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TITLE PAGE

Evaluation of piperacillin-tazobactam appropriateness and underlying drivers of inappropriate prescribing in a Belgian University Hospital: a retrospective study.

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Abstract

Background

Varying from 30% to 50% depending on the study, the high rate of inappropriate antimicrobial prescriptions is a major concern. These inappropriate prescriptions contribute to antibiotic resistance and associated morbidity and mortality. Prospective audit and feedback interventions is one of the core strategies recommended by the Infectious Diseases Society of America to improve antibiotic use. In line with this guidance, this approach was selected to evaluate piperacillin-tazobactam (PTZ) use within our institution.

Methods

A prospective audit of PTZ prescribing was conducted over an 11-week period at the CHU of Liège. Prescriptions were reviewed weekly by an infectious diseases specialist and a clinical hospital pharmacist. The primary outcome was the appropriateness of PTZ prescriptions across three main evaluation criteria -indication, spectrum and duration- and one minor criterion -notification of the indication in the medical records-. The secondary outcome was to identify potential drivers of inappropriate prescribing. Interventions involved antibiotic discontinuation, de-escalation, oral step-down therapy and optimizing the pharmacokinetic and pharmacodynamic (PK/PD) profile.

Results

Overall, 91.8% of the prescriptions were deemed appropriate for indication, 74.5 % for spectrum, and 50% for duration. Notification was adequate in 65.5% of cases. However, most prescriptions were empirical (nearly 90%). Regarding stewardship interventions, broad-spectrum antibiotics were discontinued or de-escalated in 33.6% and 19.1% of cases, respectively, with intravenous-to-oral switch and PK/PD optimization suggested in 17.3% and 11.8% of cases. Our study identified several statistically significant determinants of inappropriate antibiotic use, including the type of care unit and the Charlson Comorbidity Index.

Conclusions

Our findings point out the role of an antimicrobial stewardship program in improving antibiotic use, especially in surgical units where inappropriate indication and poor notification were most common. Importantly, antibiotic treatment duration remains problematic across all hospital units. By linking patient characteristics to outcomes, our study identifies key drivers of inappropriate use, which could be further confirmed and refined in future research.

Keywords

- Prospective audit and feedback
- Antimicrobial stewardship

- Drivers of inappropriate prescribing
- Piperacillin-tazobactam

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Introduction

An estimated 30-50% of antibiotics prescribed in healthcare settings are either unnecessary or inappropriate (1,2). Inappropriate use not only exposes patients to treatments with potentially no benefit but also heightens the baseline risk of antibiotic-related adverse events, which has been estimated at 20% among hospitalized patients (3). These adverse events range from allergic reactions to gastrointestinal disturbances such as *Clostridioides difficile* infections, organ toxicities, and the emergence of resistant pathogens (3,4). Curtailing such misuse is crucial for curbing antimicrobial resistance (AMR) and preventing the projected 10 million annual AMR-related deaths by 2050 (5), a threat the World Health Organization (WHO) has identified as a major public health concern (6).

Despite the well-documented clinical and ecological consequences of inappropriate antibiotic use, the determinants underlying suboptimal prescribing remain insufficiently characterized. Current literature has largely focused on descriptive approach, reporting antibiotic consumption, compliance to guidelines, or overall appropriateness rates, without examining the patient-, ward- or specific factors associated with inappropriate spectrum or unnecessarily prolonged antibiotic duration (7–9). Addressing this knowledge gap is essential to guide targeted antimicrobial stewardship interventions rather than non-specific approaches. In this context, antibiotic stewardship programs (ASPs) play a role in reducing antibiotic use, improving patient outcomes, and combating

AMR (10). The 2016 Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines recommend two core strategies for ASPs: pre-authorization (PA) and prospective audit with intervention and feedback (PAIF) (11). Recent research indicates that PAIF may have a more substantial impact on antibiotic consumption, suggesting that it should be prioritized (10). PAIF typically involves pharmacists and/or physicians who are trained in antimicrobial stewardship, who review antibiotic prescriptions and provide feedback to prescribers to optimize antibiotic use (2,10–12). Moreover, in recent years, evidence supporting shorter antibiotic courses for common infections has emerged and has been incorporated to updated guideline recommendations (13), reinforcing the role of antimicrobial stewardship.

