JHPHS
Journal of Hospital Pharmacy and Health Services

Original Paper

Open Access

SMART-CAZ/AVI: algorithm to guide pharmaceutical clinical reasoning in managing the rational use of ceftazidime/avibactam in adult patients

Renan GIANOTI[1], Elaine Soares BARRETO[1], Flavia Fernandes RIBEIRO[1], Paola NICOLINI[2], Renata BERANGER[3], Dandiany Camily SOFKA[4], Marinei Campos RICIERI[4]

[1]Serviço de Farmácia Clínica, Hospital Samaritano Botafogo, Rio de Janeiro, Brasil; [2]Serviço de Farmácia Clínica Corporativa, Rede Amil, São Paulo, Brasil; [3]Serviço de Controle de Infecção Hospitalar, Hospital Samaritano Botafogo, Rio de Janeiro, Brasil; [4]Esperantum Saúde, Paraná, Brasil.

Corresponding author: Gianoti R, gianoti_r@hotmail.com

Submitted: 28-02-2025 Resubmitted: 15-05-2025 Accepted: 16-05-2025

Double blind peer review

Abstract

Objectives: Develop and evaluate the application of SMART-CAZ/AVI, an algorithm designed to guide the clinical pharmacist's role in managing the use of ceftazidime/avibactam (CAZ/AVI). The algorithm supports pharmaceutical monitoring as a clinical decision-support tool, facilitating the identification of opportunities to optimize antibiotic therapy and ensuring the rational use of CAZ/AVI. **Methods:** The Stewardship & Monitoring Algorithm for Rational Therapy (SMART) model was developed based on antimicrobial stewardship principles and divided into three sections: Initial Pharmaceutical Assessment, Microbiology, and Time-Out. SMART-CAZ/AVI refers to the application of the SMART model to the pharmaceutical assessment of CAZ/AVI in adult patients. Each section contains specific questions and guidelines to direct the clinical pharmacist's role in ensuring effective and safe antibiotic therapy. The analysis of the algorithm's application was conducted retrospectively and descriptively, using data collected before and after the implementation of SMART-CAZ/AVI in a private hospital in Rio de Janeiro, from January 2023 to September 2024. The data were divided into three 7-month periods: pre-implementation, immediate post-implementation, and late post-implementation. **Results:** A total of 93 Time-Outs and 23 pharmaceutical interventions were recorded, with overdosing based on creatinine clearance (ClCr) being the most frequent issue (68.4%). The analysis between the immediate and late post-implementation periods revealed a 55.2% reduction in overdose interventions and the elimination of administration scheduling errors; however, prolonged antibiotic therapy increased by 300%. The percentage of treatments without formal indication increased by 108.33%, and the analysis of the mean days of therapy (DOT) showed an initial reduction of 64.15% in the immediate period, followed by a late increase of 242.11%. **Conclusion:** SMART-CAZ/AVI has the potential to become an essential tool to support clinical pharmacists in managing CAZ/AVI use, identifying key issues in antimicrobial therapy. Its implementation directly contributed to reducing overdose and administration errors. SMART-CAZ/AVI may be established as a standardized tool to streamline pharmaceutical monitoring in hospitals, ensuring effective and safe antibiotic therapy.

Keywords: ceftazidime, antimicrobial stewardship, clinical pharmacy service, drug utilizations, workflow

SMART-CAZ/AVI: algoritmo para guiar o raciocínio clínico farmacêutico no gerenciamento do uso racional de ceftazidima/avibactam em pacientes adultos

Resumo

Objetivos: Desenvolver e avaliar a aplicação do SMART-CAZ/AVI, um algoritmo para orientar a atuação do farmacêutico clínico no gerenciamento do uso de ceftazidima/avibactam (CAZ/AVI), conduzindo o acompanhamento farmacêutico como uma ferramenta de suporte à decisão clínica que facilita a identificação de oportunidades de otimização da antibioticoterapia, garantindo o uso racional de CAZ/AVI. **Métodos:** O modelo *Stewardship & Monitoring Algorithm for Rational Therapy* (SMART) foi elaborado baseado nos princípios do *stewardship* de antimicrobianos, dividido em três seções: Avaliação Farmacêutica Inicial, Microbiologia e *Time-Out*. Denomina-se SMART-CAZ/AVI o modelo SMART aplicado à avaliação farmacêutica do CAZ/AVI, em pacientes adultos. As seções contêm perguntas e orientações específicas, que direcionam a atuação do farmacêutico clínico na garantia da antibioticoterapia efetiva e segura. A análise da aplicação do algoritmo foi realizada de forma retrospectiva descritiva, com dados antes e após a implementação do SMART-CAZ/AVI, em um hospital privado do Rio de Janeiro, no período entre janeiro/2023 a setembro/2024. Os dados foram divididos em três períodos de 7 meses que correspondem aos períodos pré-implantação, imediato pós implantação e tardio pós implantação. **Resultados:** Foram registrados 93 *Time-Outs* e 23 intervenções farmacêuticas, sendo sobredose baseada no *clearance* de creatinina (ClCr) a mais frequente (68,4%). A análise entre o período imediato e tardio revelou uma redução de 55,2% nas intervenções de sobredose, eliminação de erros de aprazamento,

mas um aumento de 300% na antibioticoterapia prolongada. Os tratamentos sem indicação formal cresceram 108,33%, e a análise da média de dias de terapia (DOT) mostrou uma redução inicial de 64,15% no período imediato, seguida de um aumento tardio de 242,11%. **Conclusão:** O SMART-CAZ/AVI apresenta potencial para se tornar uma importante ferramenta de auxílio da atuação do farmacêutico clínico no gerenciamento do uso de CAZ/AVI, revelando os principais problemas da terapia antimicrobiana. Sua utilização contribuiu diretamente para a redução de erros de sobredose e erros de administração. O SMART-CAZ/AVI poderá ser consolidado como uma ferramenta para padronizar e agilizar o acompanhamento farmacêutico nos hospitais, orientando a antibioticoterapia efetiva segura.

Palavras-chave: ceftazidima, gestão de antimicrobianos, serviço de farmácia clínica, uso racional de medicamentos, fluxograma

Introduction

Ceftazidime/Avibactam (CAZ/AVI) is an intravenous antibiotic approved in Brazil in 2018, consisting of a combination of a third-generation cephalosporin (Ceftazidime) and a β-lactamase enzyme inhibitor (Avibactam)[1-3], which together offer a highly effective spectrum of activity against gram-negative pathogens. Avibactam broadens the spectrum of Ceftazidime, making CAZ/AVI an effective alternative for treating infections caused by bacteria with various resistance mechanisms[3,4]. CAZ/AVI is indicated for cases of complicated intra-abdominal infections (cIAI), complicated urinary tract infections including pyelonephritis (cUTI), hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP), and for the treatment of adult patients with associated bacteremia.

