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ORIGINAL ARTICLE

Multiple-step antimicrobial stewardship approach in a neonatal intensive care unit: a quasi-experimental study

Abordagem de controle antimicrobiano em múltiplas etapas em uma unidade de terapia intensiva neonatal: um estudo quase experimental

Enfoque de administración de antimicrobianos en múltiples etapas en una unidad de cuidados intensivos neonatales: un estudio cuasiexperimental

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ABSTRACT

Background and objectives: Antimicrobial resistance is considered one of the biggest global health challenges of the 21st century. Anti-infectives are the most frequently used medications in Neonatal Intensive Care Units, and their misuse and overuse facilitate the selection of infections caused by multidrug-resistant organisms and increase the risk of adverse effects. In this context, the aim of this study was to assess the effectiveness of a multi-step antimicrobial stewardship approach in a Neonatal Intensive Care Unit. **Methods:** This quasi-experimental longitudinal study used a pre-test/post-test design to evaluate the implementation of antimicrobial stewardship interventions delivered in four stages. In stage I, the profile of newborns was mapped. In Stage II, pharmacotherapeutic protocols for parenteral medications were developed. In Stage III, parenteral medication management for the Neonatal Intensive Care Unit was implemented. In Stage IV, an electronic dosage calculator was integrated into the Computerized Physician Order Entry. In Stage V, physicians and professionals responsible for dispensing medications were trained by clinical pharmacists. Effectiveness was assessed by comparing the incidence of prescribing errors before and after implementation. **Results:** There were 513 prescriptions during the implementation period: 332 for vancomycin, 149 for cefepime and 42 for piperacillin-tazobactam. A statistically significant reduction in the incidence of prescription errors involving dose and infusion time was observed. **Conclusion:** The implementation of multiple pharmacy-based antimicrobial stewardship interventions improved the safety profile of antimicrobial prescriptions.

Keywords: Antimicrobial stewardship. Intensive Care Units; Neonatal. Patient Safety Medication Errors.

RESUMO

Justificativa e objetivos: A resistência antimicrobiana é considerada um dos maiores desafios globais de saúde do século XXI. Os antimicrobianos são os medicamentos mais utilizados nas Unidades de Terapia Intensiva Neonatal

e seu uso indevido e excessivo facilita a seleção de infecções causadas por organismos multirresistentes e aumenta o risco de efeitos adversos. Nesse contexto, o objetivo deste estudo foi avaliar a eficácia de uma abordagem de gestão antimicrobiana em múltiplas etapas em uma Unidade de Terapia Intensiva Neonatal. **Métodos:** Este estudo longitudinal quase experimental usou um desenho de pré-teste/pós-teste para avaliar a implementação de intervenções de gestão antimicrobiana realizadas em 4 etapas. Na etapa I, foi mapeado o perfil dos recém-nascidos. Na Etapa II, foram desenvolvidos protocolos farmacoterapêuticos para medicamentos parenterais. Na Etapa III, foi implementado o gerenciamento de medicamento parenteral para a Unidade de Tratamento Intensivo Neonatal. Etapa IV, uma calculadora eletrônica de dosagem foi integrada ao sistema informatizado de prescrição médica. Na Etapa V, médicos e profissionais responsáveis pela dispensação de medicamentos foram treinados por farmacêuticos clínicos. A efetividade foi avaliada comparando a incidência de erros de prescrição antes e depois da implementação. **Resultados:** Houve 513 prescrições durante o período de implantação, sendo 332 de vancomicina, 149 de cefepima e 42 de piperacilina-tazobactam. Foi observada uma redução estatisticamente significativa na incidência de erros de prescrição envolvendo dose e tempo de infusão. **Conclusão:** A implementação de múltiplas intervenções de gestão antimicrobiana baseadas em farmácias resultou numa melhoria no perfil de segurança das prescrições antimicrobianas.

Descritores: Gestão de antimicrobianos. Unidades de Terapia Intensiva. Neonatal. Segurança do paciente. Erros de medicação.

