Review Article

Performance of nitric oxide in sepsis: a scoping review

Desempenho do óxido nítrico na sepse: uma revisão de escopo

Desempeño del óxido nítrico en la sepsis: una revisión de alcance

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Abstract

Objective: Map the available evidence on the actions of nitric oxide in the pathophysiology of sepsis and its relationship with the severity of sepsis in patients.

Method: Scoping review following the *Joanna Briggs Institute methodology*. A search was carried out for studies that highlighted the actions of nitric oxide in sepsis, informing whether its increase is associated with the severity of sepsis in patients. Two independent reviewers mapped the information using a previously designed data extraction instrument. The data was analyzed for its relevance and then extracted and synthesized.

Results: Eleven of 1342 studies were included in the review. The first of them was published in 2017 and the last in 2022. Most of them were developed in the USA, China, and Germany. Studies have reported the actions and bioavailability of nitric oxide and endogenous inhibitors related to its production, and related nitric oxide to the severity of sepsis.

Conclusion: The physiological production of nitric oxide during sepsis acts as a vascular protector, mainly in the microcirculation but contributes to vascular dysfunction in high concentrations, subverting the regulation of blood pressure, causing deep vasodilation and refractory hypotension, and increasing the severity of sepsis in patients.

Resumo

Objetivo: Mapear as evidências disponíveis sobre as ações do óxido nítrico na fisiopatologia da sepse e sua relação com a gravidade de pacientes sépticos.

Método: Revisão de escopo de acordo com a metodologia do *Joanna Briggs Institute*. Realizou-se busca por estudos que evidenciaram as ações do óxido nítrico na sepse e se o seu aumento está associado à gravidade de pacientes sépticos. Dois revisores independentes fizeram o mapeamento das informações utilizando um instrumento de extração de dados previamente elaborado. Os dados foram analisados quanto à sua relevância, sendo posteriormente extraídos e sintetizados.

Resultados: De 1342 estudos, 11 foram incluídos na revisão. O primeiro foi publicado em 2017 e o último, em 2022. A maioria foi desenvolvida nos Estados Unidos, na China e na Alemanha. Os estudos apresentaram informações referentes as ações do óxido nítrico, sintetizando sua biodisponibilidade e os inibidores endógenos relacionados a sua produção, além de abordarem a relação do óxido nítrico com a gravidade da sepse.

Conclusão: A produção de óxido nítrico fisiológico durante a sepse atua como protetor vascular, principalmente na microcirculação, porém, em altas concentrações, contribui para a disfunção vascular, que subverte a fisiologia da regulação da pressão arterial, causando profunda vasodilatação e hipotensão refratária e aumentando a gravidade de pacientes sépticos.

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Conflicts of interest: The authors have nothing to declare.

Resumen

Objetivo: Mapear las evidencias disponibles sobre las acciones del óxido nítrico en la fisiopatología de la sepsis y su relación con la gravedad de pacientes sépticos.

Métodos: Revisión de alcance de acuerdo con la metodología del *Joanna Briggs Institute*. Se realizó una búsqueda de estudios que evidenciaron las acciones del óxido nítrico en la sepsis y si su aumento estaba asociado a la gravedad de pacientes sépticos. Dos revisores independientes hicieron el mapeo de la información utilizando un instrumento de extracción de datos previamente elaborado. Los datos se analizaron respecto a su relevancia, para luego extraerlos y sintetizarlos.

Resultados: De 1342 estudios, se incluyeron 11 en la revisión. El primero fue publicado en 2017 y el último en 2022. La mayoría se realizó en Estados Unidos, China y Alemania. Los estudios presentaron información referente a las acciones del óxido nítrico, sintetizando su biodisponibilidad y los inhibidores endógenos relacionados con su producción, además de abordar la relación del óxido nítrico con la gravedad de la sepsis.

