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ORIGINAL ARTICLE

# Fecal calprotectin levels in preterm infants with and without feeding intolerance☆

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**KEYWORDS**
Fecal calprotectin;
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**Abstract**
*Objectives:* To assess the level of fecal calprotectin in preterm neonates with feeding intolerance, as well as to evaluate it as a marker of feeding intolerance and to determine a cut-off level of fecal calprotectin in feeding intolerance.
*Methods:* Analytical, multicenter, case–control study, which was carried out in neonatal intensive care units in Egypt, in a period from August 1, 2014 to March 1, 2015 on 52 preterm neonates. Neonates were classified into two groups; a study group including 26 neonates who met inclusion criteria and a control group including 26 neonates for comparison.
*Results:* Fecal calprotectin levels ranged from 3.9 μg/g to 971.8 μg/g, and there was a significant increase in fecal calprotectin in the study group when compared to the control group (334.3 ± 236.6 μg/g *vs.* 42.0 ± 38.2 μg/g, respectively) with moderate inverse significant correlation between fecal calprotectin and birth weight. Furthermore, there was moderate, significant correlation between fecal calprotectin and duration of breastfeeding range. On the other hand, there was no correlation between fecal calprotectin and post-natal age, gestational age, or volume of feeding. A cut-off at the 67.0 μg/g level, with 100.0% sensitivity and 76.9% specificity, was considered.
*Conclusion:* Fecal calprotectin level increased significantly in neonates with feeding intolerance; it can be used to detect early cases with necrotizing enterocolitis in neonates, but this subject still needs more investigations on more patients.


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**PALAVRAS-CHAVE**
Calprotectina fecal;
Intolerância alimentar;
Neonatos prematuros

## Níveis de calprotectina fecal em neonatos prematuros com e sem intolerância alimentar

### Resumo

*Objetivos:* Avaliar o nível de calprotectina fecal em neonatos prematuros com intolerância alimentar, além de avaliá-lo como um indicador de intolerância alimentar e determinar um nível de corte da calprotectina fecal na intolerância alimentar.
*Métodos:* Estudo caso-controle analítico, realizado em um multicentro de unidades de terapia intensiva neonatais no Egito, no período de 1° de agosto de 2014 a 1° de março de 2015, com 52 neonatos prematuros. Os neonatos foram classificados em dois grupos; um grupo de estudo incluindo 26 neonatos que atenderam aos critérios de inclusão e um grupo de controle incluindo 26 neonatos para comparação.
*Resultados:* Os níveis de calprotectina fecal variaram de 3,9 μg/g a 971,8 μg/g e houve um aumento significativo da calprotectina fecal no grupo de estudo quando comparado ao grupo de controle (334,3 ± 236,6 μg/g em comparação a 42,0 ± 38,2 μg/g, respectivamente) com correlação inversa, moderada significativa entre a calprotectina fecal e o peso ao nascer. Adicionalmente, houve correlação moderada significativa entre a calprotectina fecal e a duração do intervalo de amamentação. Por outro lado, não houve correlação entre a calprotectina fecal e a idade pós-natal, a idade gestacional ou o volume de amamentação. Foi considerado um corte nos níveis de 67,0 μg/g; com sensibilidade de 100,0% e especificidade de 76,9%.
*Conclusão:* O nível de calprotectina fecal aumentou significativamente em neonatos com intolerância alimentar e podemos utilizá-lo para detectar casos precoces com enterocolite necrosante em neonatos, porém ainda são necessárias mais investigações em mais pacientes.'


## Introduction

Feeding of preterm neonates is one of the main challenges faced by neonatal practitioners, especially those in the low birth weight groups.[1] Preterm neonates have greater mortality and morbidity with long-term disorders.[2]

Feeding intolerance is known as a difficulty in feeding milk, causing a change in the usual enteral feeding due to the appearance of one or more of the following gastrointestinal clinical symptoms: gastric residuals, vomiting, abdominal distention, distended bowel loops, and change in character of stool. Apnea, bradycardia, and temperature instability are also included as symptoms of feeding intolerance, but only for the reason of nursing judgment, in order to give guidance on detection of progression to more serious complications such as necrotizing enterocolitis (NEC).[3]

Many risk factors may aggravate feeding intolerance, including poor coordination of sucking and swallowing, weak lower esophageal sphincter, small stomach capacity, delayed stomach emptying time, and intestinal hypomotility[4]; on the other hand, human milk is the best for neonates and fortifiers derived from human milk act as a good substratum for preterm infant feeding.[5]

Abnormal bacterial colonization may be a factor in feeding intolerance in neonates, mainly due to dysfunction of the intestinal barrier, the immune responses, and functions of the intestine. Abnormal intestinal colonization, poor balance between microbiota, immune response, and tolerance mechanisms may result in feeding intolerance in postnatal life and also in gastrointestinal disease in childhood.[6]

In 1970, Fagerhol et al. searched for a marker of leukocyte turnover, and in 1980 they published their discovery of a protein in the cytoplasm of neutrophils, which they termed leukocyte-derived L1 protein, or calprotectin.[7] Calprotectin is a member of the S100 family of calcium and zinc binding proteins; it is the heterodimer of S100 A8/A9. It is found in neutrophils, monocytes, and some squamous epithelium cells. The complex accounts for up to 60% of the soluble protein content of the neutrophil cytoplasm. It is released by activation of leucocytes as consequences of inflammatory diseases.[8] S100 A8 is also called calgranulin A and myeloid-related protein 8 (MRP8), and S100A9 is called calgranulin B (MRP14). They both are linked to the innate immune system.[9]

Calprotectin has bacteriostatic and fungistatic actions, as it can isolate manganese and zinc in their cells[10]; it also has several biological properties including antimicrobic and imunomodulatory activity, and it is released during cell activation (active release) or cell death (passive release).[11] It has been suggested as a useful indicator to determine the severity of inflammation in the intestine.[12] The most significant factors that affect fecal calprotectin (FCP) excretion include ante- and perinatal antibiotic treatment, volume of enteral feeding, the occurrence of unplanned interruptions of enteral feeding, and the gastrointestinal bacterial colonization.[13]

Several studies have strongly suggested that a rise in FCP above baseline levels may be a candidate for a noninvasive marker of gastrointestinal diseases.[14–17] FCP levels in 6-month-old infants were higher than in children.[18]