Since 2017, the WHO has advocated strict antibiotic use monitoring. The AWaRe classification categorizes antibiotics into “Access”, “Watch” and “Reserve” based on their impact on resistance and appropriate use. “Access” antibiotics are antibiotics with a narrow spectrum of activity and a low potential to select for antibiotic resistance. “Watch” antibiotics are more associated with the selection for antibiotic resistance and are usually used in patients in hospital settings. “Reserve” antibiotics are last-resort antibiotics that should only be used to treat infections caused by multidrug-resistant bacteria (14). Monitoring these latter two categories is imperative for ASPs (6).

Among WHO AWaRe “Watch” antibiotics, piperacillin-tazobactam (PTZ), a combination of a β-lactam and a β-lactamase inhibitor, deserves

particular attention (6). PTZ exhibits a broad spectrum of activity against Gram-positive, Gram-negative (including *Pseudomonas aeruginosa*), and anaerobic bacteria (15). It is used to treat a variety of infections, including respiratory tract, urinary tract, intra-abdominal, skin and soft tissue infections, as well as febrile neutropenia and bloodstream infections (15). Globally, PTZ accounts for approximately 6-15% of hospital antibiotic prescriptions for systemic use, either as empirically or as targeted therapy (7). In line with international findings, PTZ is also widely used in Belgian hospitals. Its use increased by 52% from 2012 to 2022 (16).

Therefore, the present study aims to evaluate the appropriateness of PTZ prescribing in a Belgian university hospital, using a PAIF approach, with a focus on indication, spectrum and duration. In addition, this study investigates patients' characteristics and care settings associated with inappropriate prescribing and examines how stewardship interventions, delivered by an infectious diseases (ID) specialist-hospital pharmacist team, influence prescribing practices. By targeting inappropriate use of a frequently used WHO AWaRe "Watch" antibiotic, this study seeks to support efforts to limit AMR and improve public health outcomes.

Materials and Methods

Study design and definitions

This retrospective descriptive study analyzed data collected through a PAIF. A weekly evaluation of PTZ prescriptions was performed over 11 weeks (from March 17, 2023 - to June 30, 2023) by an infectious diseases

(ID) physician and a clinical hospital pharmacist, from the antimicrobial stewardship team, at the University Hospital (CHU) of Liège, a 1038-bed tertiary teaching hospital in Belgium. All patients, regardless of age, were eligible for inclusion if they were hospitalized in a care ward (internal medicine, surgery, intensive care unit, emergency or long-term care) at 9:00 am on the day of the audit and had an active prescription for PTZ. Patients were excluded if they were discharged, transferred to another hospital or deceased before the audit time point. Patients, exclusively treated in outpatient or day-care clinics, were also excluded. Patients receiving PTZ were identified electronically (Omnipro Version 4.6.5.b). Information was extracted from the medical electronic files and included age, gender, comorbidities, immunocompromised status, hospital ward, and complete data on PTZ prescriptions, including dose, route of administration and treatment duration, obtained from electronic prescribing systems. Infection characteristics were determined by reviewing each patient's medical file jointly with an ID specialist and a clinical hospital pharmacist and included the infection source and microbiological culture results, if available.

The primary outcome was the appropriateness of PTZ prescriptions across three main evaluation criteria -indication, spectrum and duration- and one minor criterion, defined as notification of the indication in the medical records. The secondary outcome was to identify potential drivers of inappropriate prescribing.

The main criteria were selected using the Centers for Disease Control and Prevention (CDC) audit tools, focusing on diagnosis (indication), de-escalation (spectrum), and treatment duration (1). Notification in medical records was assessed as a minor criterion, since it was not part of CDC audit tools but was still considered of interest.

Appropriate indication was defined as antibiotic use warranted by clinical, biological and/or radiological evidence consistent with suspected or documented bacterial infection. Appropriate spectrum referred to PTZ use when its antimicrobial coverage aligned with the suspected or documented pathogen, based on available culture results when present, and when narrower-spectrum alternatives were either unsuitable or not preferred based on local susceptibility data. Duration was deemed appropriate if it was consistent with local recommendations for the infection type and adapted to the patients' clinical improvement, microbiological data, and adequate source control. Appropriate notification was defined as the presence of a clearly stated indication for PTZ in the patients' medical charts.