RESUMEN

Justificación y Objetivos: La resistencia a los antimicrobianos se considera uno de los mayores desafíos de salud global del siglo XXI. Los antiinfecciosos son los medicamentos más utilizados en las Unidades de Cuidados Intensivos Neonatales, y su uso indebido y excesivo facilita la selección de infecciones causadas por organismos resistentes a múltiples fármacos y aumenta el riesgo de efectos adversos. El objetivo de este estudio fue evaluar la efectividad de un programa de optimización de antimicrobianos en múltiples etapas en una Unidad de Cuidados Intensivos Neonatales. **Métodos:** Estudio longitudinal cuasiexperimental con un diseño de antes y después para evaluar la implementación de intervenciones en cuatro etapas. En la etapa I, se trazó el perfil de los recién nacidos. En la Etapa II, se desarrollaron protocolos farmacoterapéuticos para medicamentos parenterales. En la Etapa III, se implementó el manejo de medicamentos parenterales en la Unidad de Tratamiento Intensivo Neonatal. En la Etapa IV, se integró una calculadora de dosis electrónica en sistema informatizado de prescripción médica. En la Etapa V, los médicos y profesionales responsables de dispensar medicamentos fueron capacitados por farmacéuticos clínicos. La efectividad se evaluó comparando la incidencia de errores de prescripción antes y después de la implementación. **Resultados:** Durante el período de implementación se realizaron 513 prescripciones: 332 de vancomicina, 149 de cefepima y 42 de piperacilina-tazobactam. Se observó una reducción estadísticamente significativa en la incidencia de errores de prescripción relacionados con la dosis y el tiempo de infusión. **Conclusiones:** La implementación de múltiples intervenciones de administración de antimicrobianos basadas en las farmacias mejoró el perfil de seguridad de las prescripciones de antimicrobianos.

Palabras Clave: Programas de Optimización del Uso de los Antimicrobianos. Unidades de Cuidados Intensivos. Neonatales. Seguridad del paciente. Errores de medicación.

INTRODUCTION

According to leading regulatory, economic, and political institutions, including the International Monetary Fund, the World Health Organization (WHO), the World Bank and the G8, antimicrobial resistance is one of the greatest global health challenges of the 21st century.[1]

The high incidence of infections caused by multidrug-resistant organism (MDRO) is one of the main consequences of antimicrobial resistance and a growing concern in the field of patient safety, especially in the Intensive Care Unit (ICU) and among vulnerable groups, such as neonates. Anti-infectives are the most frequently used medications in Neonatal Intensive Care Units (NICUs), and their misuse and overuse facilitate the selection of MDROs and increase the risk of adverse effects, making antimicrobial stewardship an important tool to prevent antimicrobial resistance.[2-4]

Antimicrobial stewardship is defined as "coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen, including dosing, duration of therapy, and route of administration".[5] In this manner, antimicrobial stewardship interventions have the potential to improve clinical outcomes and minimize harms by enhancing antimicrobial prescribing pratices.[3] Their relevance is even greater in NICUs, where very complex antimicrobial dosing regimens are used and there is still a high incidence of preventable adverse drug events involving antimicrobials.[6]

Among antimicrobial stewardship interventions, the "pharmacy-based interventions" include dose adjustment and optimization, definition of stop dates and duplicate therapy alerts, among others.[3] To streamline pharmacy-based interventions, electronic resources, such as a

Computerized Physician Order Entry (CPOE) system with clinical decision support (CDS) and standardized drug concentrations can be used and are recommended to facilitate the identification of opportunities to optimize antibiotic regimens. However, the impact of those initiatives still needs further exploration.[5]

In this context, the aim of this study was to assess the effectiveness of a multiple-step antimicrobial stewardship approach in a NICU.

METHODS

Study design and setting

This is a quasi-experimental longitudinal study in which a pre-test/post-test design was adopted to evaluate the implementation of antimicrobial stewardship interventions using retrospective data on February 2013. The study was developed according to the Standards for Reporting Implementation Studies (StaRI) statement.[7] This type of study design is encouraged by the WHO to evaluate real-world health interventions.[8]

The study took place in a 60-bed NICU of a private maternity hospital located in the city of Rio de Janeiro, Brazil. The maternity is a referral center for high-risk pregnancies and its NICU primarily cares for patients born in the hospital. The group of professionals working in the NICU was composed of a multidisciplinary team, including nurses, neonatologists, infectious diseases physicians, information technology specialists, and eleven clinical pharmacists. The clinical pharmacists had at least three years of experience. Before the intervention, medications were dispensed individually according to the prescription for each patient. The preparation and administration of medications were performed by the nursing team. Data on dispensing and administration were recorded only in the physical prescription.

