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ORIGINAL ARTICLE

Role of serum 1,3β-D-glucan assay in early diagnosis of invasive fungal infections in a neonatal intensive care unit☆

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KEYWORDS
(1,3)-β-D-Glucan;
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Abstract

Objectives: To study the microbiological pattern of late onset neonatal sepsis cultures and to assess the diagnostic performance of serum (1,3)-β-D-glucan level for early diagnosis of invasive fungemia in high-risk infants admitted to a neonatal intensive care unit.

Methods: A prospective multicenter clinical trial conducted on infants at high risk for invasive fungal infections, with suspected late onset sepsis, admitted to a neonatal intensive care unit at Mansoura University Children's Hospital and Mansoura General Hospital between March 2014 and February 2016.

Results: A total of 77 newborn infants with high risk of invasive fungal infection were classified based on blood culture into three groups: no fungemia (41 neonates with proven bacterial sepsis), suspected fungemia (25 neonates with negative blood culture), and definite fungemia group (11 neonates with culture-proven *Candida*). The growing organisms were *Klebsiella* spp. (14/54); *Escherichia coli* (12/54); *Staphylococcus* spp. (12/54; coagulase-negative *Staphylococcus* [9/54]; *Staphylococcus aureus* [3/54]); *Pseudomonas aerouginosa* (3/54); and *Proteus* spp. (2/54). Moreover, 11/54 presented *Candida*. Serum (1,3)-β-D-glucan concentration was significantly lower in the no fungemia group when compared with the definite fungemia group. The best cut-off value of (1,3)-β-D-glucan was 99 pg/mL with sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 63.6%, 95.1%, 77.8%, 90.7%, and 88.5%, respectively.

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Conclusion: (1,3)-β-D-glucan assay has a limited sensitivity with excellent specificity and negative predictive value, which allow its use as an aid in exclusion of invasive neonatal fungal infection. Accurate diagnosis and therapeutic decisions should be based on combining (1,3)-β-D-glucan assay with other clinical, radiological, and microbiological findings.

PALAVRAS-CHAVE
(1,3)-β-D-glucano;
Candidíase invasiva;
Sepse neonatal

Papel do Ensaio sobre (1.3)-β-D-Glucano no Soro no Diagnóstico Precoce de Infecções Fúngicas Invasivas em uma unidade de terapia intensiva Neonatal

Resumo

Objetivos: Estudar o padrão microbiológico das culturas de sepse neonatal de início tardio e avaliar o desempenho diagnóstico do nível de (1,3)-β-D-glucano no soro para diagnóstico precoce de fungemia invasiva em neonatos de alto risco internados em uma unidade de terapia intensiva neonatal.
Métodos: Ensaio clínico multicêntrico prospectivo conduzido em neonatos internados em uma unidade de terapia intensiva neonatal com suspeita de sepse de início tardio que estavam em risco de infecções fúngicas invasivas no hospital universitário infantil de Almançora e no hospital geral de Almançora entre março de 2014 e fevereiro de 2016.
Resultados: 77 neonatos recém-nascidos com risco de infecção fúngica invasiva foram classificados, com base na hemocultura, em: Grupo sem fungemia, incluindo 41 neonatos com sepse bacteriana comprovada, Grupo com suspeita de fungemia, incluindo 25 neonatos com hemocultura negativa; e Grupo com fungemia definida, incluindo 11 neonatos com Candida comprovada por cultura. Os organismos em crescimento foram: {*Klebsiella* spp 14/54; *E. coli* 12/54; *Staphylococcus* spp 12/54 (*Staph* coagulase negativa 9/54; *Staph aureus* 3/54); *pseudomonous aerouginosa* 3/54 e *Proteus* spp 2/54}, além de 11/54 Candida. A concentração de (1,3)-β-D-glucano no soro foi significativamente inferior no Grupo sem fungemia em comparação ao Grupo com fungemia definida. O melhor valor de corte da (1,3)-β-D-glucano foi 99 pg/mL com sensibilidade, especificidade, valor preditivo positivo, valor preditivo negativo e precisão de 63,6%, 95,1%, 77,8%, 90,7% e 88,5%, respectivamente.
Conclusão: O ensaio de (1,3)-β-D-glucano possui sensibilidade limitada com especificidade e valor preditivo negativo excelentes que possibilitam seu uso e ajudam na exclusão de infecção fúngica invasiva neonatal. O diagnóstico preciso e as decisões oterapêuticas devem ter como base a combinação di ensaio de (1,3)-β-D-glucano com outros achados clínicos, radiológicos e microbiológicos.

Introduction

Neonatal sepsis (NS), together with pneumonia and meningitis, account for 1.4 million annual neonatal deaths worldwide.[1] Newborn infants are at high risk for infection due to underdevelopment of their immune barriers, including fragile skin and relative immune tolerance.[2] Fungal sepsis is a type of late onset sepsis (LOS) and should be considered in neonates with prolonged hospitalization and in those on prolonged antibiotic treatment.[3] The incidence of fungal sepsis ranges from 0.4 to 2 cases per 1000 live births, and from 3.8% to 12.9% among very low birth weight infants.[4] The most commonly reported risk factors for invasive fungal infection (IFIs) are prematurity, low birth weight, major congenital malformations, exposure to broad spectrum antibiotics, central venous catheters, delayed enteral feeds, prolonged parenteral nutrition, endotracheal intubation, surgery, postnatal steroids, and longer neonatal intensive care unit (NICU) stay.[5,6] IFI manifestations are non-specific, and blood culture is considered the gold standard for its diagnosis.[7] Unfortunately, preliminary results of blood cultures are usually obtained after 48 h or more. Moreover, diagnosis of IFI in neonatal infants is difficult, due to the high rate of false negative in cultures[8]; blood cultures are negative in approximately 50% of cases of autopsy-proven disseminated candidiasis.[9] Therefore, new tools are required for early diagnosis of IFIs in neonates. 1,3-β-D-Glucan (BG) is a component of the outer cell wall of fungi, including *Candida* spp., *Aspergillus* spp., and *Pneumocystis jiroveci*, and it is released into the blood stream during IFI.[10] To date, only three small trials were conducted in neonates; they concluded that BG is a useful adjunctive diagnostic method of IFI.[11–13]

The authors hypothesized that early assessment of serum BG in neonates with suspected fungal sepsis is a good substitute to fungal blood culture. Accordingly, this study aimed