To ensure consistent feedback, all prescribers were directly informed by telephone and a written note was added to the patients' medical records as part of the PAIF intervention.

The number of PTZ days saved was calculated as the difference between the planned end date mentioned by the prescriber and the actual end date following the PAIF intervention, when the intervention led to an earlier discontinuation.

Empirical treatment referred to the initiation of antibiotics prior to pathogen identification, based on clinical signs, suspected site of infection and patient history, with guidance from local susceptibility patterns. In contrast, targeted treatment followed microbiological confirmation of the pathogen and its susceptibilities, guiding a switch to pathogen-specific therapy after the initial empiric regimen.

De-escalation was defined as the narrowing of empiric broad-spectrum antibiotic therapy, typically within 72 to 96 hours, based on clinical reassessment and microbiological data, to optimize targeting of the pathogen and reducing unnecessary antibiotic exposure. In contrast, escalation was defined as the addition of a new antibiotic or a switch to a broader-spectrum antibiotic therapy.

Pharmacokinetic and pharmacodynamic (PK/PD) optimization of PTZ administration was pursued through the use of extended (4-hour) or continuous infusions, mainly in cases of deep-seated infections (e.g. endocarditis, osteomyelitis, undrained abscess,...), prolonged antibiotic courses (usually 4-6 weeks, and longer courses in cases of unresolved infections) and/or infections caused by pathogens with PTZ minimum inhibitory concentrations (MICs) close to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) susceptibility breakpoint, particularly those falling within or adjacent to the area of technical uncertainty (e.g. MICs of 8-16mg/L for Enterobacterales or *Pseudomonas aeruginosa*) (17).

Patients were categorized according to their comorbidities using the Charlson Comorbidity Index (CCI) updated by Quan et al. and their immunocompromised profile to assess the impact of main and minor criteria on different groups of patients (18). The diagnoses were defined using the International Classification of Diseases, Tenth Revision (ICD-10) coding system. Immunocompromised status was defined as the presence of at least one of the following criteria: ongoing oncological follow-up, being infected with Human Immunodeficiency Virus (HIV), or current use of immunosuppressive therapy (e.g. tacrolimus, mycophenolate mofetil, leflunomide, methotrexate,…) or chemotherapy for active cancer (e.g. paclitaxel, 5-fluorouracil, capecitabine,…).

Statistical analysis

Quantitative variables, related to patient characteristics, are measured using means and standard deviations (± SD), medians and interquartile ranges (Q1 - Q3) and extreme values (Minimum -Maximum). Qualitative variables, related to patient characteristics, are described using frequency tables (Numbers and %). Determinants of inappropriate antibiotic use were analyzed using simple logistic (= univariate) regression models. In those models, all available characteristics (gender, age, Charlson Comorbidity Index, immunosuppression, number of days under antibiotic therapy and type of care units) were considered separately for their impact on the probability of each risk considered. The primary outcome was measured using ‘Odds Ratios’ (OR) and 95% confidence intervals (95% CI) as well as p-values (p). Results were considered statistically significant at

the 5% threshold ($p<0.05$). Analyses were performed using SAS software (version 9.4).

Results

Population characteristics

In total, 110 distinct hospital stays, corresponding to 110 patients, were analyzed. When multiple evaluations were performed during the same hospital stay, only the first evaluation was considered.

Table 1 summarizes the population characteristics. Patient ages ranged from 27 to 97 years, with a mean age of 71 (± 15) years. Males comprised 60% of the sample. CCI scores varied from 0 to 9, with a mean score of 3.1 (± 2.2) and a median of 3 (Q1-Q3: 1-5). Immunosuppression was present in 23.6% of cases. Hospital stays (N =110) were distributed across units as follows: internal medicine (46.4%), surgery (44.5%), intensive care (3.6%), emergency (0.9%) and long-term care (4.5%).

