Neonatal sepsis with neutropenia: granulocyte-colony stimulating factor (G-CSF)

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

Sepsis is a serious complication in newborns and an important cause of mortality, especially in premature infants. One of the factors that contribute to the susceptibility of these patients to infections is the immaturity of their immune system. One of the possible genesis of this phenomenon seems to lie in the presence of an inhibitor of placental origin, which acts by decreasing the endogenous production of the granulocyte-colony stimulating factor (G-CSF). A systematic review was performed using the PICO search system. Newborns with neonatal sepsis and neutropenia (patient), Treatment with G-CSF plus antibiotics compared with conventional therapy (intervention), Death (any cause), and adverse effects (outcome). The search resulted in 85 articles, of which 12 studies were included. The details of the methodology and results of this guideline are set out in Annex 1.

INTRODUCTION

Sepsis is a serious complication in newborns and an important cause of mortality, especially in premature infants[1,2]. Although there has been a reduction in its incidence in recent decades[3], it is estimated that 1.4 million newborns still die annually as a result of invasive infection[4].

In addition to mortality, septic conditions are associated with a worse neurological prognosis and the occurrence of chronic pulmonary disease[5,6], impairing the quality of life and raising the social costs of survivors.

One of the factors that contribute to the susceptibility of these patients to infections is the immaturity of their immune system[4]. Structural and functional abnormalities of the immune components have been described in this age group, and the changes probably more related to the occurrence of sepsis are those of

polymorphonuclear cells[7]. Among them, neutrophils also presented a quantitative reduction in up to 58% of preterm infants, depending on the definition of neutropenia used[8].

Neutrophils play a fundamental role in the defense against bacterial infections, and people with a chronic deficiency of these cells exhibit recurrent infections and early mortality. In neonates, risk factors such as gestational hypertension, intrauterine growth restriction, fetus-fetal transfusion syndrome, and hemolytic anemia due to Rh incompatibility are related to the absolute reduction in the count of these cells[9].

One of the possible genesis of this phenomenon seems to lie in the presence of an inhibitor of placental origin, which acts by decreasing the endogenous production of the granulocyte-colony stimulating factor (G-CSF)[10]. In addition, it has been observed that newborns with a low number of neutrophils in the bloodstream, in fact, have a hidden a medullary reserve, which can quickly respond to the use of a recombinant stimulating factor (rG-CSF)[11].

For this reason, rG-CSF has been suggested as prevention and adjuvant treatment of infections in the neonatal period[12]. Clinical trials and systematic reviews concluded that the drug is safe for this population, but were not sufficient to recommend its routine use[13].

RESULTS

The population included 355 newborns with sepsis and undergoing treatment with G-CSF plus antibiotics (N=183), compared (N=172) with conventional therapy (N=179), and followed-up to measure the death outcomes due to all causes related (in time) to the septic episode during hospitalization and death at 14 or 28 days, in addition to adverse events (Table 1).

In order to achieve some comparability between studies, the data for the death outcome were recovered in such a way as to allow an analysis of mortality at the 14th or 28th day, from the beginning G-CSF therapy.

Among the studies selected, the mean gestational age of the patients ranged from 24 to 40 weeks (only one study included NB <40 weeks[24]; seven studies[17-23] included NB <37 weeks). The body weight ranged from 500 to 3,667g, and age was ≤28 days. The median duration of G-CSF treatment was four days (range: 3-14 days) with a dose of 10 mcg/kg/