Although CAZ/AVI is a promising option for treating gram-negative bacterial infections, several studies have reported resistance through different mechanisms of action, such as antibiotic inactivation via metallo-β-lactamases (MβLs)[2,5,6].

Given the growing threat of resistance to CAZ/AVI treatment, a differentiated approach by the multidisciplinary healthcare team is required to ensure its rational use. The clinical pharmacist plays a key role in managing safe use, bringing expertise in areas such as: support for clinical decision-making; usage strategies based on microbiological profiles; pharmacotherapeutic follow-up; dose adjustments; de-escalation; and even generating pharmacoeconomic benefits by reducing unnecessary healthcare costs[7-9].

The use of pharmaceutical monitoring tools is a promising strategy that has been employed to identify opportunities for improvement in drug therapy[10] and can be applied in antibiotic stewardship to ensure standardized and appropriate use of CAZ/AVI. Health authorities recommend strategic pauses for antibiotic use review, using the "Time-Out" as an evaluation tool[11]. The Time-Out is a pause, commonly used in surgeries, during which a set of questions is asked to clarify any uncertainties before the procedure[12] is carried out. This tool has been adapted for antimicrobial stewardship, and studies show that when led by a pharmacist, it appears to be even more effective in optimizing treatment[13,14].

The implementation of clinical decision-support strategies can offer significant benefits. Instead of complex decisions being made in an unstructured way, the use of structured approaches—such as algorithms—is proposed to guide clinical reasoning, which can contribute to more secure decision-making[15].

Recent studies have used algorithms to guide rational antibiotic therapy, demonstrating several advantages[16-23]. However, there is a lack of studies on structured clinical decision-support tools specifically aimed at the safe use of CAZ/AVI. This gap is even more significant in Brazil, where CAZ/AVI was only recently approved, and its integration into healthcare services has been gradual. Therefore, having tools to guide CAZ/AVI use is essential to support accurate therapeutic decisions.

The objective of this article is to propose an algorithm to guide clinical pharmaceutical reasoning in the effective and safe management of CAZ/AVI use in adult patients. This algorithm standardizes and directs pharmaceutical follow-up, serving as a clinical decision-support tool, divided into strategic steps to facilitate the identification of opportunities to optimize CAZ/AVI antibiotic therapy.

Methods

This is a descriptive, quantitative study with retrospective data collection. It was divided into three stages: algorithm development, application, and data analysis.

Algorithm Development

The algorithm model developed in this study was named *Stewardship & Monitoring Algorithm for Rational Therapy* (SMART) and was designed for use by clinical pharmacists, from the initiation of antibiotic therapy to its discontinuation. The tool was created in a flowchart format, based on antimicrobial[11] stewardship principles and on studies that utilize antibiotic monitoring tools[13,24].

SMART is divided into three sections: Section 1 – Initial Pharmaceutical Assessment (analysis of prescription and indication); Section 2 – Microbiology (evaluation of the microbiological profile of the infection); Section 3 – Time-Out (monitoring and optimization of antibiotic therapy, applied to the patient's clinical status at scheduled periodic intervals)

All stages include direct questions and specific guidelines that direct the actions of the clinical pharmacist. The model was developed to be applicable to any antimicrobial agent, requiring only minor adaptations in some questions and guidelines according to the specific characteristics of the antibiotic being analyzed. Furthermore, SMART can be used regardless of the type of medical prescription system, whether electronic or manual. In this study, we refer to the application of the SMART model focused on the effective and safe use of ceftazidime/avibactam in adult patients as SMART-CAZ/AVI.

JHPHS
Journal of Hospital Pharmacy and Health Services

The algorithm was validated by two external pharmacists who specialize in antimicrobial stewardship and by the hospital's infectious disease specialist. It was also previously validated by the hospital's clinical pharmacists, who applied it in their routines to assess the tool's feasibility and applicability one month before the start of the study.

Study Design and Setting

The study involved the descriptive application of the algorithm, with retrospective data collection before and after the implementation of SMART-CAZ/AVI, covering a 21-month period (January 2023 to September 2024).

SMART-CAZ/AVI was developed and implemented in August 2023 in a private hospital in Rio de Janeiro, which has 132 beds, a mixed medical staff, Intensive and Semi-Intensive Care Units, onco-hematology, surgical center, and emergency services. The Clinical Pharmacy Service comprises six clinical pharmacists responsible for reviewing 100% of electronic prescriptions. Each clinical pharmacist identified CAZ/AVI antibiotic therapy by analyzing prescriptions and applied the algorithm to all patients who initiated treatment. Pharmaceutical interventions were carried out with the medical team during rounds or by phone, and were considered accepted once the adjustment was recorded in the patient's electronic medical record. All treatments performed were included in the data analysis, with no exclusion criteria.

Data Collection and Consolidation

Pharmaceutical follow-up using SMART-CAZ/AVI was documented in structured and individualized spreadsheets for each patient, created in Microsoft Excel®. These spreadsheets included the algorithm's questions and a space to describe the pharmaceutical intervention performed (Figure 1 – Supplementary Material). Follow-up based on SMART-CAZ/AVI was also recorded in the electronic medical record at each Time-Out. The interventions performed were recorded in the electronic platform Epimed Solutions® and later consolidated in Excel® spreadsheets for subsequent analysis.

Data Analysis

For more detailed comparative analysis, data were divided into three 7-month periods: the pre-implementation period (January to July 2023); the immediate post-implementation period (August 2023 to February 2024); and the late post-implementation period (March to September 2024). Classification of pharmaceutical interventions was conducted using the Antimicrobial Therapy-Related Problem (PRAT)[25] tool. The impact of using SMART-CAZ/AVI was assessed through descriptive statistics, using data on: pharmaceutical intervention rate; types of interventions performed; number of treatments without appropriate indication; and analysis of the average Days of Therapy (DOT).

Ethical Considerations

The study was conducted in accordance with the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) guidelines and approved by the Research Ethics Committee (CEP) of Hospital Pró-Cardíaco – Esho Empresa de Serviços Hospitalares – HPC (CAAE: 77108523.5.0000.5533).

Results

SMART-CAZ/AVI was initiated with the identification of patients who began antibiotic therapy with CAZ/AVI, followed by the prescription and indication assessment stage (Figure 1 – Section 1). The clinical pharmacist verified whether CAZ/AVI had been prescribed with the recommended initial dosage and whether it included preparation and administration instructions. If not, the prescriber was to be asked to correct it.