Table 1. Description of stays (N=110 stays)

	Results * (N= 110)
Gender,	
Male	66 (60.0)
Female	44 (40.0)
Age (Years)	70.9 ± 15.2
Charlson Comorbidity Index (0 – 24)	3.1 ± 2.2
0	*13 (11.8)*
1	*15 (13.6)*
2	*18 (16.4)*
3	*22 (20.0)*
4	*14 (12.7)*
5	*14 (12.7)*
6	*3 (2.7)*
7	*4 (3.6)*
8	*5 (4.5)*
9	*2 (1.8)*

Immunosuppression	
Yes	26 (23.6)
No	84 (76.4)
Care units	
Internal medicine	51 (46.4)
Surgery	49 (44.5)
Intensive care	4 (3.6)
Emergency	1 (0.9)
Long-term care	5 (4.5)

** Number (%) or Mean ± Standard deviation (SD)*

A detailed description of hospital stays related to targeted antibiotic therapy is provided in the Supplementary Data. (Supplementary Tables 1 and 2)

Antibiotic therapy evaluation

Evaluations were performed on average on the fourth day of antibiotic therapy (± 4 days) [median (Q1-Q3): 4 (2-6); range: 0-38 days]. At the moment of evaluation, antibiotic therapy was more often administered empirically (89.9%), whereas targeted therapy was used in only 10.1%. The most common indications were respiratory infections (46.6%), followed by gastrointestinal infections (15.5%), urinary tract infections (12.7%), and skin and soft tissue infections (10%).

The indication was deemed appropriate in 91.8% of cases, the antibiotic spectrum in 74.5%, the duration in 50.0%, and the notification in medical records in 65.5%, as described in Table 2.

Table 2. Antibiotic therapy evaluation (N =110 stays)

	N (%)
Treatment type[a]	
Empirical	98 (89.9)
Targeted	11 (10.1)
Appropriate indication	101 (91.8)
Appropriate spectrum	82 (74.5)

Reason for which it was considered as inappropriate[b]	
No indication	*6*
Isolates with susceptibility to narrower-spectrum antibiotics	*17*
Source control failure[¥]	*2*
PTZ-resistant strains	*2*
Isolate with susceptibility to narrower-spectrum antibiotics and PTZ-resistant strain	*1*
Appropriate duration	55 (50.0)
Appropriate notification in medical records	72 (65.5)

[a] Data available for 109 hospital stays
[b] Data available for 28 hospital stays
[¥]Source control failure was defined as the persistence of infection despite appropriate interventions, such as drainage or removal of an infected device
Abbreviation: PTZ: Piperacillin-tazobactam

Detailed information supporting the evaluation of targeted antibiotic therapies is provided in the Supplementary Data. (Supplementary Table 3)

Outcomes

As detailed in Table 3, antibiotic therapy was either discontinued or an end date proposed in 37 prescriptions (33.6%); spectrum was narrowed in 21 (19.1%) and broadened in 2 (1.8%); and the duration of therapy was shortened in 35 (31.8%). An oral step-down approach was proposed in 19 (17.3%), and PK/PD optimization was performed in 13 (11.8%). In total, 149 PTZ antibiotic days were spared as a direct result of these interventions. Overall, 40 hospital stays (36.4%) did not lead to any intervention after evaluation. This included cases in which all three major criteria were appropriate and therapy was continued, as well as, cases with at least one inappropriate major criterion (inappropriate spectrum or duration) for which no intervention was possible because discontinuation was already scheduled on the day of the audit.

Table 3. Interventions (N=110 stays) - Multiple interventions were possible for the same antibiotic prescription

	N (%)
Discontinuation (effective or proposed end date) of broad-spectrum antibiotics without de-escalation or escalation	37 (33.6)
De-escalation and escalation of antibiotic therapy	23 (20.9)
De-escalation	*21*
Escalation	*2*
PTZ duration reduction	35 (31.8)
PTZ dose reduction	3 (2.7)
Oral step-down therapy	19 (17.3)
PK/PD Optimization	13 (11.8)

Abbreviations: PK/PD: Pharmacokinetic and pharmacodynamic, PTZ: Piperacillin-tazobactam

Detailed data on interventions associated to targeted antibiotic therapies are provided in the Supplementary Data. (Supplementary Table 4)

Determinants of inappropriate antibiotic use

Determinants of inappropriate antibiotic use were highlighted using simple univariate logistic regression modeling the probability of each risk considered according to each available characteristic (gender, age, Charlson Comorbidity Index, immunosuppression, number of days under antibiotic therapy and type of care units). (Table 4)

Type of care units

Surgical units were associated with a statistically significant 9.8-fold higher risk of inappropriate indication (OR = 9.8; 95% CI:1.2 - 81.2; p = 0.035). Inappropriate indications were observed in 8 out of 49 antibiotic prescriptions (16.3%) in surgical units, compared to 1 out of 51 (2.0%) in internal medicine and antibiotic prescriptions in surgical units were associated with a statistically significant 7.8-fold higher risk of inappropriate

notification compared to internal medicine units (OR 7.8; 95% CI: 3.0 - 20.1; p<0.0001), with 29 out of 49 (59.2%) in surgical units versus 8 out of 51 (15.7%) in internal medicine.