TABLE 1. SEPSIS IN NEWBORNS WITH NEUTROPENIA ≤5,000 CELLS/MM³

DESCRIPTION OF THE STUDIES INCLUDED				
Study	Population	Intervention	Control	Outcome/ Time
Bedford-Russell, 2001 Multicenter	28 NB with clinical signs of sepsis and neutrophils <5 x 10(9)/L. IG >25s, PC 500 – 1,500g, Id ≤28 d	13 NB, G-CSF 10 mcg/kg/d, IV, maximum of 14 d	15 NB, placebo	Death during hospitalization Death at 14 days Death at 28 days
Drossou-Agakidou, 1998 Single Center	35 NB with clinical signs of sepsis and neutrophils <5 x 10(9)/L. IG 24 – 37s, PC 720 – 2,940 g, Id <28 d	19 NB, G-CSF 10 mcg/kg/d, SC, 3 d	16 NB, placebo	Death at 14 days
Schibler, 1998 Multicenter	20 NB with early-onset sepsis and neutropenia <1.7x10⁹/L. IG 24 – 40s, PC 530 – 3,667 g, Id <3 d	10 NB, G-CSF 10 mcg/kg/d, IV, 3 d	10 NB, placebo	Death during hospitalization Death at 14 days Death at 28 days
Gathwala, 2011 Single Center	40 NB with clinical signs of sepsis and neutrophils <5 x 10(9)/L. IG <37 s, PC <2,000 g	20 NB, G-CSF 10 mcg/kg/d, IV, 5 d	20 NB, conventional therapy	Death during hospitalization
Chaudhuri, 2012 Single Center	78 NB with early-onset sepsis, neutropenia <1,500 cells/mm³ IG <34 s; PC 1,100 to 2,500 g; Id 3 d	39 NB, G-CSF 10 mcg/kg/d, 3 d	39 NB, placebo	Death during hospitalization
Borjianyazdi, 2013 Single Center	46 NB with clinical signs of sepsis; neutropenia (CAN ≤5,000/μL) IG 30 – 37 s, PC 530 – 3,667 g, Id <10 d	23 NB, G-CSF 10 mcg/kg/d, SC, 5 d	23 NB, placebo	Death at 14 days
Aktaş, 2015 Single Center	56 NB with sepsis, neutropenic (<1.0 x 10⁹/L) IG 32 s, PC 1,001 ± 240	33 NV, G-CSF 10 mcg/kg/d, IV, (1– 4 d; median, 2 d) up to CAN ≥1.0 x 10⁹/L	23 NB, conventional therapy	Death during hospitalization
Gupta, 2016 Single Center	52 NB with clinical signs of sepsis, neutropenia <1,800 cells/mm³ IG 32 s, PC 1500.38 ±306.35, Id <25 d	26 NB, G-CSF 10 mg/kg/d, 3 d, SC	26 NB, conventional therapy	Death during hospitalization

NB = newborns, CAN = absolute neutrophil count, IG = gestational age, s = weeks, PC = body weight, Id = age, d = days, IV = intravenous, SC = subcutaneous

TABLE 2. DESCRIPTION OF THE BIASES OF THE STUDIES INCLUDED

Study/Year	Rand	Blinded allocation	Blinded partici-pants and team	Blinded evaluator	Losses	Prog. character-istics	Appro-priate outcomes	AITT	Sample size calcu-lation
Aktas 2015									
Bedford-Russel 2001									
Borjianyazdi 2013									
Chaudihuri 2012									
Drossou-Agakidou 1998									
Gathwala 2011									
Gupta 2016									
Schibler 1998									

ITTA = Intention to Treat Analysis; Boxes: green = absence of bias, red = presence of bias, yellow = uncertain risk of bias

day, intravenously, or subcutaneously. Four studies[20,23,24,17] included NB with a cutoff point for neutropenia <1,800 cells/mm^3, and four others[18,19,21,22] with neutropenia ≤5,000 cells/mm^3.

In relation to the risk of bias, there was no description of the randomization in two studies[17.21] and of the blinded allocation in three[17,21,24]. No blinding of the team was described in one study[17,] and there was no double-blinding in another[21]. One study presented a loss of ≥20%, and no intention to treat analysis was conducted[17]. The overall risk of bias of the studies included is considered not severe (Table 2).

META-ANALYSIS FOR THE DEATH OUTCOME

The meta-analyzed outcomes were death during hospitalization and death at 14 or 28 days from the beginning of the G-CSF therapy.

In the analysis of in-hospital mortality, there was a reduction in the risk by 19% (95% CI, 10 to 29; I^2=26%) with the use of G-CSF in comparison to the conventional treatment with or without placebo; it was necessary to treat about 5 NB to prevent one death (NNT). The quality of evidence is high to sustain this outcome (Table 3).