Antimicrobial Stewardship interventions

The implementation of antimicrobial stewardship interventions began in August 2011 and finished in January 2013. In Stage I, which took place in August 2011, the neonates' profiles were mapped according to their sex, gestational age, birth weight and height, and antimicrobials used. The workflow involved in prescribing, dispensing, and administering parenteral drugs used in the NICU was also mapped.

Stage II took place from September to October 2011. Based on the profile identified in Stage I, the pharmacotherapeutic protocols for parenteral drugs and the standard concentration guide used in the NICU were developed. For this purpose, the following references were consulted: 2011 Neofax® textbook (Thomson Reuters, New York, USA), 2011 Lexicomp Pediatric and Neonatal Dosing Handbook (American Pharmacists Association, USA), and Handbook on Injectable Drugs (16ª Edition; American Pharmacists Association, USA).

In Stage III, from November 2011 to April 2012, intravenous admixture preparation for the NICU was implemented in the central pharmacy at the study location.

During Stage IV, conducted between October and December 2012, an electronic dosing calculator was integrated into the CPOE system. Although the entire multidisciplinary team participated in organizing the calculator, a team with information technology professionals and one pharmacist was formed during the process of implementing and integrating the calculator. It automatically calculates the appropriate concentration and dose (daily dose, unitary dose, loading dose, maintenance dose, and intervals between successive administrations) for the selected drugs using the recorded weight and age of the neonate. Additionally, the CPOE system was configured to automatically provide the appropriate reconstitution solvent, details of the dilution process (when multiple dilutions were required), and the total drug volume needed from a complete standardized drug concentration. The system also emits alerts to the prescriber whenever a medication dose is out of the recommended range.

Finally, during the three months of Stage V, the health professionals working in the NICU responsible for drug prescribing and dispensing were trained by clinical pharmacists to use and understand the electronic dosing calculator and the CPOE system with CDS. The use of the prescribing system began in January 2013.

Assessment of the effectiveness of the antimicrobial stewardship interventions

The effectiveness of the antimicrobial stewardship interventions was assessed by comparing the incidence of prescribing errors involving antimicrobials ordered to newborns before (October 2011 to December de 2012 – n=868) and after (January 2013 to March 2014 – n=915) the implementation.

To identify prescribing errors, every prescription order for cefepime, vancomycin, and piperacillin-tazobactam for the newborns in the studied NICU was evaluated. These specific antimicrobials were selected because they were the most used in the NICU according to the profile drawn in Stage I of the antimicrobial stewardship intervention.

The following prescribing errors were quantified: dose; compatibility and volume of the diluent to reconstitute the antimicrobial powder; compatibility and volume of the diluent to dilute the antimicrobial after reconstitution; final concentration of the antimicrobial after reconstitution and dilution; and time of infusion. Clinical pharmacists with at least three years of experience in clinical pharmacy in the NICU evaluated the prescription errors. The number of prescription orders for each of the aforementioned antimicrobials was also evaluated in the pre- and post-implementation periods.

Data analysis

All data were retrospectively collected from electronic medical charts available in the Enterprise Resource Planning Tasy (Philips, Netherlands). Data were statistically analyzed by the χ2-test (or Fisher's exact test when pertinent) with GraphPad Prism 8.0 to compare the pre- and post-implementation incidence of prescribing errors. Probability values of 0.05 or less were considered

significant. The characteristics (sex, birth weight and gestational age) of patients admitted before and after the implementation were compared using the t-test in order to ensure minimal influence of the patients' profile on the antimicrobial stewardship outcomes, and no statistically significant difference was identified (p<0,05).

This study is part of the project "Medications in pediatrics and neonatology: development of tools for the safe use of medicines". It was conducted in accordance with the required ethical standards – Resolutions 466/2012 - 510/2016 - 580/2018, of the Ministry of Health. The project was approved by the Brazilian Ethics Committee designated by the Ministry of Health of the Federal Government of Brazil on 18/12/2017, under CAAE registration - 82153617.5. 0000.5235, opinion number 2564476.

RESULTS

Before the implementation of the antimicrobial stewardship interventions, the NICU received a total of 884 prescription orders for antimicrobial drugs: 592 for vancomycin, 246 for cefepime, and 46 for piperacillin-tazobactam. After the implementation, although the number of newborns in the NICU increased, the total number of antimicrobial prescription orders was lower (n=513), with 332 were for vancomycin, 149 for cefepime and 42 for piperacillin-tazobactam (Figure 1).