Charlson Comorbidity Index

Higher Charlson Comorbidity Index (CCI) scores were significantly associated with a lower risk of spectrum inappropriateness (p = 0.013).

Antibiotic treatment duration, gender, age and immunosuppression

No significant impact of antibiotic treatment duration, gender or immunosuppression on inappropriate antibiotic use was showed and although not statistically significant, a trend toward inappropriateness in spectrum and duration with older age was observed. However, this observation should be interpreted cautiously, as the study population was predominantly elderly (mean age of 71 years), potentially introducing sampling bias.

Table 4. Determinants of inappropriate antibiotic use (N=110 stays) – Modeling of inappropriateness risks: for each risk modeled, a simple logistic regression model per explanatory factor.

Risk	Explanatory factor	OR (95% CI)	p-value
Indication inappropriateness	Gender (reference = Male)	0.73 (0.17 – 3.1)	0.67
	Age (years)	0.99 (0.95 – 1.04)	0.80
	Charlson Comorbidity Index (0 – 24)	0.94 (0.69 – 1.3)	0.71
	Immunosuppression (reference = No)	0.38 (0.045 – 3.2)	0.37
	Number of days since PTZ initiation	0.88 (0.66 – 1.2)	0.40
	Care units: surgery vs internal medicine	9.8 (1.2 – 81.2)	**0.035**
Spectrum inappropriateness	Gender (reference = Male)	1.2 (0.49 – 2.8)	0.72
	Age (years)	0.98 (0.95 – 1.002)	0.069

	Charlson Comorbidity Index (0 – 24)	0.74 (0.59 – 0.94)	**0.013**
	Immunosuppression (reference = No)	0.63 (0.21 – 1.9)	0.41
	Number of days since PTZ initiation	1.1 (0.97 – 1.3)	0.13
	Care units: surgery vs internal medicine	2.3 (0.89 – 5.8)	0.087
Duration inappropriateness	Gender (reference = Male)	1.0 (0.47 – 2.1)	1.0
	Age (years)	1.0 (0.997 – 1.05)	0.087
	Charlson Comorbidity Index (0 – 24)	0.99 (0.84 – 1.2)	0.90
	Immunosuppression (reference = No)	0.54 (0.22 – 1.3)	0.18
	Number of days since PTZ initiation	0.94 (0.83 – 1.1)	0.29
	Care units: surgery vs internal medicine	1.1 (0.50 – 2.4)	0.83
Notification in medical records inappropriateness	Gender (reference = Male)	0.69 (0.30 – 1.6)	0.37
	Age (years)	0.98 (0.96 – 1.006)	0.12
	Charlson Comorbidity Index (0 – 24)	1.0 (0.85 – 1.2)	0.85
	Immunosuppression (reference = No)	1.2 (0.50 – 3.1)	0.63
	Number of days since PTZ initiation	0.87 (0.74 – 1.03)	0.10
	Care units: surgery vs internal medicine	7.8 (3.0 – 20.1)	**<0.0001**

Discussion

The key findings of our study can be summarized as follows for the main criteria: the indication was appropriate in 91.8% of prescriptions, spectrum in 74.5% and duration in 50%. However, these findings should be interpreted with caution, as nearly 90% of prescriptions in our cohort were initiated empirically. The high rate of appropriateness for indication reflects the frequent use of PTZ in clinical scenarios where broad empirical coverage is justified, rather than definitive targeted therapy. For the minor criterion, notification of the indication in medical records was appropriate in 65.5% of prescriptions.