In the analyses of mortality at 14 or 28 days, there was no difference in the use of G-CSF in comparison to the conventional treatment, with or without a placebo. The quality of evidence is moderate to sustain this outcome (Table 3- Annexes).

Heterogeneity

There was no evidence of significant heterogeneity between the studies.

Adverse effects of G-CSF administered in newborn sepsis

No serious adverse effects were reported with the use of G-CSF in the studies evaluated in this review. There were mild adverse effects, such as cutaneous reactions, irritability, electrolytic alterations, cardiac alterations, peripheral edema, and thrombocytopenia, but with no significant difference between G-CSF and the placebo. Four of the eight studies reported no adverse effects[19-22].

SYNTHESIS OF EVIDENCE

In newborns with sepsis and neutropenia ≤5,000 cells/mm^3, the use of G-CSF reduces the risk of in-hospital death by 19% (NNT = 5). G-CSF has proved to be a safe drug.

DISCUSSION

In a previous meta-analysis conducted by Bernstein (2001), five studies with a total of 155 patients were evaluated, and the mortality rate was lower among patients who received G-CSF than among those who received the placebo. However, when the non-randomized studies were excluded, the beneficial effects of

TABLE 3. G-CSF COMPARED TO THE CONVENTIONAL TREATMENT IN NEONATAL SEPSIS WITH NEUTROPENIA (CAN <5,000 CELLS/MM³)

Evaluation of certainty							Summary of Results				
No. of Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Overall certainty of the evidence	Study event rates (%)		Relative Effect (95% CI)	Potential absolute effects	
							With control	With G-CSF		Risk with control	Risk difference with G-CSF
DEATH (HOSPITALIZATION)											
274 (6 RCTs)	not severe	not severe	not severe	not severe	None	⊕⊕⊕⊕ HIGH	46/133 (34.6%)	22/141 (15.6%)	RR 0.43 (0.27 to 0.69)	346 per 1,000	minus 197 per 1,000 (from minus 252 to minus 107)
DEATH (14 DAYS)											
129 (4 RCTs)	not severe	not severe	not severe	severe [a]	none	⊕⊕⊕○ MODERATE	10/64 (15.6%)	8/65 (12.3%)	RR 0.79 (0.34 to 1.81)	156 per 1,000	33 less per 1,000 (from 103 less to 127 more)
DEATH (28 DAYS)											
48 (2 RCTs)	not severe	not severe	not severe	severe [a]	none	⊕⊕⊕○ MODERATE	7/25 (28.0%)	3/23 (13.0%)	RR 0.46 (0.13 to 1.57)	280 per 1,000	151 less per 1,000 (from 244 less to 160 more)

CI: Confidence interval; RR: Risk ratio. Explanations = [a] Non-significant difference.

FIGURE 2.- DEATH DURING HOSPITALIZATION. COMPARISON CHART: G-CSF *VERSUS* CONVENTIONAL THERAPY, OUTCOME: ALL-CAUSE MORTALITY DURING HOSPITALIZATION.