In the next step, the clinical pharmacist evaluated the indication for CAZ/AVI use. Formal indications were considered to be cases of complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), or hospital-acquired/ventilator-associated pneumonia (HAP/VAP), with or without associated bacteremia, in which bacterial cultures showed sensitivity to CAZ/AVI based on antimicrobial susceptibility testing (AST). Cases were also considered formal indications when cultures showed resistance to CAZ/AVI but with evidence of metallo-β-lactamase (MβL) production or multi-drug resistant *Stenotrophomonas maltophilia*. Treatments in patients with a history of colonization or a prior formal indication were also included in this category. All other cases were considered empirical initiations.

For cIAI cases with suspected or confirmed anaerobic bacterial infection, the clinical pharmacist was advised to recommend combining CAZ/AVI with Metronidazole. In cultures with AST resistance to CAZ/AVI but with confirmed MβL production or multi-drug resistant *S. maltophilia*, the clinical pharmacist was advised to suggest combining CAZ/AVI with Aztreonam.

The clinical pharmacist initiated the Time-Out on the third day of CAZ/AVI treatment (Figure 1 – Section 3), regardless of the initial indication. However, for empirical initiations, the pharmacist was also required to proceed to Section 2 – Microbiology (Figure 1 – Section 2).

This section began by checking whether a bacterial culture had been ordered. If not, the algorithm recommended suggesting to the medical team that a culture be collected to determine whether it was indeed a bacterial infection.

If the results showed no bacterial growth, the pharmacist was to discuss the necessity of continuing antibiotic therapy and suggest discontinuation. In cases of positive cultures, the possibility of de-escalating antibiotic therapy was to be assessed based on AST results. If AST showed resistance to CAZ/AVI, it was essential to verify whether the bacteria expressed MβL, in which case Aztreonam should be added to the treatment. For other resistance mechanisms, the recommendation was to re-evaluate the antibiotic regimen using the AST data, considering alternatives such as aminoglycosides, polymyxin B, or tigecycline as potential therapeutic options[26].

When the identified bacteria were either sensitive to CAZ/AVI or resistant but exhibiting MβL, the empirical initiation of CAZ/AVI was deemed an appropriate decision. In such cases, the treatment was reclassified as a formal indication, and the Time-Out process continued (Figure 1 – Section 3).

In the immediate post-implementation period of SMART-CAZ/AVI, 88% of treatments had a formal indication for use, and only 12% were initiated empirically without later being reclassified as formal. However, in the late post-implementation period, this rate rose to 25%, showing a 108.33% increase in inappropriate treatments (Figure 2).

JHPHS
Journal of Hospital Pharmacy and Health Services

The results obtained from the application of SMART-CAZ/AVI showed that 23 pharmaceutical interventions were carried out following 93 Time-Outs conducted during the study (Figure 3). The Time-Out was applied every three days, evaluating CAZ/AVI antibiotic therapy using the following key questions to optimize treatment:

Is the treatment duration defined?

Treatment duration recommendations were included in SMART-CAZ/AVI. If the treatment duration was already established by the medical team, the clinical pharmacist continued monitoring the patient. If not, the pharmacist monitored the patient's clinical progression to determine it alongside the team. From the sixth day of treatment onwards, the clinical pharmacist would ask whether the therapy should be continued. If discontinuation was decided, the pharmacist would check the prescription to ensure the antibiotic had been discontinued and would close the Time-Out. If continuation was chosen, the pharmacist would reassess the possibility of discontinuation at the next Time-Out. Notably, if antibiotic therapy was likely to exceed the recommended duration, the pharmacist was advised to intervene with the Hospital Infection Control Service (HICS). Our results showed that prolonged antibiotic therapy accounted for 26.3% of the interventions performed (Figure 4A).

Is the patient responding to treatment?

If the patient showed progressive improvement in vital and infectious signs, the pharmacist continued monitoring. If not, the pharmacist should suggest extending the infusion time to 3 hours or using continuous infusion, especially in infections caused by *P. aeruginosa* or multi-drug resistant *S. maltophilia*. If no clinical improvement was observed at the next Time-Out, re-evaluation of the antibiotic therapy based on AST results was recommended.

Is the dosage adjusted according to renal function?

In patients with renal impairment, the pharmacist recommended dose adjustments according to creatinine clearance (CrCl—Cockcroft-Gault formula)[27,28]. If Aztreonam was also prescribed, it needed to be adjusted accordingly. Dosage guidelines and alerts about proper preparation and administration for patients on intermittent hemodialysis (HD) were included in SMART-CAZ/AVI. Our results revealed a high need for interventions related to overdosing based on CrCl (68.4%) and a small proportion of interventions for incorrect scheduling of dialyzable drugs (5.3%) (Figure 4A).

Did the patient experience an adverse drug reaction (ADR)?

The pharmacist assessed whether the patient experienced any ADRs through active chart review or by detecting prescriptions intended to treat potential ADRs. If an ADR was identified, the pharmacist was advised to apply the Naranjo Algorithm[29] to assess the causal relationship with CAZ/AVI. If the relationship was classified as definite, probable, or possible, the risk/benefit of continuing antibiotic therapy and the need for ADR management should be discussed with the team. SMART-CAZ/AVI listed the main ADRs associated with CAZ/AVI, as well as those linked to Aztreonam and Metronidazole in cases of combination therapy.

Are there any relevant drug interactions?

Although CAZ/AVI is not associated with severe drug interactions, monitoring for nephrotoxicity risks was important, particularly when combined with aminoglycosides or potent diuretics such as furosemide. If harmful effects were identified, a risk/benefit assessment of maintaining the combination therapy was suggested. The main interactions related to Metronidazole use were included in the algorithm. No drug interaction cases were recorded in this study.

The Time-Out was concluded when CAZ/AVI antibiotic therapy was discontinued, thereby finalizing the use of SMART-CAZ/AVI.

When classifying the pharmaceutical interventions conducted during the immediate and late post-implementation periods of the algorithm, a predominance of interventions related to overdosing based on creatinine clearance (CrCl) was observed (68.4%), followed by prolonged antibiotic therapy (26.3%) and inappropriate scheduling of dialyzable medications (5.3%) (Figure 4A). Furthermore, a significant overall reduction in CrCl-based overdose interventions was identified, decreasing from 69.2% in the immediate post-implementation period to 30.8% in the late period—representing a 55.2% reduction. Interventions addressing inadequate scheduling of dialyzable drugs were entirely eliminated (100% reduction), while interventions related to prolonged antibiotic therapy increased from 20% to 80% (Figure 4B).