A statistically significant reduction in the incidence of prescribing errors involving the dose, time of infusion, and diluent prescribed for all the studied antimicrobials was identified after the implementation of the antimicrobial stewardship interventions (Figure 2).
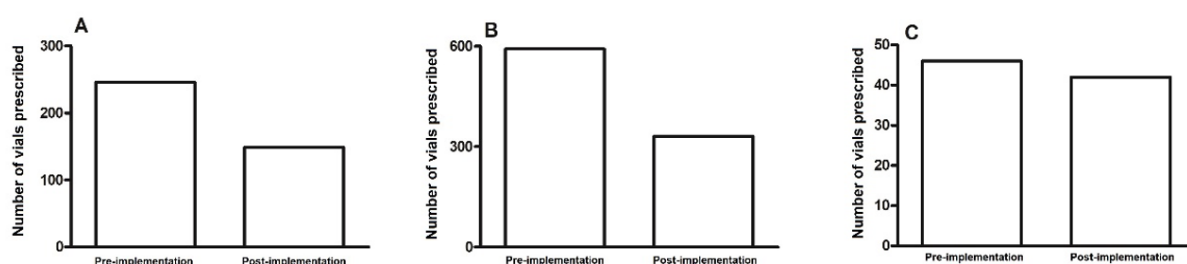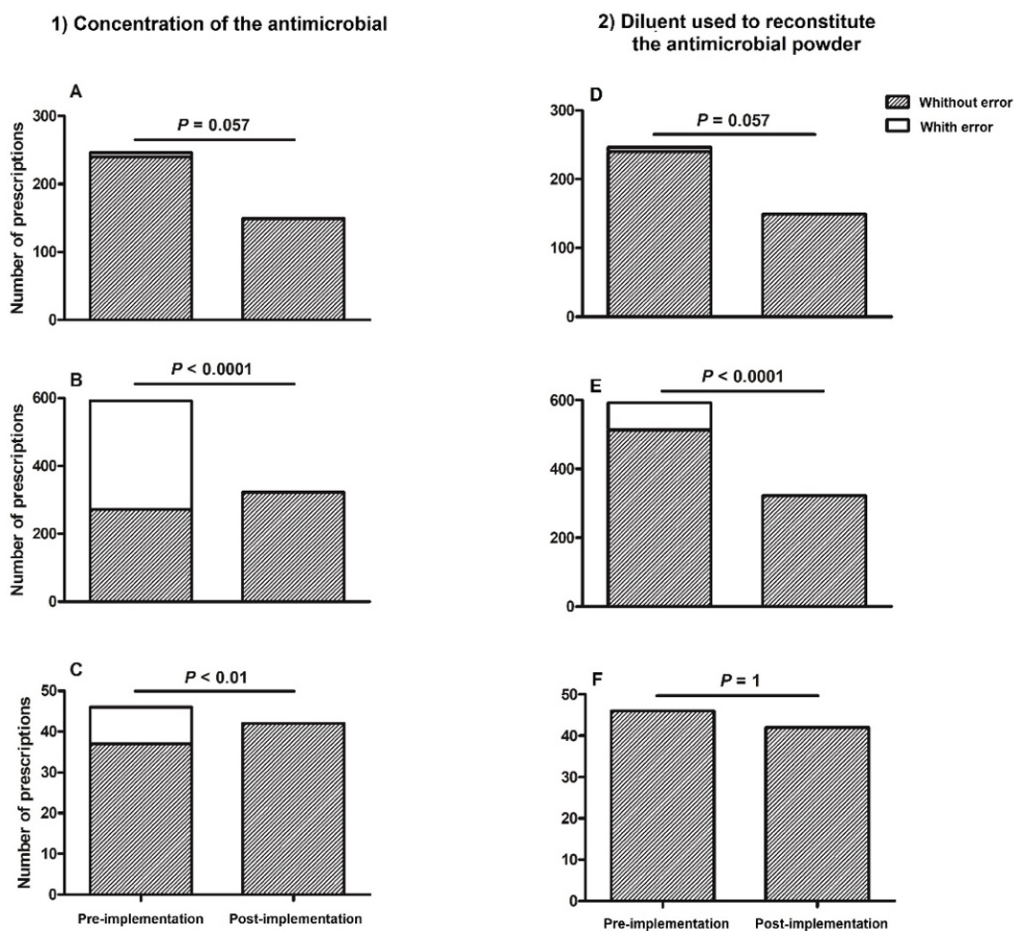