Conclusión: La producción de óxido nítrico fisiológico durante la sepsis actúa como protector vascular, principalmente en la microcirculación. Sin embargo, en altas concentraciones, contribuye a la disfunción vascular, que subvierte la fisiología de la regulación de la presión arterial, causa una profunda vasodilatación e hipotensión refractaria y aumenta la gravedad de pacientes sépticos.

Registration of the scoping review in the Open Science Framework: https://doi.org/10.17605/OSF.IO/MXDK2

Introduction

Sepsis and septic shock are important global health problems. They are two of the leading causes of health loss that affect millions of people around the world each year.[1] Sepsis is a serious recurring problem in hospital environments, especially in intensive care units (ICU).[2]

In Brazil, sepsis is responsible for almost all ICU admissions. The number of deaths related to hospital sepsis increased by about 6% from 2000 to 2010. In Brazilian ICUs, incidence, prevalence, and mortality rates from sepsis are high, and more than 200,000 deaths have been estimated in adult patients with sepsis per year.[3]

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defined sepsis as a life-threatening organ dysfunction caused by the dysregulated host response to infection. Sepsis is one of the main causes of mortality among ICU patients, and changes in serum nitric oxide (NO) levels have been associated with mortality in critically ill patients.[4,5]

In the late stage of sepsis, the increase in NO plays a role as a mediator of the loss of vascular tone (vasoplegia), resulting in refractory vasodilation and increased severity during sepsis.[5] High levels of cytokines produced in oxidative stress cause increased production of NO and possible harmful effects on cells (due to an increase in vasodilation and hypotension), which can be related to the severity of sepsis.[6]

Sepsis and septic shock are characterized by several cardiovascular abnormalities and possible cellular damage, requiring a better understanding of the symptoms of sepsis.[5] The NO actions must be discussed and understood within this complex pathophysiological picture of sepsis. The objective of this review was to map the available evidence on the performance action of NO in the pathophysiology of sepsis and its relationship with the severity of sepsis in patients.

Methods

This scoping review study was carried out according to the method proposed by the Joanna Briggs Institute (JBI) and described according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Check-list.[7] This type of review is used to map evidence that supports certain areas of knowledge, clarify areas of research, and identify knowledge gaps.[8]

To prepare the review question, the phases recommended by the Joanna Briggs Institute (JBI) were fulfilled by identifying the issue and searching for relevant studies by taking the following steps: definition of the objectives and questions of the study; development of inclusion and exclusion criteria; development of a search and selection strategy for articles, identification, selection, extraction, data mapping, and presentation of results.

To define the search, the PCC (Population, Concept, and Context) strategy was adopted, defining **P** as patients with sepsis/septic shock, **C** as NO, and **C** as during sepsis. Based on these definitions, the following guiding questions were established: "What is the scientific evidence on the performance action of nitric oxide in the pathophysiology of sepsis? Is increased plasma nitrate during sepsis associated with greater severity in sepsis in patients?"

Data collection was carried out from November to December 2022 in the following databases: Medical Literature Analysis and Retrieval System Online (MedLine), National Library of Medicine (PubMed), Latin American and Caribbean Literature in Health Sciences (Lilacs), and EMBASE. The Scientific Electronic Library Online (SciELO) virtual library was also accessed as an additional source.

The following Medical Subject Headings (MeSH) terms were used for the search: sepsis, shock septic, nitric oxide, nitric oxide synthase, dysfunction, multiple organ failure, and patient acuity. The descriptors were combined using the Boolean operators *AND* (restrictive combination) and *OR* (additive combination). The Scientific Electronic Library Online (SciELO) virtual library was also accessed as an additional source (Chart 1).