In terms of the acceptability of interventions, we observed that 44.4% of overdose interventions were accepted during the immediate post-implementation period, compared to 100% acceptance in the late period. Interventions regarding inappropriate scheduling of dialyzable medications were fully accepted (100%) during the immediate post-implementation period and were not needed in the late period. However, interventions for prolonged antibiotic therapy showed a decrease in acceptance, from 100% in the immediate period to only 25% in the late period (Figure 4B).

The analysis of the mean Days of Therapy (DOT) revealed a reduction from 53 to 19 DOTs when comparing the pre-implementation period to the immediate post-implementation period of SMART-CAZ/AVI—corresponding to a 64.15% decrease. However, when comparing the immediate to the late post-implementation period, an increase from 19 to 65 DOTs was observed, representing a 242.11% rise (Figure 5).

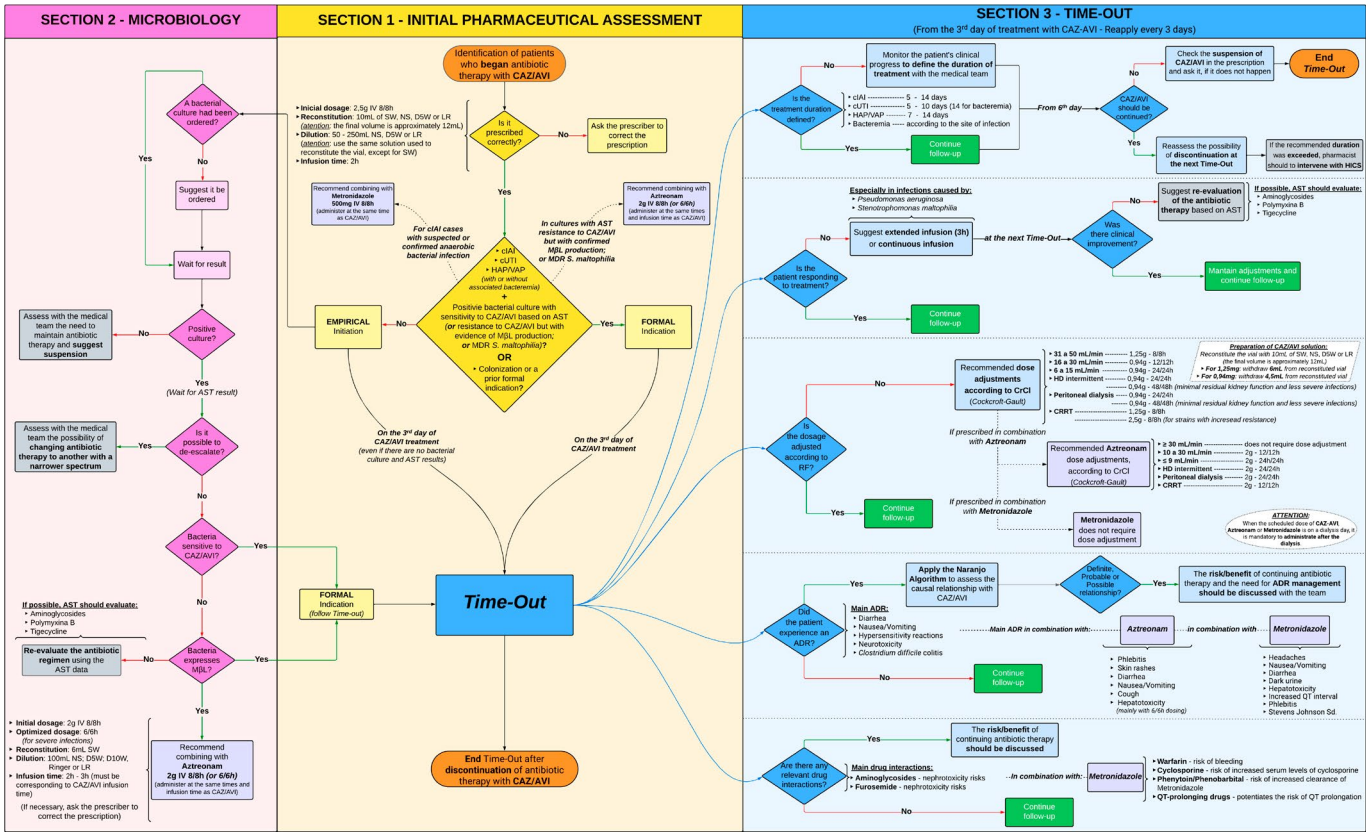
Discussion

CAZ/AVI antibiotic therapy was introduced as an innovative treatment for infections caused by multidrug-resistant gram-negative bacteria, including strains producing extended-spectrum beta-lactamases (ESBL), AmpC, and carbapenemases[1]. CAZ/AVI has been recognized as one of the most effective antimicrobials for treating infections caused by KPC-producing strains. However, with the widespread use of CAZ/AVI, new bacterial strains exhibiting resistance mechanisms that compromise its efficacy have emerged, leading to therapeutic failure[5,6,26].

Therefore, safe-use strategies are essential to ensure that CAZ/AVI is reserved for cases with limited therapeutic alternatives. In this context, clinical pharmacists play a critical role in CAZ/AVI stewardship, serving as a crucial safety barrier to minimize associated risks and promote rational antibiotic use[31]. The SMART-CAZ/AVI algorithm emerges as a comprehensive tool that enhances the pharmacist's role, positioning them as a key player in patient care by providing a broad perspective on all factors involved in CAZ/AVI use, tailored to each care setting and the patient's clinical stage.

JHPHS
Journal of Hospital Pharmacy and Health Services

Figure 1. SMART-CAZ/AVI: clinical pharmacist intervention algorithm for the safe use management of Ceftazidime/Avibactam in adults (Rio de Janeiro, 2024).



Caption: AST: Antimicrobial susceptibility testing; CAZ/AVI: Ceftazidime-Avibactam; ADR: Adverse drug reaction; cIAI: Complicated intra-abdominal infections; CrCL: Creatinine Clearance; CRRT: Continuous Renal Replacement Therapy; cUTI: urinary tract infections (including pyelonephritis); D5W: Dextrose 5% in water; D10W: Dextrose 10% in water; HAP/VAP: hospital-acquired pneumonia, including ventilator-associated pneumonia; HICS: Hospital Infection Control Service; IV: Intraevenous infusion; LR: Lactate Ringer solution; MβL: Metalo-β-lactamase; MDR: Multi-drug resistant; NS: Normal Saline 0.9%; RF: Renal function; Sd.: Syndrome; SW: Sterile water for injection.