Figure 1. Number of prescription orders of cefepime (A), vancomycin (B), and piperacillin-tazobactam (C) prescribed in the period pre- and post-implementation of the antimicrobial stewardship interventions in the Neonatal and Intensive Care Unit. Rio de Janeiro, Brazil, 2013.
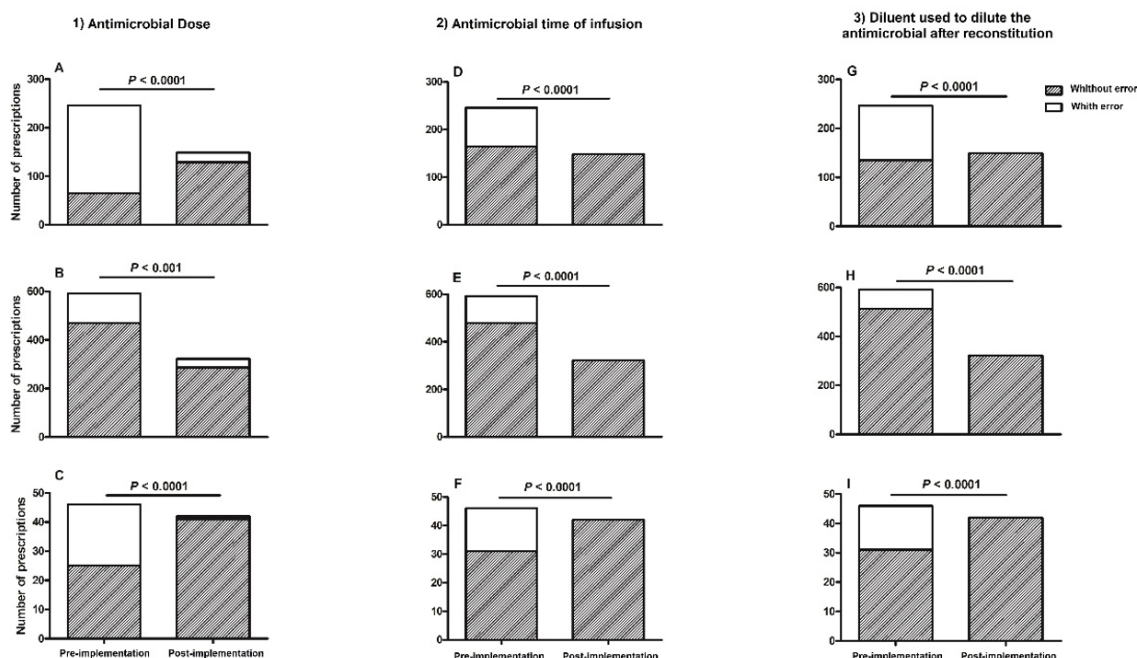
Figure 2. Comparison of the number of prescription orders with and without errors involving the (1) antimicrobial dose, (2) the antimicrobial time of infusion of cefepime, or (3) the diluent used to dilute the antimicrobial after the reconstitution for cefepime (A, D, and G), vancomycin (B, E, and H), and piperacillin-tazobactam (C, F, and I) in the period pre- and post-implementation of the antimicrobial stewardship interventions in the Neonatal and Intensive Care Unit. Rio de Janeiro, Brazil, 2013.

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Figure 3. Comparison of the number of prescription orders with and without errors involving the (1) concentration of the antimicrobial or (2) the diluent used to reconstitute the antimicrobial powder for cefepime (A and D), vancomycin (B and E), and piperacillin-tazobactam (C and F) in the period pre- and post-implementation of the antimicrobial stewardship interventions in the Neonatal and Intensive Care Unit. Rio de Janeiro, Brazil, 2013.

Although an absolute reduction was observed in the number of prescribing errors involving the concentration of the antimicrobial after reconstitution and dilution for all the studied antimicrobials, the difference was statistically significant only for vancomycin and piperacillin-tazobactam. Additionally, a statistically significant difference in the incidence of prescribing errors involving the diluent prescribed to reconstitute the antimicrobial powder was identified only for vancomycin (Figure 3).

DISCUSSION

In the present study, the implementation of a multiple-step antimicrobial stewardship approach, which included the adoption of the CPOE system with CDS and standardized drug concentrations, had a positive impact on the incidence of prescribing errors.