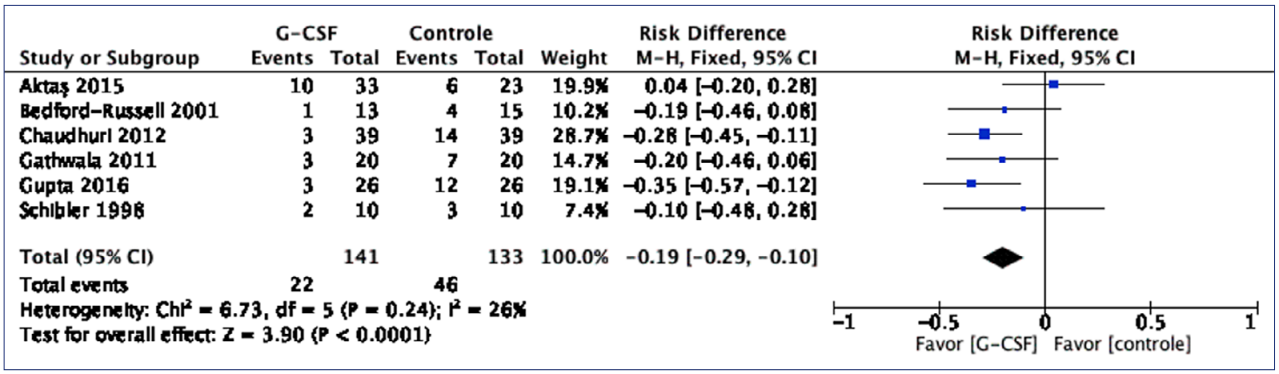


FIGURE 3. DEATH AT 14 OR 28 DAYS FROM THE BEGINNING OF THE G-CSF THERAPY. COMPARISON CHART: RHG-CSF *VERSUS* CONVENTIONAL THERAPY, OUTCOME: MORTALITY DUE TO ALL CAUSES: 14 DAYS

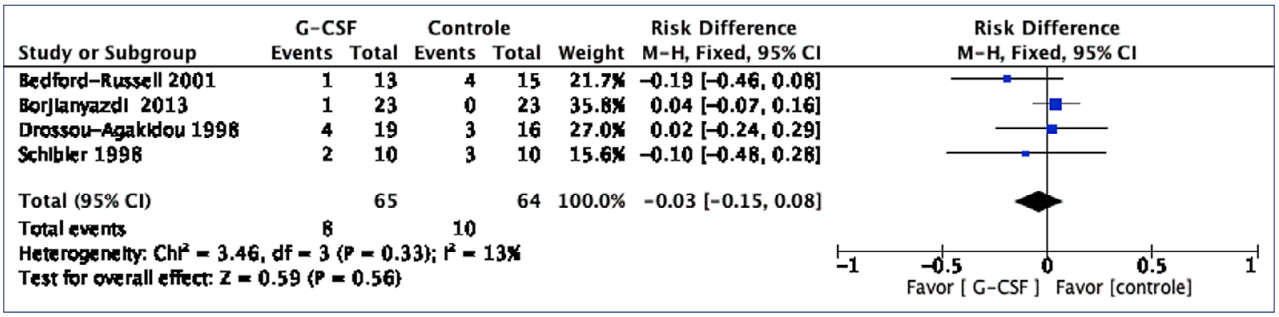
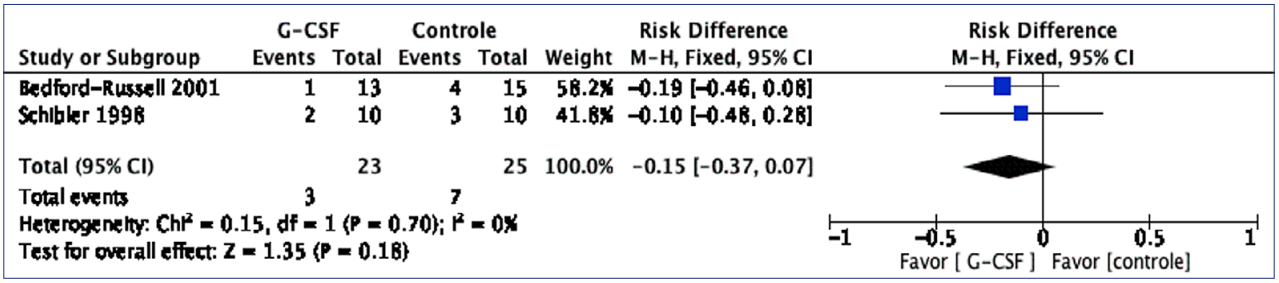


FIGURE 4. COMPARISON CHART: RHG-CSF *VERSUS* CONVENTIONAL THERAPY, OUTCOME: MORTALITY DUE TO ALL CAUSES AT 28 DAYS.



G-CSF therapy were found to be less consistent. Thus, the routine use of G-CSF could not be recommended for all newborns with sepsis[25].

In the Cochrane Systematic Review, Carr and Modi (2003) published a meta-analysis of seven studies to determine the safety and efficacy of rhG-CSF to reduce mortality in the treatment of suspected or proven systemic infections. They concluded there was no evidence to support the addition of G-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF) to antibiotic therapy in preterm infants with suspected systemic infection to reduce mortality. A subgroup analysis of 97 infants of three treatment studies which, in addition to systemic infection, presented clinically significant neutropenia (<1.7, 109/L) at the time they were enrolled in the study shows a significant reduction in mortality until the 14th day [RR, 0.34 (95% CI, 0.12, 0.92); RD, 0.18 (95% CI, 0.33, 0.03); number needed to treat, 6 (95% CI, 3,33)][26].