Duration was the most frequent area of suboptimal prescribing in our study, with 50% of PTZ prescriptions being inappropriate for duration,

mainly due to excessive treatment durations and resulting in a cumulative reduction of 149 days of PTZ exposure across the audited prescriptions. This translated into a high proportion of stewardship actions targeting duration, including treatment shortening (31.8%) and antibiotic discontinuation, either through a clearly proposed end date or an immediate stop (33.6%). These results exceed those commonly reported in literature. In the audit by Langford et al., only 25% of interventions involved duration reduction and 20% resulted in discontinuation (12). This difference in magnitude is likely attributable to differences in study design and endpoints. Langford et al. examined the distribution of antimicrobial stewardship recommendations across a wide range of systemic antibiotics (both broad- and narrow - spectrum) over several years. In contrast, our analysis focused specifically on PTZ and applied treatment appropriateness criteria, with duration considered as a major component. This targeted approach likely captured more prolonged treatment courses, which resulted in a higher proportion of duration-related interventions. In addition, the PAIF-based strategy employed by Langford et al, may also have differed in terms of implementation, feedback intensity or prescriber responsiveness, which could partly explain the differences between their intervention rates and ours. These findings reinforce prior evidence that the PAIF model effectively shortens antibiotic courses. Tamma et al. reported lower antibiotic use with PAIF - median of 6 days of therapy (DOT) per 1000 patient-days (PD) compared to 8 DOT/1000 PD with a preauthorization model - and shorter therapy durations with a median length of therapy (LOT) reduced to 5 LOT/1000 PD with PAIF versus 7 LOT/1000 PD with the other alternative

stewardship approach (10). In our study, the PAIF was associated with a reduction of 3.7 PTZ DOT per 1000 PD. This magnitude of reduction is similar to the -2.45 DOT per 1000 PD reported by Tamma et al. following implementation of their PAIF-strategy (10). However, direct comparison should be interpreted with caution, as their study assessed multiple systemic antibiotics using an interrupted time-series design over a 10-month period, whereas our analysis focused on a single broad-spectrum agent over an 11-week prospective audit. Nevertheless, the magnitude of effect supports the effectiveness of PAIF interventions to reduce antibiotic exposure in routine clinical practice.

Moreover, the current shift in clinical practice toward shorter antibiotic courses may also have increased the frequency of duration-related interventions observed in our study. This shift is particularly relevant for respiratory, intra-abdominal and urinary tract infections (19) - the predominant indications observed in our cohort. Several randomized trials have demonstrated that shorter antibiotic courses can be safely and effectively used for common infections, reducing treatment durations to 3 days for community-acquired pneumonia (20,21), 4-8 days for intra-abdominal infections (22,23) and 3-5 days for uncomplicated cystitis, with 7 days sufficient for complicated or bacteremic urinary tract infections when using highly bioavailable agents (24). These findings have been incorporated into updated guidelines. However, our results indicate that these recommendations have not yet been widely adopted in clinical practice, as no significant difference was observed between surgical and internal medicine wards.

Regarding the appropriateness of antibiotic indication, our findings are reassuring, with around 92% of prescriptions judged appropriate across all hospital units. This high rate was particularly prevalent within internal medicines units, where the initial choice was generally appropriate. In contrast, surgical units presented more challenges, as they were associated with a statistically significant 9.8-fold increased risk of inappropriate indication, underscoring the need for intervention at the very onset of antibiotic prescribing in these surgical settings. Encouragingly, prior research highlights the benefits of infectious diseases consultation (IDC) in improving antimicrobial appropriateness. Bork et al. showed that IDC improved significantly prescribing appropriateness, particularly in surgical units, where the odds of appropriateness were nearly three times higher with IDC involvement (OR: 2.9; 95% CI, 2.1-3.8), compared with a more modest impact in medical specialties (OR: 1.6; 95% CI, 1.1-2.2) (25).

In terms of antibiotic spectrum, our data indicated a moderate level of appropriateness, with 75% of prescriptions considered appropriate, thus suggesting room for improvement in optimizing empirical choices and promoting de-escalation strategies. Notably, 19.1% of our PAIF interventions involved a reduction in antibiotic spectrum, a proportion comparable to that reported by Langford et al., in whom de-escalation accounted for 17% of of PAIF recommendations, suggesting a similar magnitude of de-escalation opportunities across these stewardship programs (12). Using the European Centre for Disease Prevention and Control (ECDC) methodology, a large European Point Prevalence Survey has reported that de-escalation was documented in fewer than 5% of

