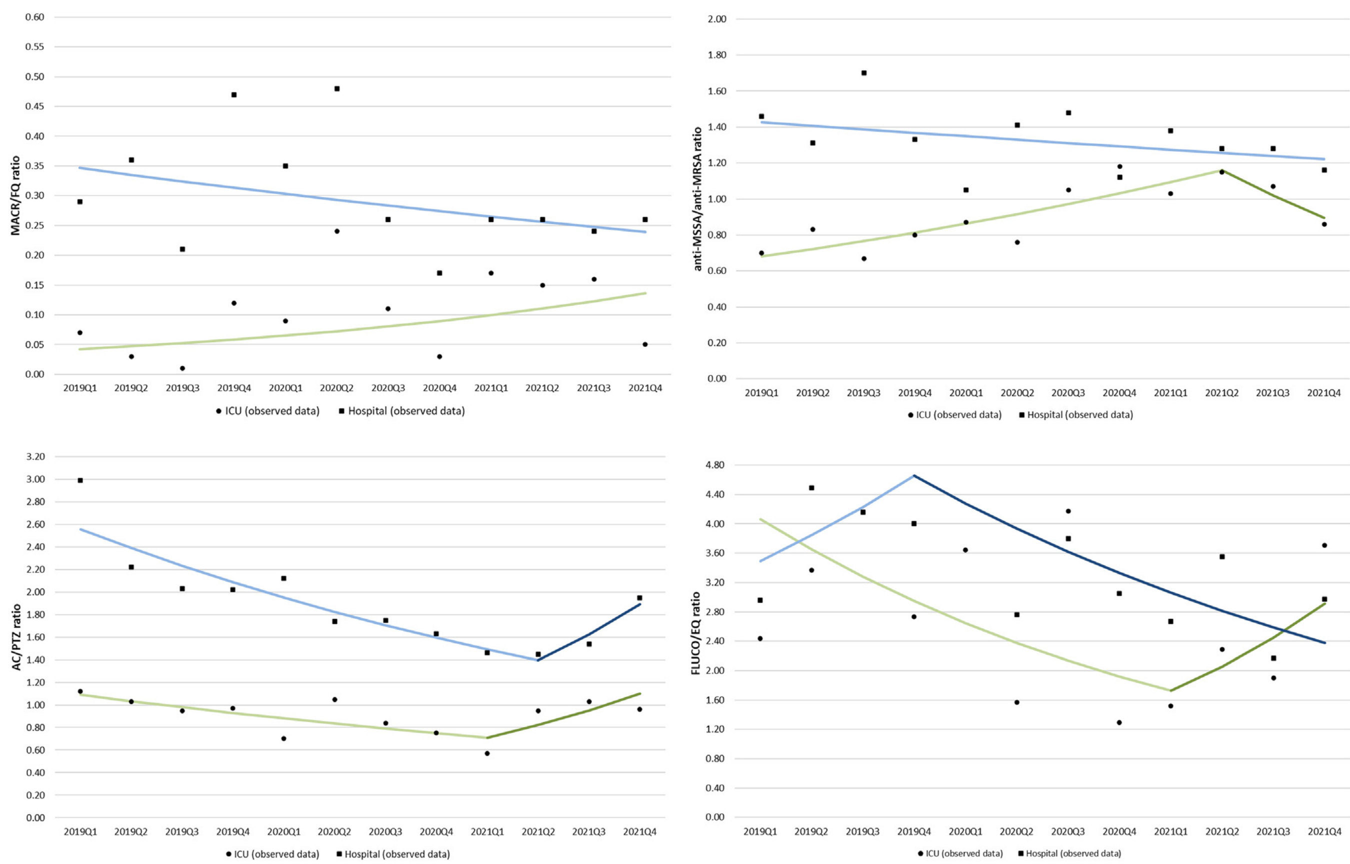

Figure 1. Trend analysis of ratios. MACR/FQ, intravenous macrolides/intravenous respiratory fluoroquinolones ratio; anti-MSSA/anti-MRSA, anti-methicillin-susceptible *Staphylococcus aureus*/anti-methicillin-resistant *S. aureus* agents ratio; AC/PTZ, amoxicillin-clavulanic acid/piperacillin-tazobactam ratio; FLUCO/EQ, fluconazole/echinocandins ratio; ICU, intensive care unit. Green lines (ICU) and blue lines (hospital) represent the modelled regression trend segments characterized by the joinpoint regression analysis.

29.32) was observed, driven by a rise in the use of MACR (AQPC 11.47%, 95% CI -1.80 to 26.52).

The anti-MSSA/anti-MRSA ratio in the ICU showed an upward trend (AQPC 6.1%, 95% CI 3.22 to 9.07), characterized by wider use of anti-MSSA agents (AQPC 8.80%, 95% CI 4.94 to 12.79), until the second quarter of 2021. From this point until the end of the study period, a steady-to-downward trend was seen (AQPC -12.26%, 95% CI -45.86 to 42.53).