Sedatives and antimicrobials are the most common class of drugs prescribed to children [9], leading to more prescription errors with antimicrobials than other agents.[9-11] Multiple pharmacy-based antimicrobial stewardship interventions were implemented in the studied NICU to avoid these errors. Note that this was made possible by involving a multidisciplinary team composed of health professionals and information technology specialists throughout the entire implementation process. Furthermore, the clinical pharmacists had prior experience and trained all the professionals involved in prescribing and dispensing drugs with the use of the CPOE system with CDS. This approach was crucial since staff inexperience and heavy workload are considered risk factors for medication errors.[12]

Overall, a reduction in prescribing errors of antimicrobial drugs was observed, especially for vancomycin. These data are extremally important because a decrease in prescribing errors for antimicrobial drugs is associated with a reduction of antimicrobial resistance, one of the greatest Global Health challenges of the 21st century.[1] Also, medication errors are the most frequent source of healthcare associated harm in the world, and according to the World Health Organization, anti-infectives should be targeted as a priority drug class when it comes to reducing avoidable harm from medicines.[13] Therefore, the implementation of effective actions to improve anti-microbial drugs utilization, such as the ones described in the present study, is paramount.

It is also important to highlight the significant

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reduction in prescription orders for cefepime and vancomycin after the implementation of antimicrobial stewardship interventions, even though there was a greater number of newborns admitted to the NICU in the post-implementation period. This indicates that the pharmacy-based antimicrobial stewardship interventions might have decreased inappropriate empirical therapy with these antimicrobial drugs, one of the major important causes of antimicrobial resistance.[14] Furthermore, reducing antimicrobials prescription avoids potential side effects caused by these drugs, such as vancomycin-induced phlebitis and red man syndrome.[15,16]

In the NICU, there is a high potential for adverse drug events, and medication errors frequently involve incorrect dosages.[6, 17,18] In the present study, a decrease in prescribing errors involving inappropriate dosing was observed for all evaluated antimicrobials after the implementation of the interventions. The ideal dosage of antimicrobial is crucial for increasing the effectiveness and safety of treatment, as differences in weight and glomerular filtration rates often vary during the newborn's hospitalization.[4] A reduction in dosage prescription errors was also identified with the use of a CPOE in a study conducted in France[i], which suggested that manual prescriptions should be completely avoided in neonatal units.[19]

Errors involving the wrong diluent are also common in NICUs.[6] A significant drop in the incidence of prescribing errors involving diluents used to dilute cefepime, vancomycin, and piperacillin-tazobactam was identified. However, the errors involving diluents prescribed to reconstitute the antimicrobial powder dropped significantly only for vancomycin. Usually, sodium chloride is the diluent most frequently used by healthcare teams to reconstitute antimicrobial powders. This poses no problem for cefepime and piperacillin-tazobactam, which are compatible with this diluent. However, vancomycin powder should be reconstituted with sterile water.[20]

In the present study, a significant decrease in prescription errors involving drug concentration for vancomycin and piperacillin-tazobactam was also observed after the implementation of antimicrobial stewardship interventions. Similar results were found in a prospective cohort study developed at a children's hospital in the Netherlands, which evaluated the replacement of "free text" prescriptions with CPOE[21]. Infusion rates are frequently prescribed incorrectly to newborns in the NICU, exposing them to negative outcomes.[22] In the studied NICU, the measures adopted reduced infusion time errors for all evaluated antimicrobial drugs.

Although the findings suggest that pharmacy-based antimicrobial stewardship interventions may aid in better antimicrobial management in NICUs, it would be interesting to extend this study to less frequently used antimicrobials. Another limitation of our work was not assessing whether the implementation of the interventions could affect the clinical course of disease.

In conclusion, the implementation of multiple pharmacy-based antimicrobial stewardship interventions, including the adoption of a CPOE system with CDS and standardized drug concentrations, results in an improvement in the safety profile of antimicrobial prescriptions and contributes to safer medication practices and patient safety.

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AUTHORS' CONTRIBUTIONS

Francisco Alves Farias-Filho contributed to project management, contributed to literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Philipe Vieira Souza** contributed to literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Susana Nunes da Rocha Nascimento** contributed to literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Rafaela de Carvalho Rodrigues** contributed to literature search, writing of the abstract, introduction, methodology, discussion and review. **Mariana Martins Gonzaga do Nascimento** contributed to project administration, contributed to literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Vinicius de Frias Carvalho** contributed to literature search, writing of the abstract, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics.

All authors approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.

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