prescriptions at the time of survey (26). However, direct comparison between PAIF studies and Point Prevalence Surveys (PPS) data must be interpreted with caution. While PPS capture whether de-escalation has occurred at a single point in time, they do not assess whether de-escalation opportunities were clinically appropriate. In contrast, our prospective audit actively identified possibilities for spectrum narrowing which may explain the higher proportion observed. Furthermore, in literature, appropriateness of indication or spectrum is more commonly captured indirectly through the "compliance to local guidelines", rather than evaluated as distinct outcomes. The "compliance to local guidelines" evaluates the choice of antibiotic selected, without considering the route of administration, dosage or duration. Versporten et al. reported "compliance to local guidelines" rates ranging from 70.8% to 85.7% across European countries (7). This aligns with national-level data, such as Belgian Point Prevalence Survey (Belgian-PPS), which showed a 76.6% overall compliance rate, decreasing to 63.5% in tertiary hospitals (8).

Although recognized as a quality indicator within ASP, the notification of antibiotic prescribing in medical records remained suboptimal in our study, with indications recorded in only 65.5% of prescriptions. This is lower than the 76.9% global rate reported by Global-PPS (7), but it is consistent with the 2017 Belgian-PPS data, reporting a documentation rate of 81.9% in total and 70.1% in tertiary hospitals (8). Beyond benchmarking considerations, suboptimal notification may have important clinical implications, as poor recording can lead to ineffective communication and reluctance to discontinue unnecessary treatment. Interestingly, in our

study, the type of care unit also significantly influenced the risk of inadequate notification in medical records, with surgical units exhibiting a 7.8-fold higher risk compared to internal medicine wards. This finding underscores persistent gaps in clinical documentation, suggesting that targeted efforts to improve recording practices may be particularly necessary in surgical units.

Other noteworthy interventions in our study included the intravenous-to-oral switch and PK/PD optimization, with substantial intervention rates of 17.3% and 11.8% respectively. The 17.3% rate of oral step-down therapy observed in our cohort was markedly higher than the 2-6% typically reported in literature (8,9,26). This may reflect the ID specialist's proactive approach, using the audit to anticipate the most appropriate high-bioavailability oral options based on the antibiogram and to initiate an oral switch when appropriate. More generally, such differences are likely attributable to methodological variations rather than discrepancies, as PAIF actively highlights optimization opportunities that cross-sectional surveys may not detect. Additionally, PTZ PK/PD optimization, through the use of 4-hour extended or continuous infusions, was actively promoted to improve pharmacodynamic target attainment and potentially enhance clinical outcomes, although further clinical evidence is still needed to support widespread implementation of such strategies (27).

Strength, limitations & opportunities for further research

A key strength of our study is its ability to go beyond purely descriptive analyses, which dominate existing literature. Many previous studies, such as Point Prevalence Surveys, have focused on reporting interventions, describing patient characteristics and outcomes separately without exploring a correlation between patient profiles and effectiveness of interventions (7–9). In contrast, our study sought to establish these connections, providing a deeper understanding of where interventions are most impactful.

Our study has several limitations, including its single-center design, which may restrict the applicability of the findings to other settings with different patient demographics, stewardship protocols and levels of antimicrobial resistance. In addition, the actual implementation of the recommendations made during the PAIF was not systematically assessed. Another limitation of our study lies in the high proportion of empirical antibiotic use, which was expected with PTZ, but limited our ability to precisely assess spectrum appropriateness in targeted treatments. Future studies should, therefore, specifically evaluate the appropriateness of broad-spectrum antibiotics in targeted therapy settings, as this may reveal different prescribing patterns. Interestingly, spectrum appropriateness did not decline among immunocompromised patients, which contrasts with initial expectations. This may partly be explained by the empirical PTZ use, where broad-spectrum coverage is generally considered appropriate,

particularly in nosocomial contexts. Another possible explanation is the increased level of supervision and multidisciplinary decision-making often involved in the management of complex or high-risk patients.