The AC/PTZ ratio in the ICU was defined by a downward trend (AQPC -5.23%, 95% CI -8.13 to -2.23) due to an increase in the use of PTZ (AQPC 4.86%, 95% CI 2.84 to 6.93), with a subsequent change to a steady-to-upward trend in the first quarter of 2021 until the end of the study (AQPC 15.7%, 95% CI -2.89 to 37.85).

Anti-pseudomonal cephalosporins and carbapenems showed an upward trend throughout the study period. Nevertheless, the upward trend in PTZ detected initially for the ICU until the first quarter of 2021, shifted to a non-significant downward trend after this point (AQPC -7.12%, 95% CI -17.28 to 4.28).

Regarding the FLUCO/EQ ratio for the ICU, the trend was downward (AQPC -10.16%, 95% CI -18.29 to -1.22) until the first quarter of 2021, when it changed to a steady-to-upward trend (AQPC 19.06%, 95% CI -31.63 to 107.04) until the end of the study.

4. Discussion

DDD is a widely used indicator to monitor antimicrobial consumption in ICUs, being essential to correlate consumption data with microbiological information [10]. To the authors' knowledge, this is the first study to report the outcomes of the real-life application of new indicators proposed by two Spanish scientific societies to assess the quality of antimicrobial use based exclusively on consumption data.

Application of these indicators in the ICU brought to light a progressive increase in the use of macrolides compared with respiratory fluoroquinolones, in line with recent changes in guidelines [11], prioritizing the use of azithromycin in combination with ceftriaxone in serious community-acquired pneumonia. It could also be influenced by the increased use of azithromycin, not only for its bactericidal properties but also for its immunomodulatory properties, in combination with hydroxychloroquine for the treatment of coronavirus disease 2019 (COVID-19) in the early phases of the pandemic, as previous studies have shown [12]. Greater use of anti-MSSA agents compared with anti-MRSA agents reflects the low prevalence of MRSA in the study hospital, as shown in cumulative antibiogram reports [13]. Over the 3-year analysis period, the mean percentage of bacteraemia caused by MRSA in the ICU was 1.5%. It must be taken into account that there was an increase in the number of bacteraemias caused by MSSA during the first phase of the COVID-19 pandemic. During the last three quarters of 2021, the increase in the number of immunocompromised patients diagnosed with COVID-19 admitted to the ICU could explain the broad use of anti-MRSA agents. Use of the echinocandins was variable, so the results of the FLUCO/EQ ratio were inconclusive.

The AC/PTZ ratio highlighted extended use of piperacillin-tazobactam. This trend has been useful to detect inappropriate empirical treatments in which amoxicillin-clavulanic acid could be used (e.g. aspiration pneumonia in patients without risk of *Pseudomonas* spp.), but it could also be explained by increased incidence of extended-spectrum beta-lactamase-producing bacteria. Diversification of anti-pseudomonal beta-lactams was high