Figure 2 . Percentage of CAZ/AVI antibiotic therapies with and without appropriate clinical indication (Rio de Janeiro, 2024).

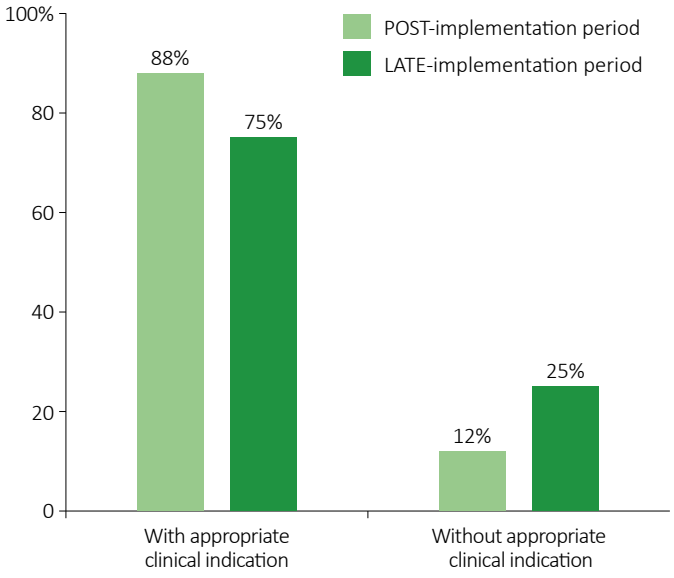


Figure 3 . Number of Time-Outs and Pharmaceutical Interventions conducted from August 2023 to September 2024 (Rio de Janeiro, 2024).

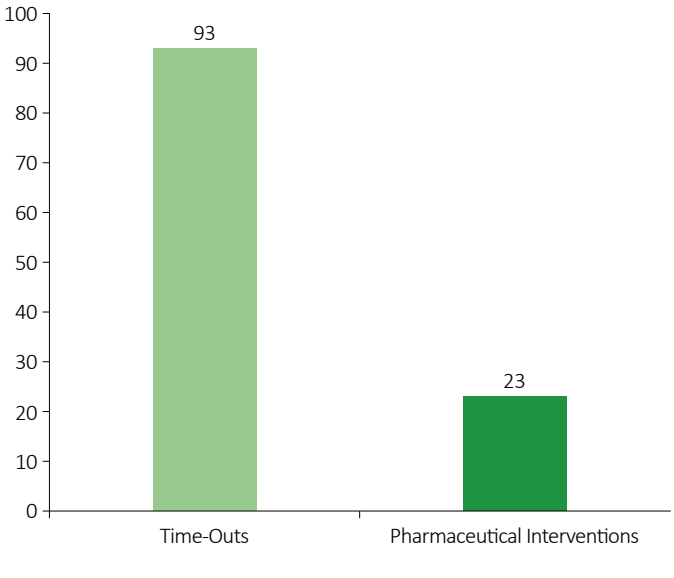
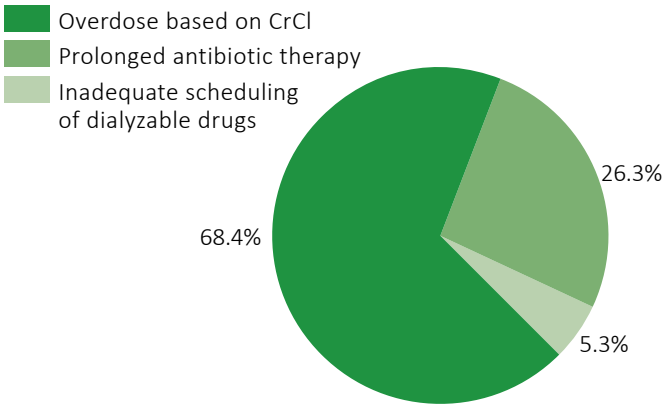


Figure 4. Pharmaceutical interventions performed using the SMART-CAZ/AVI algorithm.

A: Percentage of pharmaceutical interventions categorized by type.



B: Percentage of pharmaceutical interventions by category, comparing immediate and late post-implementation periods, and intervention acceptance rates (Rio de Janeiro, 2024)

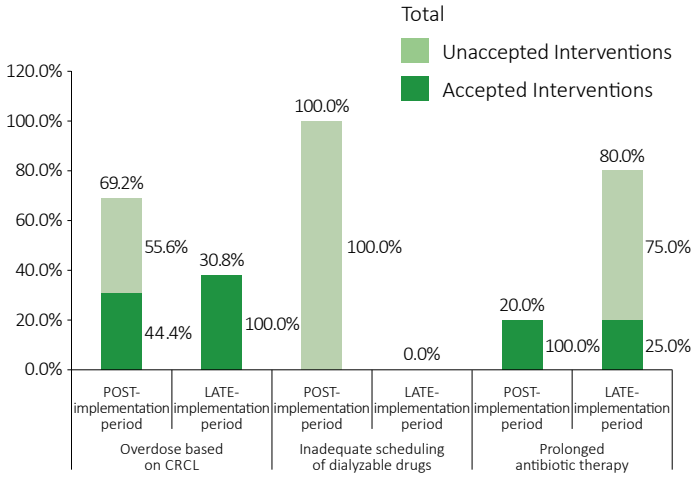
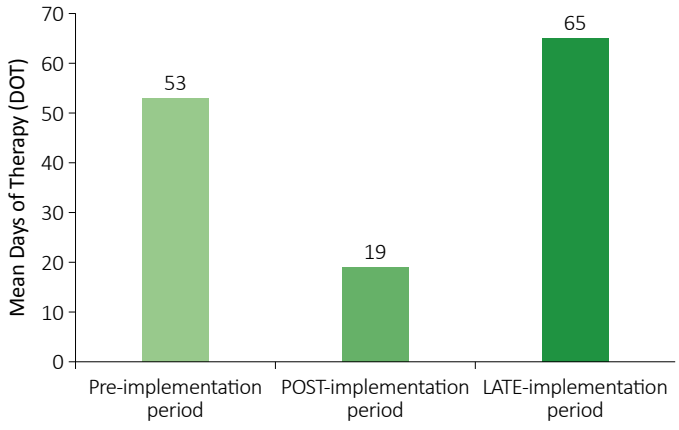


Figure 5 . Average DOT (Days of Therapy) analyzed during the pre-implementation period and the immediate and late post-implementation periods of SMART-CAZ/AVI (Rio de Janeiro, 2024).