Another potential area for improvement would be a more detailed quantification of inappropriate antibiotic durations. Although our study identified cases of overtreatment, we could not quantify unnecessary antibiotic days by subgroups, such as immunocompetent and immunosuppressed patients, due to the frequent absence of predefined treatment durations. Such an analysis could have provided valuable information to determine if the impact of ASP is even greater in reducing antibiotic overexposure among high-risk patients. Notably, emerging evidence supports the safety and efficacy of shorter antibiotic courses in immunosuppressed patients, including solid organ transplant recipients. As highlighted by Imlay et al., shorter regimens have been shown to be effective in these high-risk patients, for example, a 5- to 7-day treatment for uncomplicated urinary tract infections in kidney transplant recipients and a shortened perioperative prophylaxis in liver transplant recipients (28). These findings challenge the standard practices' presumption that immunosuppressed patients always require extended courses of antibiotic, particularly when a clinical improvement is observed and with adequate source control.

In this context, given the limitations of the present study, future antimicrobial stewardship strategies may benefit from the integration of Clinical Decision Support Systems. These tools have been associated with

reduced antimicrobial consumption and health care costs (29,30) and may facilitate a prompt reassessment of empirical therapy. Moreover, advances in artificial intelligence offer promising opportunities for antimicrobial stewardship, as machine-learning approaches can analyze large clinical datasets to predict antibiotic resistance and provide personalized recommendations, which may help reduce inappropriate PTZ use, especially in urinary tract infections (31,32). Although these approaches were not directly assessed in the present study, they could be considered as potential strategies to address some of the identified limitations and to optimize antibiotic use in future research.

Conclusions

This study assessed the appropriateness of PTZ use in a university hospital through a structured prospective audit and feedback and identified key factors associated with inappropriate prescribing. Our findings reinforce the importance of ASP in guiding antibiotic therapy, particularly in surgical settings where inappropriate indication and poor notification are most prevalent. While internal medicine units demonstrated relatively high adherence to appropriate prescribing, treatment duration remains a huge ongoing concern across all units. The originality of our work lies in its ability to link patient characteristics with stewardship outcomes, enabling a more refined analysis of factors driving inappropriate antibiotic use. Future research should explore whether spectrum de-escalation is under-utilized and whether treatment durations remain inappropriate in high-risk populations, potentially revealing disparities between immunocompetent

and immunocompromised patients. Monitoring efforts should not be limited to PTZ but should also include other AWaRe “Watch” and “Reserve” broad-spectrum antibiotics, which may equally contribute to inappropriate prescribing and require targeted assessment.

List of abbreviations

95% CI: 95% confidence interval

AMR: Antimicrobial resistance

ASPs: Antibiotic stewardship programs

CCI: Charlson Comorbidity Index

CDC: Centers for Disease Control and Prevention

CHU: Centre Hospitalier Universitaire; University Hospital

DDDs: Defined Daily Doses

DOT/1000 PD: Days of therapy per 1000 patient-days

ECDC: European Centre for Disease Prevention and Control

EUCAST: European Committee on Antimicrobial Susceptibility Testing

HIV: Human Immunodeficiency Virus

ICD-10: International Classification of Diseases, Tenth Revision

ID: Infectious diseases

IDC: Infectious diseases consultation

IDSA: Infectious Diseases Society of America

LOT/1000 PD: Length of therapy per 1000 patient-days

MICs: Minimum inhibitory concentrations

OR: Odds Ratio

p: p-value

PA: Pre-authorization

PAIF: Prospective audit with intervention and feedback

PPS: Point Prevalence Survey

PK/PD: Pharmacokinetic and pharmacodynamic

PTZ: Piperacillin-tazobactam

SHEA: Society for Healthcare Epidemiology of America

WHO: World Health Organization

Declarations

Ethics approval and consent

Approval for the study protocol was obtained from the local ethics review committee (Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège, reference number 2023/223). All participants were assigned unique identification numbers to ensure anonymization and protect confidentiality. The need to obtain individual consent was waived due to the retrospective nature of the study and the anonymized dataset. All procedures were conducted in accordance with the local ethics review committee.

Availability of data and materials' statement

The data that support the findings of this study are available on request from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors'contributions

VG: Writing - original draft, Project administration, Methodology, Investigation, Conceptualization, Resources, Formal analysis, Data curation. CO: Project administration, Methodology, Investigation, Conceptualization, Resources. NM: Writing - review & editing, Software, Formal analysis, Data curation. GD: Writing - review & editing, Formal analysis, Data curation, Validation, Supervision.

All authors read and approved the final manuscript

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