Chart 1. Database search strategies

Bases	Strategies
Medline / PubMed	("*sepsis*" *AND* "*nitric oxide*"), ("*sepsis*" *AND* "*nitric oxide*" *AND* "*dysfunction*"), ("*sepsis*" *AND* "*nitric oxide*" *AND* "*multiple organ failure*") ("*sepsis*" *AND* "*nitric oxide*" *OR* "*nitric oxide sintase*"), ("*nitric oxide*" *AND* "*patient acuity*" *AND* "*sepsis*"), ("*nitric oxide*" *AND* "*patient acuity*" *AND* "*Shock septic*").
LILACS	("*sepsis*" *AND* "*nitric oxide*"), ("*sepsis*" *AND* "*nitric oxide*" *AND* "*multiple organ failure*") ("*sepsis*" *AND* "*nitric oxide*" *OR* "*nitric oxide sintase*"), ("*nitric oxide*" *AND* "*patient acuity*" *AND* "*Shock septic*").
EMBASE	("*sepsis*" *AND* "*nitric oxide*"), ("*sepsis*" *AND* "*nitric oxide*" *AND* "*multiple organ failure*"), ("*nitric oxide*" *AND* "*patient acuity*" *AND* "*sepsis*").
SCIELO	("*sepsis*" *AND* "*nitric oxide*"), ("*sepsis*" *AND* "*nitric oxide*" *AND* "*multiple organ failure*"), ("*nitric oxide*" *AND* "*patient acuity*" *AND* "*sepsis*"), ("*nitric oxide*" *AND* "*patient acuity*" *AND* "*Shock septic*").

The eligibility criteria were as follows: studies published in English and Portuguese in the last 5 years, carried out with adult patients over 18 years of age, and studies carried out with laboratory animals addressing the performance {action} or behavior {effect} of NO in sepsis as a topic. Quantitative clinical primary and randomized studies, systematic/integrative reviews, clinical trials, and basic research were included. Narrative reviews, internet texts, editorials, books, documents, and articles partially available in the databases, and duplicate articles were excluded.

The selection of studies according to title and abstract was carried out using the Rayyan QCR digital tool.[9] Then, the two reviewers independently and blindly read the titles and abstracts to reduce the possibility of interpretative bias. After reading and critically evaluating the full text of the pre-selected studies, those that did not meet the eligibility criteria were excluded. After selection, the studies were sent to the Mendeley bibliography manager.

An instrument to extract data was developed, and the information was mapped by two independent researchers. The following information from each article was recorded: Authors, year, country where the study was carried out, objective, and study design. The protocol for this scoping review was registered on Open Science.

Results

A total of 1342 articles with potential eligibility were found in the databases, and 251 of them were discarded due to duplicity; 1091 of them underwent title and abstract analysis, and 1037 articles were excluded after it. Then, only 54 were selected for full reading. After reading to assess eligibility, 15 studies were selected, 4 were excluded because they did not answer the guiding questions, and 11 remained in the final sample (figure 1). Information was extracted from the included studies and the results are presented in chart 2.

Regarding the characteristics of the 11 selected studies, the first of them was published in 2017 and the others until 2022. The largest production occurred in 2021 (three articles). The studies were carried out in the USA (n=2), China (n=2), Germany (n=2) Japan, India, England, France, and Brazil (one article each). All of them were published in English, being integrative reviews (45.4%) and with an approach of randomized studies (36.3%). As for the population studied, four studies were about