The division of the SMART model into three sections is justified by the need to guide the pharmacist's clinical reasoning—from the initiation of therapy to microbiological considerations, and finally, to patient-specific opportunities for treatment optimization. SMART-CAZ/AVI offers crucial guidance that empowers pharmacists to perform more challenging interventions with medical teams.

The combination of CAZ/AVI with Aztreonam has shown therapeutic potential, especially in infections involving bacteria with metallo-beta-lactamase (MβL) production[32]. In a study involving 102 patients with bloodstream infections caused by MβL-producing Enterobacterales, 30-day mortality was lower among those treated with CAZ/AVI plus Aztreonam compared to those receiving alternative therapy[33]. The Infectious Diseases Society of America (IDSA) supports this recommendation and advises that CAZ/AVI and Aztreonam be administered simultaneously over a 3-hour infusion. The Aztreonam dose may be optimized to 2g every 6 hours, with careful monitoring for hepatotoxicity[34].

Regarding Time-Out application, SMART-CAZ/AVI recommends a 3-day interval, which allows adequate time to assess treatment duration and microbiological follow-up. Depending on the capabilities of the hospital's microbiology service, the pharmacist may already have access to preliminary culture results by the first Time-Out. Other early findings may include premature discontinuation of CAZ/AVI, the need for therapy optimization based on clinical response, dose adjustments due to renal function, adverse drug reactions (ADRs), and drug interactions. By the second Time-Out, the clinical pharmacist is expected to propose interventions based on antimicrobial susceptibility testing (AST) results and consider discontinuation of CAZ/AVI in cases where a 5-day treatment course is sufficient.

Given the pharmacokinetic profile of β-lactams[35], SMART-CAZ/AVI also emphasizes the option of extended infusions (3 hours) in patients showing no clinical improvement—especially in infections caused by *P. aeruginosa* and multidrug-resistant *S. maltophilia*[34,36]. Although more robust evidence is needed, some findings suggest a therapeutic benefit from continuous CAZ/AVI infusion regimens[37,38]. Nevertheless, this approach may be limited by the challenge of securing exclusive intravenous access. If the patient's condition does not improve, SMART-CAZ/AVI recommends that the pharmacist re-evaluate the antibiotic regimen based on AST findings.

The inclusion of alerts within the SMART-CAZ/AVI algorithm regarding proper preparation and administration of CAZ/AVI in cases requiring renal dose adjustment represents another key advantage of this tool. Although no formal data were reported, professional experience indicates that nursing staff often lack awareness about the expansion of the CAZ/AVI solution upon reconstitution, despite this information being provided in the package insert. This knowledge gap can result in significant administration errors and subtherapeutic dosing.

One proposed solution is the implementation of standardized electronic prescribing protocols in hospitals with computerized systems. Each protocol should be customized according to specific renal dose adjustments and include detailed information on dosage, frequency, route of administration, preparation, and dilution. These guidelines can assist nursing teams in ensuring safe drug administration. Additional instructions for patients undergoing hemodialysis (HD) should also be incorporated to ensure CAZ/AVI is administered only after dialysis procedures (see Supplementary Material – Table 1). An added benefit of this strategy is that it prompts physicians to consider dose adjustments during prescribing, expedites the process, and reduces the need for pharmacist interventions aimed at correcting prescriptions.

JHPHS
Journal of Hospital Pharmacy and Health Services

Our data suggest a 4:1 ratio between Time-Outs performed and pharmaceutical interventions. The predominance of interventions related to overdose based on creatinine clearance (ClCr) highlights ongoing reluctance among prescribers to adjust CAZ/AVI dosing according to patients' renal function. Similar findings have been reported in previous studies, one of which found that dose adjustment in patients with impaired renal function was omitted in 59.58% of cases, even in a large hospital with access to nephrologists who are presumably more knowledgeable in this area[39]. Another study reported that 18.5% of patients with severe sepsis or septic shock received overdoses of antibiotics[40]. These findings suggest that such prescription errors may stem from physicians underestimating renal impairment or lacking knowledge of dosing guidelines and the pharmacokinetics of antimicrobials[40].

Our observations support this evidence[40], particularly regarding limited medical knowledge on optimal dosing strategies for CAZ/AVI, especially in patients undergoing HD. In this context, SMART-CAZ/AVI can serve as an educational tool for both physicians and nurses, reinforcing its role as a clinical decision support system aimed at optimizing patient outcomes.

This conclusion is further supported by a 55.2% reduction in interventions related to overdosing based on ClCr from the immediate to the late post-implementation period. During the late period, 100% of such interventions were accepted, indicating greater awareness among physicians regarding the importance of dose adjustment in renally impaired patients. The implementation of standardized CAZ/AVI prescription protocols may also explain the complete elimination of interventions related to inappropriate timing of dialysis-dependent drug administration, as the templates included an alert specifying that CAZ/AVI should be administered after HD on dialysis days.

However, the 300% increase in interventions related to prolonged antibiotic therapy from the immediate to the late period suggests that opportunities for improvement remain in optimizing CAZ/AVI treatment duration. Even after pharmacist intervention, 75% of treatments were continued beyond the recommended 14-day duration. Although this outcome was not ideal, the algorithm effectively identified a key area for improvement—an issue likely present in many other hospitals as prolonged antimicrobial use remains one of the greatest challenges in antimicrobial stewardship[41,42]. Extended treatment durations are associated with increased toxicity, resistance development, and higher healthcare costs[43–45].

Another important finding was the use of CAZ/AVI in patients without appropriate clinical indications. Although this represented a small percentage, it serves as an important alert regarding the need to reinforce CAZ/AVI stewardship guidelines within the institution, and it presents an opportunity to discuss with the medical team the risks associated with the indiscriminate use of antimicrobials[5,6,26].

CAZ/AVI consumption was assessed using the average DOT (Days of Therapy) for each study period, considering that a patient may initiate treatment in one month and complete it in the next, which can affect monthly data interpretation. The sharp decrease in this indicator following the implementation of SMART-CAZ/AVI highlights the positive impact of the tool in reducing CAZ/AVI utilization. Conversely, the subsequent increase in average DOT during the late period may be associated with factors such as the rise in multidrug-resistant bacterial infections and infection severity; increased initiation of empirical treatments; and the involvement of attending physicians unfamiliar with the hospital's CAZ/AVI stewardship guidelines. Further studies are needed to elucidate these variables and to support the development of targeted strategies to improve CAZ/AVI use.