In this systematic review with meta-analysis, we included eight randomized clinical trials on G-CSF therapies in newborns with sepsis and neutropenia ≤5,000 cells/mm³ comparing them with the conventional treatment, and that reported all-cause mortality. The review showed evidence, based on data from six studies included in the meta-analysis, that the addition of G-CSF to antibiotic therapy in newborns with sepsis and neutropenia <5,000 cells/mm³ reduces mortality in hospitalization due to all causes [RD -0.19 (95% CI -0.29, 0.10); number needed to treat, 5 (95% CI, 3, 11)].

No significant advantage in survival was observed at 14 and 28 days from the beginning of therapy [RD -0.03 (95% CI -0.15, 0.08) and RD -0.15 (95% CI -0.37, 0.07), respectively]. However, all eight treatment studies were small, with the largest including only 78 newborns.

Our study has some limitations. The studies included in our meta-analysis were performed in a wide range of time, during which the definition of neonatal sepsis and the diagnostic and treatment methods changed. Four different definitions of neutropenia were used in different studies, and the definitions of sepsis varied between the clinic one and proof through positive culture. Patients of multiple birth weights and gestational ages were reported in all eight studies, and it is possible that this is a significant confounding factor.

ANNEX I

Clinical question

What is the impact on overall mortality outcomes (death from any cause) and adverse events of G-CSF in the treatment of newborns with neonatal sepsis and neutropenia [Absolute Neutrophil Count (ANC)<5,000 mm³] compared to the conventional therapy?

Objective

The objective of this assessment is to identify the efficacy and safety of granulocyte-colony stimulating factor (G-CSF) in the treatment of neonatal sepsis with neutropenia less than 5,000 cells/mm³, in comparison with conventional therapy.

Structured question

P	Newborns with neonatal sepsis and neutropenia (CAN ≤5,000 cells/mm³)
I	Treatment with G-CSF plus antibiotics compared with the conventional therapy
C	-
O	Death (due to any cause) and adverse effects

Eligibility criteria

We followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Prism) to conduct this systematic review[14].

The selection of the studies and the evaluation of the titles and abstracts obtained from the search strategy in the databases consulted were independently and blindly conducted in total accordance with the inclusion and exclusion criteria. Finally, studies with potential relevance were separated.

When the title and the summary were not enlightening, we sought for the full article.

Only studies with texts available in its entirety were considered for critical evaluation.

Excluded outcome - failure in the correction of pre-existing neutropenia during treatment.

Randomized clinical trial studies were selected.

Without time or language restrictions.

Full text available for access.

Search for papers

Databases and research strategy

The search for evidence will be conducted on virtual scientific information databases, using the following search strategy:

- Medline/PubMed - (Granulocyte Colony-Stimulating Factor OR rG-CSF OR G-CSF OR GCSF OR

Recombinant Proteins) AND (Infant, Newborn OR Infant, Premature OR neonates OR preterm infants) AND (Sepsis OR Neutropenia) AND Random*.

- Central/Cochrane Library - (Granulocyte Colony-Stimulating Factor OR rG-CSF OR G-CSF OR GCSF OR Recombinant Proteins) AND (Infant, Newborn OR Infant, Premature OR neonates OR preterm infants) AND (Sepsis OR Neutropenia).

- Lilacs via BVS - same search as in Central/Cochrane Library.

We also searched sources of data still unpublished, in progress, in gray literature and manual, performed by checking the list of "References" of the studies included in this review or in previous reviews.

All searches were performed by October 2019.

CRITICAL EVALUATION

Relevance - clinical importance

This guideline was prepared by means of a clinically relevant question in order to gather information in medicine to standardize approaches and assist in decision-making.

