Hematologic Aspects of Early and Late-Onset Sepsis in Preterm Infants

Paolo Manzoni, MD, PhD

KEYWORDS

• Preterm neonates • Infection • Hematology • Neutropenia • Thrombocytopenia • *Candida spp* • CMV

KEY POINTS

- Hematologic changes during neonatal sepsis may occur and may be of diagnostic and prognostic help.
- Suspicion of a specific pathogen based on hematologic changes during sepsis is an open issue.
- Neutropenia and neutrophilia are frequently associated with sepsis, but correction of neutropenia is not associated with improved outcomes in sepsis.
- Thrombocytopenia is very common in sepsis and is a marker of severity with high predictivity for poor outcomes.
- *Candida spp* and cytomegalovirus are the pathogens most frequently associated with severe thrombocytopenia in preterm neonates.

INTRODUCTION

Hematologic changes during sepsis and infection in preterm neonates are frequent and may be seen as a diagnostic sign on one hand as well as a prognostic sign on the other hand.

As a preliminary consideration, it is important to remember that the reference ranges for the various blood cell elements in the neonatal period are not stable but change considerably according to gestational and postnatal age. The normal ranges established in healthy adults cannot be used; therefore, reference ranges originating from analysis of large neonatal datasets are mandatory in order to appropriately assess and guide diagnostics and treatment.[1]

Conflict of Interest Statement: The author has no commercial or financial conflicts of interest as well as no funding sources to disclose related to this article.
Division of Neonatology and NICU, Sant'Anna Hospital, Azienda Ospedaliera Universitaria Città della Salute e della Scienza, Torino 10126, Italy
E-mail address: paolomanzoni@hotmail.com

Clin Perinatol 42 (2015) 587–595
http://dx.doi.org/10.1016/j.clp.2015.04.012 **perinatology.theclinics.com**
0095-5108/15/$ – see front matter

The extent of all hematologic changes ultimately depends on the severity of sepsis, on the peripheral consumption, and on the bone marrow reserve—this last being specifically decreased in preterm infants.

During neonatal sepsis, leucocytes and platelets are more frequently affected than red blood cells. **Table 1** summarizes the main trends of all possible hematologic changes that may occur during neonatal sepsis for all the different blood cells.

The most frequently encountered features are an abnormal total leukocyte count, an abnormal total neutrophil (polymorphonuclear neutrophil [PMN]) count, an elevated immature PMN count, an elevated immature to total PMN ratio, an abnormal immature to mature PMN ratio (eg, $\geq$0.3), a low platelet count (eg, $\leq$80,000/mm^3), and the occurrence of pronounced degenerative changes in PMNs.

A specific association of each of these features with specific causative pathogens has been occasionally suggested only for some of these features.

This article reviews and updates the state of the art on this topic, discussing all hematologic changes occurring during neonatal sepsis and their implications both as diagnostic and prognostic parameters to guide clinicians at the bedside.

Red Blood Cells

In preterm neonates, anemia is commonly observed; its onset, or worsening, is not specifically related to infections, at least not in the same way that it may occur in older patients.

Nonetheless, although clearly anemia itself is not a diagnostic clue for sepsis, an episode of infection may unchain clusters of immune or nonimmune hemolysis, hemophagocytosis, or direct infection of progenitor cells (eg, by parvovirus B19), and so forth.[1]

Measurements of the red cell distribution width (RDW) ranges at birth have been evaluated for potential association with several neonatal diseases, including late-onset sepsis (LOS) in full-term, preterm, and intrauterine growth–restricted infants. Preterm newborns with such conditions feature higher RDW than others; specifically, those affected by sepsis have statistically significant higher RDW before 3 days of life; hence, some investigators speculate that high RDW might be an indication of risk for critical newborns at risk of LOS.[2] It is likely that an instable erythropoiesis can occur, and often the general inflammatory state typically occurring in the critical preterm infant may add to the sepsis-driven stress condition, thus furthermore impacting on the RDW values of septic neonates that might be higher than normal under such conditions.

Leucocytes

Neutrophils

It is well known that neonatal neutrophil function and kinetics are hugely different from those of adults, specifically during infection. The neutrophil response in such patients

Table 1
Summary of hematologic changes in neonatal sepsis

Pathogen or Group of Pathogens	RBC Count	WBC Count	Neutrophils Count	Lymphocytes Count	Platelets Count
Gram positives	[a]	↑ or ↓	[a] (rarely ↓)	[a]	↓↓
Gram negatives	[a]	↑or ↓	↓	[a]	↓
Fungi	[a]	↑or ↓	↓↓	[a]	↓↓↓

Abbreviations: RBC, red blood cells; WBC, white blood cells.
[a] Inconsistent and unpredictive changes.