The effective and sustainable implementation of SMART-CAZ/AVI faces several challenges, primarily due to limited adherence among the multidisciplinary healthcare team. This resistance is multifactorial and may stem from a lack of continuous professional training, high physician turnover, perceived loss of medical autonomy, and insufficient institutional support. These factors compromise the legitimacy and consistent application of the tool, leading to its improper and intermittent use, ultimately hindering the optimization of antimicrobial therapy. Despite these challenges, our findings demonstrate that the algorithm has the potential to significantly support clinical pharmacists in the rational management of CAZ/AVI use.

Conclusion

SMART-CAZ/AVI shows great potential as a valuable tool to support clinical pharmacists in managing CAZ/AVI therapy in adult patients. Its implementation contributed to the reduction of overdose errors in patients with renal dysfunction and administration-related errors. The SMART-CAZ/AVI tool may be established as a standardized and efficient approach for pharmaceutical follow-up in hospitals. It supports appropriate clinical indication of antibiotic use, guides the interpretation of microbiological profiles, optimizes antibiotic therapy, enables individualized pharmaceutical care through patient-specific clinical adjustments, and ensures the safe and rational use of CAZ/AVI.

Funding Sources

The authors declare that there were no sources of funding for the development of this study.

Contributors

RSGT, ELS: Conception and development of SMART-CAZ/AVI, data analysis, and manuscript drafting. DCKS, MCR: Scientific guidance and manuscript writing. RWBG: Discussion of the practical application of the algorithm. FFR, PN: Critical content review.

Conflict of Interest Statement

The authors declare no conflicts of interest.

JHPHS
Journal of Hospital Pharmacy and Health Services

References

1. Shirley M. Ceftazidime-Avibactam: A Review in the Treatment of Serious Gram-Negative Bacterial Infections. Drugs. 2018;78(6):675-692. doi:10.1007/s40265-018-0902-x
2. Hobson CA, Pierrat G, Tenaillon O, et al. Klebsiella pneumoniae Carbapenemase Variants Resistant to Ceftazidime-Avibactam: an Evolutionary Overview. Antimicrob Agents Chemother. 2022;66(9):e0044722. doi:10.1128/aac.00447-22
3. Lagacé-Wiens P, Walkty A, Karlowsky JA. Ceftazidime-avibactam: an evidence-based review of its pharmacology and potential use in the treatment of Gram-negative bacterial infections. Core Evid. 2014;9:13-25. doi:10.2147/CE.S40698
4. Aktaş Z, Kayacan C, Oncul O. In vitro activity of avibactam (NXL104) in combination with β-lactams against Gram-negative bacteria, including OXA-48 β-lactamase-producing Klebsiella pneumoniae. Int J Antimicrob Agents. 2012;39(1):86-89. doi:10.1016/j.ijantimicag.2011.09.012
5. Gaibani P, Giani T, Bovo F, et al. Resistance to Ceftazidime/Avibactam, Meropenem/Vaborbactam and Imipenem/Relebactam in Gram-Negative MDR Bacilli: Molecular Mechanisms and Susceptibility Testing. Antibiotics (Basel). 2022;11(5):628. doi:10.3390/antibiotics11050628
6. Chaïbi K, Jaureguy F, Do Rego H, et al. What to Do with the New Antibiotics?. Antibiotics (Basel). 2023;12(4):654. doi:10.3390/antibiotics12040654
7. Garau J, Bassetti M. Role of pharmacists in antimicrobial stewardship programmes. Int J Clin Pharm. 2018;40(5):948-952. doi:10.1007/s11096-018-0675-z
8. Dighriri IM, Alnomci BA, Aljahdali MM, et al. The Role of Clinical Pharmacists in Antimicrobial Stewardship Programs (ASPs): A Systematic Review. Cureus. 2023;15(12):e50151. doi:10.7759/cureus.50151
9. Parente DM, Morton J. Role of the Pharmacist in Antimicrobial Stewardship. Med Clin North Am. 2018;102(5):929-936. doi:10.1016/j.mcna.2018.05.009
10. Lee SS, Schwemm AK, Reist J, et al. Pharmacists' and pharmacy students' ability to identify drug-related problems using TIMER (Tool to Improve Medications in the Elderly via Review). Am J Pharm Educ. 2009;73(3):52. doi:10.5688/aj730352
11. CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta: GA- US Department of Health and Human Services, CDC. 2019.
12. Joint Commission International. Joint Commission International Accreditation Standards for Hospital. 8th ed. Joint Comission Resources; 2025.
13. Paulson CM, Handley JF, Dilworth TJ, et al. Impact of a Systematic Pharmacist-Initiated Antibiotic Time-Out Intervention for Hospitalized Adults. J Pharm Pract. 2022;35(3):388-395. doi:10.1177/0897190020980616
14. Hasegawa S, Tagashira Y, Murakami S, et al. Antimicrobial Time-Out for Vancomycin by Infectious Disease Physicians Versus Clinical Pharmacists: A Before-After Crossover Trial. Open Forum Infect Dis. 2021;8(6):ofab125. doi:10.1093/ofid/ofab125
15. Dennstädt F, Treffers T, Iseli T, Panje C, Putora PM. Creation of clinical algorithms for decision-making in oncology: an example with dose prescription in radiation oncology. BMC Med Inform Decis Mak. 2021;21(1):212. doi:10.1186/s12911-021-01568-w
16. Lee TC, Frenette C, Jayaraman D, Green L, Pilote L. Antibiotic self-stewardship: trainee-led structured antibiotic time-outs to improve antimicrobial use. Ann Intern Med. 2014;161(10 Suppl):S53-S58. doi:10.7326/M13-3016
17. Taylor AP, Coe K, Stevenson K, Wardlow L, Boghdadly ZE, Reed E. Clinical Impact of an Antibiotic Time Out Initiative at an Academic Medical Center. Hosp Pharm. 2021;56(4):343-346. doi:10.1177/0018578719901274
18. Adams SM, Ngo L, Morphew T, Babbitt CJ. Does an Antimicrobial Time-Out Impact the Duration of Therapy of Antimicrobials in the PICU?. Pediatr Crit Care Med. 2019;20(6):560-567. doi:10.1097/PCC.0000000000001925
19. Stang CRT, Jaggi P, Tansmore J, et al. Implementation of a Pharmacist-Led Antimicrobial Time-Out for Medical-Surgery Services in an Academic Pediatric Hospital. J Pediatr Pharmacol Ther. 2021;26(3):284-290. doi:10.5863/1551-6776-26.3.284
20. Muller MR, Mahadeo AM, Mayne JP, et al. Decreased Antibiotic Exposure for Suspected Early-Onset Sepsis in the Neonatal Intensive Care Unit Through Implementation of an Antimicrobial Time-out. J Pediatr Pharmacol Ther. 2022;27(8):746-749. doi:10.5863/1551-6776-27.8.746
21. Richardson SR, Neuner EA, Athans V, et al. Evaluation of an electronic antimicrobial time-out on antimicrobial utilization at a large health system. Infect Control Hosp Epidemiol. 2019;40(7):807-809. doi:10.1017/ice.2019.105
22. Schooneveld TC Van, Rupp ME, Lyden E, Cavalieri RJ, Marolf C, Rolek K. Randomized Trial of Team Pharmacist-Led Antimicrobial Time Out. Open Forum Infect Dis. 2016;3(suppl1). doi:10.1093/ofid/ofw172.1490
23. Patel AR, Murrey TF. 68. Impact of a Pharmacy-Driven Antimicrobial Time-out on Duration of Therapy in Community-Acquired Pneumonia. Open Forum Infect Dis. 2020;7(Suppl 1):S53. doi:10.1093/ofid/ofaa439.113
24. Graber CJ, Jones MM, Glassman PA, et al. Taking an Antibiotic Time-out: Utilization and Usability of a Self-Stewardship Time-out Program for Renewal of Vancomycin and Piperacillin-Tazobactam. Hosp Pharm. 2015;50(11):1011-1024. doi:10.1310/hpj5011-1011
25. Ricieri MC, Barreto HAG, Pasquini-Netto H, et al. Prat tool: A harmonization of antimicrobial stewardship program interventions. Rev Ciencias Farm Basica e Apl. 2021;(42):e735. doi:10.4322/2179-443X.0735