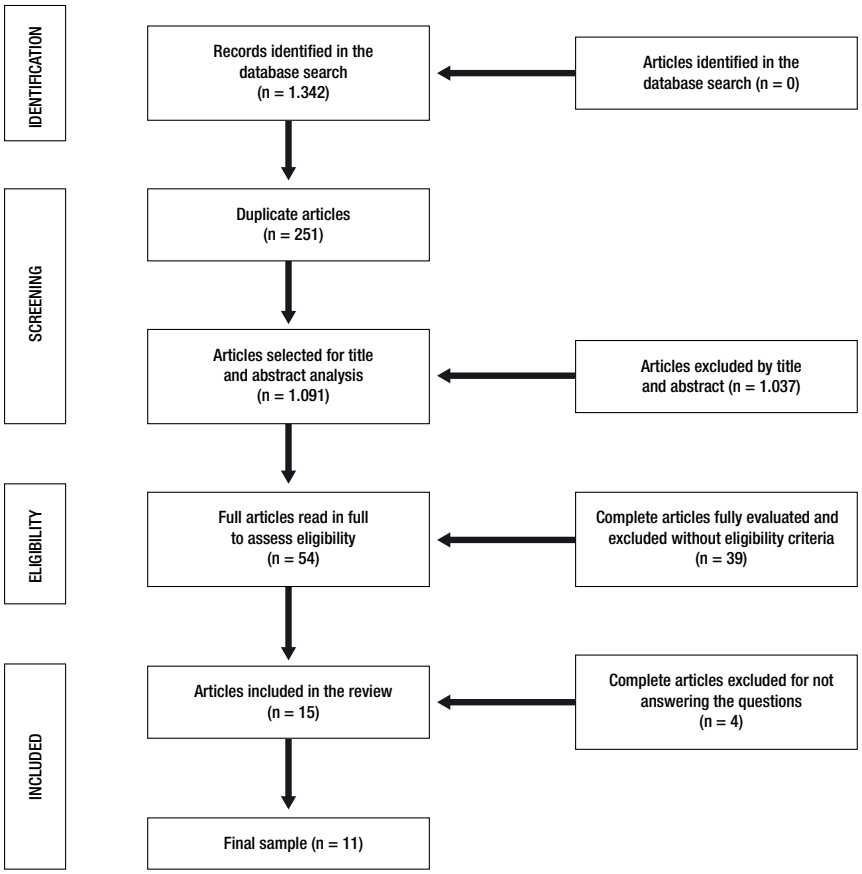

Figure 1. Identification and selection process of included studies

Chart 2. Characteristics from studies obtained on performance action of nitric oxide on sepsis

Authors Years of Publication No. of Citations	Study Countries	Objectives	Study designs
Yu MH, Chen MH, Han F, Li Q, Sun RH, Tu YX. 2018[5]	China	To evaluate serum levels of amyloid A (SAA) and NO in comparison with predictive markers of C-reactive protein (CRP) and APACHE II score in groups of patients with septic and non-septic shock.	Randomized Study
Kumar S, Gupta E, SrivastavaVK, Kaushik S, Saxena J, Goyal LK, et al. 2019[6]	India	To evaluate the link between nitrosative stress and pro-inflammatory cytokines and correlate with the severity of sepsis and associated organ dysfunction.	Randomized Study
Bath PM, Coleman CM, Gordon AL, Lim WS, Webb AJ. 2021[10]	England	To evidence the activity of NO in viral, bacterial, protozoal, and fungal infections *in vitro*, *in vivo*, and early-phase clinical studies.	Integrative Review
Winkler MS, Kluge S, Holzmann M, Moritz E, Robbe L, Bauer A. et al. 2017[11]	Germany	To investigate whether concentrations of marker surrogates for NO bioavailability are associated with sepsis severity.	Randomized Study
Porrini C, Ramarao N, Tran SL. 2020[12]	France	To know the beneficial or harmful functions of NO in humans, pathogenic bacteria, and microbiota, and the mechanisms used by them to produce, use, or resist NO.	Integrative Review
Webber RJ, Sweet RM, Webber DS. 2019[13]	USA	To analyze plasma inducible nitric oxide synthase (iNOS) as an early and specific biomarker for the onset of sepsis.	Clinical Trial
Hu S, Pi Q, Xu X, Yan J, Guo Y, Tan W. et al. 2021[14]	China	To explore the performance effect of eNOS in sepsis-induced endothelial dysfunction in septic mice and cellular models.	Randomized Study
Singh J, Lee Y, Kellum JA. 2022[15]	USA	To evidence whether reducing asymmetric dimethylarginine (ADMA) in patients with sepsis could be a potential therapeutic approach to attenuate progressive organ damage and mortality from sepsis.	Integrative Review
Dao VTV, Elbatreek MH, Fuch T, Gradler U, Schmidt HHHW, Shah, AM. et al. 2021[16]	Germany	To map the effects of NO inhibition in clinical practice in septic patients.	Integrative Review
Takatani Y, Ono K, Suzuki H, Inaba M, Sawada M, Matsuda N. 2018[17]	Japan	To analyze the NO plasma levels and their relationship with body temperature in two species of mice with sepsis.	Experimental Study
Oliveira FRMB, Assreuy J, Sordi R. 2022[18]	Brazil	To understand the pathophysiological mechanisms of NO in acute kidney injury associated with sepsis.	Integrative Review

