Review article

Inadequate use of antibiotics and increase in neonatal sepsis caused by resistant bacteria related to health care assistance: a systematic review☆

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ABSTRACT

Background: Technologies and life support management have enhanced the survival of preterm infants. The immune system of newborns is immature, which contributes to the occurrence of healthcare-associated infections (HAI). The overlap of several conditions with neonatal sepsis and the difficulty of diagnosis and laboratory confirmation during this period result in a tendency to over-treat neonatal sepsis. The use of antimicrobial agents (ATM) is a risk factor for multidrug-resistant bacterial infections. This work aimed to perform a systematic review of the relationship between inadequate use of ATM and increase in neonatal sepsis related to healthcare assistance, due to bacterial resistance.

Methods: Our PECOS acronym was as follows: P: hospitalized neonates with sepsis diagnosis, E: inappropriate use of ATM, C: adequate use of ATM or no indication of infection, O: resistant bacterial infection, and S: original studies. We performed searches in the PubMed, Scopus, Virtual Health Library (Scielo, LILACS, and MEDLINE), and Embase without limits on time, language, and the references of the articles found. Fourteen studies were included and assessed using GRADE, Newcastle, and STROBE methodologies.

Results: All studies found were observational and started with a low-quality evidence level in GRADE.

Conclusions: Despite their low-quality evidence, the studies demonstrated the association between inadequate use of ATM and increase of neonatal resistant bacterial HAI in neonatal units. However, there is significant difficulty in conducting high-quality studies in this population due to ethical issues tied to randomized trials. Therefore, new studies should be encouraged to recommend adequate treatment of newborns without increasing the risk of HAI by multidrug-resistant bacteria.

Introduction

In recent years, the improvement of technologies for advanced life support applied to prematurity complications resulted in increased survival of preterm infants with earlier gestational age and low birth weight.[1,2] Due to immaturity of the immune system and the need for several invasive procedures, hospitalized neonates, especially premature infants, are susceptible to healthcare-associated infections (HAI). This is one of the most significant adverse events associated with morbidity and mortality in this age group.[1–5]

The diagnosis of HAI in newborns is difficult due to the lack of specific symptoms. At this age, HAI commonly shares symptoms with other diseases, such as respiratory distress syndrome, prematurity hypotension, metabolic disorders, and others.[1,6–10] Beginning early treatment is fundamental for improving the prognosis of these patients. Therefore, treatment is initiated before receiving laboratory results, which contributes to the exposure of this population to antimicrobial agents (ATM), often unnecessary.[6–11] Furthermore, the difficulty in obtaining sufficient samples for cultures and the low sensitivity of this test leads many physicians to decide to continue ATM for treating presumed neonatal sepsis,[6,8] which is up to eight-fold over-treated than confirmed HAI cases, according to some studies.[6]

The increase of HAI caused by resistant bacteria is a multifactorial issue. Currently, it is a worldwide concern due to the associated high morbidity and mortality and increased hospitals costs.[1,3,8,12] The inability of the pharmaceutical industry to create new drugs at the same rate as the development of resistance is also an important issue to consider.[3,9–11] The excessive use of ATM, especially broad-spectrum agents, is already recognized as a key factor for the development of resistance.[1,6,7,9,11–16] In recent years, the emergence of increasingly resistant strains has been observed,[2,6,8] as demonstrated by clinical trials in adult and pediatric populations. However, in the neonatal population, there is a lack of studies assessing this association.[8,13,17]

The aim of this work was to perform a systematic review of the relationship between inadequate use of ATM and increase in neonatal sepsis related to healthcare assistance, due to bacterial resistance. For this review, the attributes considered when selecting the articles were: population, exposition, comparison, outcome, and study type, according to the acronym PECOS.[18,19] The definition was as follows: P, neonates with sepsis diagnosis in Neonatal Units; E: inappropriate use of ATM; C, adequate use of ATM or no indication of infection; O, resistant bacterial infection; S, original studies.

Methods

Literature review

The articles were selected using the international guideline outlined by PRISMA, which coordinates the process of performing meta-analyses and systematic reviews.[18]

The search was carried out without limits on language or date of the study, using the *PubMed*, *Scopus*, Virtual Health Library (*Scielo, LILACs, and MEDLINE*) and *Embase* using the following keywords: "Sepsis," "Infant, Newborn," "Anti-Infective Agents," and "Drug Resistance, Microbial" and their respective Portuguese and Spanish translations up to July 2017. The references from the selected articles were also evaluated and included in the selection if they met the inclusion criteria. *PubMed* was searched using the *MeSH* terms: ("Sepsis"[MeSH] AND "Infant, Newborn"[MeSH]) AND "Anti-Infective Agents"[MeSH]) AND "Drug Resistance, Microbial"[MeSH].

Inclusion and exclusion criteria

Inclusion criteria: All original articles that included patients with late-onset neonatal sepsis with multi-resistant bacteria, who were treated with broad-spectrum ATM, or with inadequate or prolonged empiric treatment. Additionally, only articles that defined the duration and type of ATM were included.

Exclusion criteria: All articles that included patients with early onset sepsis with multi-resistant bacteria, articles which did not define duration and type of ATM therapy, and articles which considered only risk factors for colonization with multidrug-resistant bacteria.

Some studies that described ATM use but did not comply with the PECOS framework were only used for the discussion section.

Article extraction and data quality evaluation

Two independent reviewers evaluated all titles and abstracts from the database search, with the goal of identifying articles that would generally accomplish the selection criteria.