26. Ding L, Shen S, Chen J, et al. Klebsiella pneumoniae carbapenemase variants: the new threat to global public health. Clin Microbiol Rev. 2023;36(4):e0000823. doi:10.1128/cmr.00008-23

27. Li J, Lovern M, Green ML, et al. Ceftazidime-Avibactam Population Pharmacokinetic Modeling and Pharmacodynamic Target Attainment Across Adult Indications and Patient Subgroups. Clin Transl Sci. 2019;12(2):151-163. doi:10.1111/cts.12585

28. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41. doi:10.1159/000180580

29. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-245. doi:10.1038/clpt.1981.154

30. Yahav D, Giske CG, Gramatniece A, Abodakpi H, Tam VH, Leibovici L. Erratum for Yahav et al., "New β-Lactam-β-Lactamase Inhibitor Combinations". Clin Microbiol Rev. 2021;34(2):e00021-21. doi:10.1128/CMR.00021-21

31. Bradley N, Lee Y. Practical Implications of New Antibiotic Agents for the Treatment of Carbapenem-Resistant Enterobacteriaceae. Microbiol Insights. 2019;12:1178636119840367. doi:10.1177/1178636119840367

32. Timsit JF, Wicky PH, de Montmollin E. Treatment of Severe Infections Due to Metallo-Betalactamases Enterobacterales in Critically Ill Patients. Antibiotics (Basel). 2022;11(2):144. doi:10.3390/antibiotics11020144

33. Falcone M, Daikos GL, Tiseo G, et al. Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients With Bloodstream Infections Caused by Metallo-β-lactamase-Producing Enterobacterales. Clin Infect Dis. 2021;72(11):1871-1878. doi:10.1093/cid/ciaa586

34. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. Clin Infect Dis. 2023. doi:10.1093/cid/ciad428

35. Pereira JG, Fernandes J, Duarte AR, Fernandes SM. β-Lactam Dosing in Critical Patients: A Narrative Review of Optimal Efficacy and the Prevention of Resistance and Toxicity. Antibiotics (Basel). 2022;11(12):1839. doi:10.3390/antibiotics11121839

36. Diarra A, Pascal L, Carpentier B, et al. Successful use of avibactam and aztreonam combination for a multiresistant Stenotrophomonas maltophilia bloodstream infection in a patient with idiopathic medullary aplasia. Infect Dis Now. 2021;51(7):637-638. doi:10.1016/j.idnow.2021.01.014

37. Goncette V, Layios N, Descy J, Frippiat F. Continuous infusion, therapeutic drug monitoring and outpatient parenteral antimicrobial therapy with ceftazidime/avibactam: a retrospective cohort study. J Glob Antimicrob Resist. 2021;26:15-19. doi:10.1016/j.jgar.2021.04.015

38. Fresan D, Luque S, Benítez-Cano A, et al. Pharmacokinetics/pharmacodynamics and therapeutic drug monitoring of ceftazidime/avibactam administered by continuous infusion in patients with MDR Gram-negative bacterial infections. J Antimicrob Chemother. 2023;78(3):678-683. doi:10.1093/jac/dkac439

39. Hassan Z, Ali I, Ullah AR, et al. Assessment of Medication Dosage Adjustment in Hospitalized Patients With Chronic Kidney Disease. Cureus. 2021;13(2):e13449. doi:10.7759/cureus.13449

40. Al-Dorzi HM, Eissa AT, Khan RM, Harbi SAA, Aldabbagh T, Arabi YM. Dosing errors of empirical antibiotics in critically ill patients with severe sepsis or septic shock: A prospective observational study. Int J Health Sci (Qassim). 2019;13(4):48-55.

41. Langford BJ, Nisenbaum R, Brown KA, Chan A, Downing M. Antibiotics: easier to start than to stop? Predictors of antimicrobial stewardship recommendation acceptance. Clin Microbiol Infect. 2020;26(12):1638-1643. doi:10.1016/j.cmi.2020.07.048

42. Yoo JS, Park JY, Chun HJ, et al. Impact of prolonged carbapenem use-focused antimicrobial stewardship on antimicrobial consumption and factors affecting acceptance of recommendations: a quasi-experimental study. Sci Rep. 2023;13(1):14501. doi:10.1038/s41598-023-41710-4

43. Delfino C, Da Silva R, Júnior MS. Estratégias para uso adequado de antibioticoterapia em unidade de terapia intensiva. Einstein. 2015;13(3):448–453. doi: 10.1590/S1679-45082015RW3145

44. Kollef MH, Shorr AF, Bassetti M, et al. Timing of antibiotic therapy in the ICU. Crit Care. 2021;25(1):360. doi:10.1186/s13054-021-03787-z

45. Busch LM, Kadri SS. Antimicrobial treatment duration in sepsis and serious infections. J Infect Dis. 2020;222(Suppl 2):S142–S155. doi:10.1093/INFDIS/JIAA247