clinical research conducted with adults in ICUs, two were carried out with laboratory animals, and five were integrative review studies, which were important to understand the actions and functionalities of NO. After summarizing the selected articles, the discussion was based on the biosynthesis and bioavailability of NO, endogenous inhibitors of NO production, and the relationship between NO and sepsis severity.

Discussion

The findings of this review showed that increased NO concentrations in patients with sepsis and septic shock may be related to their severity. Although NO has relevant actions in the pathophysiology of sepsis, its increase can cause deleterious effects on cells during sepsis.

NO is a short-lived gas in blood and a key signaling molecule that modulates vascular, neuronal, inflammatory, and immune responses. Its production is mediated by three isoforms of NO synthase (NOS): {} two of them [the neuronal (nNOS/NOS1) and endothelial (eNOS/NOS3) isoforms] are considered constitutive, which largely mediate neurotransmission, cytotoxicity, and vascular regulation. Within cells, NO interacts with mitochondrial respiration, activates metabolic regulatory pathways, and reduces oxidative stress.[10]

The other isoform corresponds to inducible NOS (iNOS /NOS2), which is expressed by the immune system in response to endotoxin and inflammatory process cytokines. It produces a much greater amount of NO than the constitutive isoforms, highlighting that endogenous antimicrobial activity is largely mediated by high local concentrations of NO produced by iNOS.[11]

The production of NO by iNOS has an essential role in host defense against infectious organisms and antitumor activity. However, prolonged production of NO and its accumulation can have pathological consequences, as its excessive production is linked to persistent inflammation.[12]

At the onset of sepsis, the presence of plasma iNOS is also observed in association with extracellular microvesicles (MV-iNOS) that produce toxic amounts of NO, resulting in organ dysfunction. It is important to highlight that the MV-iNOS found in plasma remains inactive, but they produce toxic NO inside the cell when installed in susceptible recipient cells, causing cell death.[13]

It is known that the physiological production of NO by the expression of eNOS has a protective role in microcirculation due to its ability to induce vasodilation to balance blood pressure in the presence of stress or blood vessel shear. However, an impaired microvascular vasodilation is observed in the late phase of sepsis due to the decrease in NO derived from eNOS, thus contributing to the severity of the impair microcirculation.[14]

In patients with sepsis, we highlight that the hyperproduction of NO by iNOS (in conditions of endotoxemia, microbial lipopolysaccharides, and pro-inflammatory cytokines) can lead to increased vasodilation, drop in blood pressure, endothelial hyporeactivity to conventional vasopressors, and myocardial dysfunction.[15-19]

Sepsis-induced endothelial dysfunction is a multifaceted syndrome that includes impairment of coagulation, fibrinolysis, permeability, leukocyte recruitment, and vascular tone, resulting in altered bioavailability of eNOS-derived NO. Therefore, endothelial cells are undoubtedly an important factor in the systemic response to infection and initiation of organ failure.[20]

We emphasize that the endogenous bioavailability of NO during sepsis may also decrease due to elevated levels of NOS inhibitors (such as asymmetric and symmetric dimethylarginine). These inhibitors play an important role in the pathophysiology of sepsis but may also be associated with poor outcomes in patients with sepsis.[15,21]

The decrease in NO production due to the increase in asymmetric dimethylarginine would consequently decrease hypotension, which would be a benefit during sepsis. However, microvascular protection and the innate immune response may also decrease.[11] On the other hand, long-term inhibition of NOS may be very risky due to its effects on eNOS (particularly for patients with cardiovascular risks or metabolic and renal diseases), as the phys-

iological NO derived from eNOS is considered a microvascular protector, and its inhibition must be avoided.[16]