Results application - External validity

The process of retrieving the studies, as well as the evaluation of the titles and abstracts obtained, will be conducted by two researchers with expertise in the development of systematic reviews (A. S. and W. M. B.), independently and blinded, in accordance with the eligibility criteria listed above. When there is any disagreement regarding the selection of studies between the researchers, a third reviewer will be consulted (I. F.).

RESULTS

The data extraction will be performed independently by three reviewers, the results compared, and disagreements resolved by discussing them.

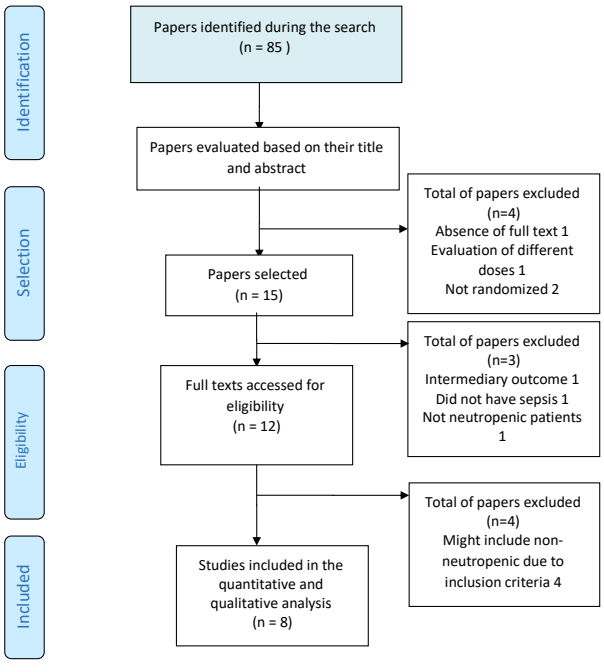
We will extract the following data from the studies: name of the author and year of publication, study population, intervention and comparison methods, the absolute number of deaths and adverse events, time of follow-up.

The methodological quality of the eligible trials will be evaluated independently by individual reviewers, not blinded, using the full text of the paper. Randomized clinical trials will have their risk of biases analyzed according to the following criteria: randomization, blinded allocation, double-blinding, losses, prognostic characteristics, presence of relevant outcome, time for the outcome, the method for outcome measurement, sample size calculation, early interruption, presence of other biases.

The results of the studies included will be meta-analyzed using the RevMan 5.3 software [15]. The heterogeneity of treatment effects between the tests was evaluated graphically and tested using the standard chi-square test. A weighted estimate of the relative risk (RR) between the studies was calculated using a fixed-effects model. The risk difference (RD) and the number needed to treat (NNT) were also calculated, and the final measure was used to sustain the synthesis of evidence, which will answer the clinical question of this review. The 95% CI was calculated for all outcomes.

During the search for evidence, we retrieved 85 papers, of which 12 were then selected based on their title and abstract; they all evaluate the use of G-CSF plus antibiotics for the treatment of newborns with sepsis and neutropenia, in comparison with conventional therapy. The 12 studies that met the eligibility criteria were then were accessed for analysis of their full text. Of the 12 studies, five[17-24] were selected to support this review; the grounds for exclusion and the list of studies excluded are available in the references and in Figure 1.

FIGURE 1. THE SELECTION OF RETRIEVED FROM THE VIRTUAL DATABASES OF SCIENTIFIC INFORMATION



Application of evidence - Recommendation

The quality of evidence will be graded as high, moderate, low, or very low using the Grade instrument[16] and taking into account the risk of bias, the presence of inconsistency, vagueness or indirect evidence in the meta-analysis of the outcomes of death and adverse events, and the presence of publication bias.

Conflict of interest

There is no conflict of interest related to this review that can be declared by any of the authors.

Final declaration

The Guidelines Project, an initiative of the Brazilian Medical Association in partnership with the Specialty Societies, aims to reconcile medical information in order to standardize approaches that can aid the physician's reasoning and decision-making process. The information contained in this project must be submitted to the evaluation and criticism of the physician responsible for the conduct to be followed, given the reality and clinical condition of each patient.

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NEUTROPENIA WAS NOT A COMPULSORY CRITERION AT ENROLLMENT

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MIGHT HAVE INCLUDED NON NEUTROPENIC