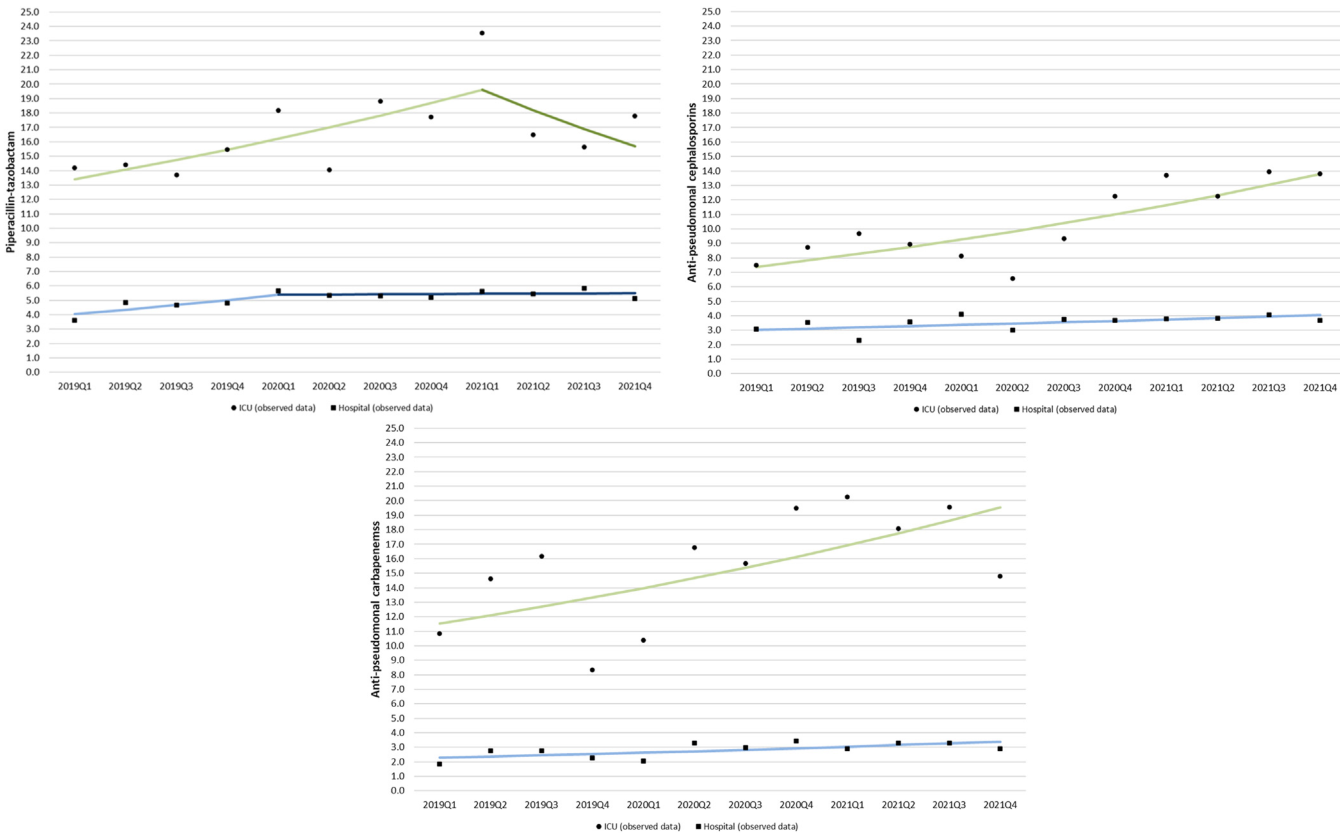

Figure 2. Trend analysis of diversification of anti-pseudomonal beta-lactams (anti-pseudomonal cephalosporins, anti-pseudomonal carbapenems and piperacillin-tazobactam). Data are expressed as defined daily dose per 100 occupied bed-days. Green lines [intensive care unit (ICU)] and blue lines (hospital) represent the modelled regression trend segments characterized by the joinpoint regression analysis.

over the 3 years of the study, which may be due to differences in susceptibility patterns of *Pseudomonas* spp. at the study centre. Over the study period, the mean percentages of bacteraemia caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae and multi-drug-resistant *Pseudomonas aeruginosa* in the ICU were 6.7 and 9.8%, respectively.

Consumption data in the ICU were similar to those presented previously [10,14]. Notwithstanding, mean global consumption (171 DDD/100 OBD) and the use of carbapenems (19.8 DDD/100 OBD) and fluoroquinolones (15.9 DDD/100 OBD) were higher in the study by Vaughn et al. [15]. Conversely, consumption of amoxicillin-clavulanic acid (2.2 DDD/100 OBD) and piperacillin-tazobactam (6.3 DDD/100 OBD) were higher in the present study [10]. Differences in antimicrobial use patterns between studies could be explained by the incidence of multi-drug-resistant organisms and the impact of the ASP in the study centre, and also by the COVID-19 pandemic as, despite relatively low detection rates of bacterial co-infections in patients with COVID-19 [15], antimicrobial consumption initially increased in ICUs [12,16].

This study has some limitations. The use of these indicators has not been validated previously, and application of the ratios may be limited by local data on susceptibility of commonly isolated micro-organisms. In addition, the selection of indicators was based on the agents of choice described in European guidelines for treatment of the major infectious syndromes and ICU consumption data at the study centre, which may differ in other countries around the world. However, these indicators are necessary due to the absence of a standardized method to evaluate the quality of antimicrobial use. The indicators are reliable and easy to calculate, which allows replication in other institutions and facilitates their widespread use.

5. Conclusions

Use of these indicators in hospitals, and specifically in ICUs, with higher rates of antimicrobial usage provides additional information to the common analysis of DDD per hospital stay. Implementation is feasible, and has led to the detection of patterns that agree with local guidelines and cumulative antibiogram reports in the study centre, and foster the implementation of targeted improvement actions within ASPs.

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Competing interests: None declared.

Ethical approval: This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the

Ethics Committee of University Hospital Virgen del Rocio (Project ID Code: PI-0361-2010).

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions: A.B.G. and M.V.G. were responsible for the conception and design of the study. E.R. and B.F. collected the data. G.P. undertook the analysis and interpretation of data. E.R. and A.B.G. drafted the article. G.P., B.F., T.A., L.H., E.D., M.M., M.A., M.L.G., J.M.C. and M.V.G. critically revised the manuscript for important intellectual content. All authors approved the final version before submission.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.106865.

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