A study carried out with 141 patients admitted to a hospital with septic shock due to necrotizing infection of soft tissues showed no difference in NO level. However, a positive correlation was observed between asymmetric dimethylarginine and the Sequential Sepsis Organization Failure Assessment (SOFA) score of these patients, inferring greater severity due to the decrease in physiological NO and greater risk of dying in the first 28 days of hospital admission.[22]

Therefore, understanding the effects of NO during sepsis is still complex as inhibition can also lead to microcirculation failure, just as the increase in NO concentration in septic patients is associated with severity and death.[23] This inhibition can also lead to organ failure and death as it induces microvascular dysfunction, leading to reduced perfusion and oxygen delivery to the organs, pro-inflammatory and pro-thrombotic states of the endothelium, release of inflammatory cytokines, oxidative stress, and mitochondrial dysfunction.[15]

Studies carried out on patients with sepsis admitted to the ICU showed a positive correlation between NO and the mortality score estimated by Acute Physiology and Chronic Health Evaluation (APACHE II), suggesting that increased NO may reflect the severity of sepsis and the degree of multi-organ dysfunction.[5,6]

In a study carried out in China in 2018, the authors compared the NO level in patients with septic and non-septic shocks and showed that NO concentration in septic patients in the initial stage is higher and remains up to three days after diagnosis.[5]

However, a study carried out with mice showed that high levels of NO are found in the late phase of sepsis. In this study, a reduction in mortality was observed after *iv injection* with a selective inhibitor of iNOS 1400W (0.5 mg/kg) at the time of sepsis induction; six hours later, it was observed that 40% of the mice survived for more than seven days.[17]

Thus, oxidative stress, inflammation, and increased serum NO levels may be reflected in the severity of patients with sepsis in their early stages. The increase in NO concentration has a mediating role in the loss of vascular tone and contributes to the myocardial depression observed in the late stage of sepsis, representing increased severity and exacerbation of sepsis.[5,23]

Studies showed high levels of NO in patients with sepsis who presented hemodynamic dysfunction and died. The high production of NO contributes to refractory hypotension associated with sepsis and damage to specific organs in cases of overproduction of NO, being also associated with impairment of pulmonary, intestinal, and hepatic functions and renal failure.[23,24]

We highlight that sepsis is also one of the main causes of acute kidney injury. An increase in NO is also involved in several mechanisms of this dysfunction in endothelial cells, as well as in microcirculatory changes and oxidative stress. In the control of renal perfusion, the endothelial eNOS and nNOS isoforms are the main sources of NO in basal conditions. However, iNOS increases NO production during sepsis, and its overexpression in the renal cortex results in spinal cord ischemia.[18]

It can be inferred that an increase in NO may be related to a severity biomarker in patients with sepsis and predict their clinical outcomes. In clinical practice, early recognition of the warning signs of sepsis is necessary to guide care for septic patients.[5]

Considering the above aspects, this study contributed to raising the main functions of NO in the pathophysiology of sepsis and its effects on the severity of sepsis in patients.

This scoping review presented as a limitation the fact that few studies related NO with the severity of patients with sepsis and septic shock, as other studies also describe increased NO in sepsis but few of them correlate them with severity scores in critically ill patients.

Conclusion

The production of physiological nitric oxide as a vascular protector during sepsis is important, especially in the microcirculation. However, it plays a critical role in vascular dysfunction when in high

concentrations, subverting blood pressure regulation, causing profound vasodilation and refractory hypotension, and increasing severity of sepsis in patients. Higher plasma levels of nitric oxide were observed in patients with sepsis who had hemodynamic dysfunction and died, reinforcing that the increase in serum levels reflects the severity of sepsis. {} Therefore, knowing the functions of nitric oxide in the pathophysiology of sepsis and understanding that it may be a biomarker of its severity is relevant for studies involving septic patients.

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