Short Communication

Lack of 1-3-B-D-glucan detection in adults with bacteraemia

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Received 6 September 2014; Revised 11 July 2014; Accepted 4 September 2014

Abstract

Bacteraemia was reported to be associated with false-positive 1→3-β-D-glucan (BG) assay results. We thus prospectively assessed the reactivity of the BG (Fungitell) in samples of 21 adults with bacteraemia. BG was negative in all and is therefore an unlikely cause of false positive BG in adults.

Key words: Beta-glucan, cross reactivity, false positive, bacteraemia, blood culture.

Introduction

Invasive fungal infections (IFI), particularly invasive aspergillosis (IA) are associated with high mortality [1]. In order to improve the early diagnosis of IFI, antigenic test such as the 1→3-β-D-glucan (BG) assay have become widely available. The BG assay detects the presence of 1→3-β-D-glucan, a component of the cell wall of most fungi [2] except Cryptococcus spp. and members of the mucorales [3]. Fungitell (Associates of Cape Cod, East Falmouth, MA, USA), is the only BG assay approved by the FDA. The BG is included in the 2008 EORTC/MSG [4] revised criteria for the diagnosis of IFI. The test uses the horseshoe crab’s LAL (Limulus Amebocyte Lysate) ability to react with the 1→3-β-D-glucan [5] to trigger a coagulation cascade that is measured by a colorimetric assay [6].

While the sensitivity of the BG assay is acceptable (up to 78%) [7], its positive predictive value is low (19–37%) [8]. Multiple causes of false positive results have been identified such as haemodialysis using nitrocellulose membranes [9], gauze-covered wounds [10], transfusion of blood products [11] and antibiotics [12,13]. Colonisation of mucous membranes with yeasts has also been associated with false positives in some studies, although results are conflicting [14–18]. In addition, haemolysis, hypertriglyceridemia or hyperbilirubinemia [19] can interfere with the interpretation of the test. In previous publications, high rates of false
positive BG results have been reported in some specific populations, such as those in ICU and haematology patients. [20,8]

The cell wall of some bacteria, such as Pseudomonas aeruginosa [21–23] contains BG. A few studies evaluated the rate of false-positive BG assay in adult patients with bacteraemia but showed conflicting results [19,21,24,25]. One of the major limitations of those studies is the inclusion of patients with other conditions known to cause false positive results. Furthermore, most investigations only included haematology patients [19,21,24,25,26] who might have unrecognized fungal infection and only one study [20] was prospective.

The goal of this prospective study is thus to assess systematically the reactivity of the BG assay in adults with bacteraemia while excluding patients with any other known cause of false positive BG.

Materials and method

This study was conducted at Hôpital Necker Enfants-Malades, Paris, France from September 2011 to June 2012. To be eligible for enrolment, patients had to be ≥ 18 years old, admitted on medical wards and diagnosed with bacteraemia according to the CDC definition [26]. A single sample for BG was collected as soon as the positivity of the blood cultures was known.

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Patients with any of the following conditions or treatments were excluded from the study: haemodialysis or haemofiltration, recent administration of immunoglobulins or surgery/extensive skin lesions covered with gauze within the last month, as well as patients with severe mucositis, uncontrolled graft-vs-host disease and patients with probable or proven IFI according to the EORTC revised criteria 2008 [4].

The history collected from each patient included: age, associated medical condition(s), bacterial species recovered from blood cultures and the presence of criteria for IFI. Antibiotics currently administered or those received in the last month were also recorded, as were other potential causes for false positive results that were not exclusion criteria (platelets or albumin administered < 1 month).

Informed consent was obtained for all patients and the study received approval from the ethics committee CPP Ile-de-France 2 on August 30th 2011.

Results

Twenty-one patients were prospectively included in this study, among whom 7 patients had Gram-positive bacteraemia (Table 1) involving 2 staphylococci, 3 streptococci,

<table>
<thead>
<tr>
<th>Patient N°</th>
<th>Age (year)</th>
<th>Current medical condition(s)</th>
<th>Bacteria(s) in blood cultures</th>
<th>Antibacterial therapy</th>
<th>Time between BC and BG sampling (day)</th>
<th>BG (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>24</td>
<td>ALL/autoSCT</td>
<td>Escherichia coli bacteraemia 10 days prior/Platelets</td>
<td>Corynebacterium jeikeium</td>
<td>PIP-TZ, AMK, TMP-SMX, VA</td>
<td>1</td>
</tr>
<tr>
<td>A2</td>
<td>66</td>
<td>Amyloidosis</td>
<td>Streptococcus oligofermentans Staphylococcus aureus</td>
<td></td>
<td>PIP-TZ, TMP-SMX</td>
<td>4</td>
</tr>
<tr>
<td>A3</td>
<td>55</td>
<td>Waldenstrom macroglobulinemia, AlloSCT</td>
<td></td>
<td>Streptococcus capitis</td>
<td>CLOX</td>
<td>3</td>
</tr>
<tr>
<td>A4</td>
<td>43</td>
<td>RT/NHL/MA</td>
<td></td>
<td>Staphylococcus capitis</td>
<td>VA</td>
<td>2</td>
</tr>
<tr>
<td>A5</td>
<td>61</td>
<td>Lymphoma</td>
<td></td>
<td>Streptococcus spp.</td>
<td>VA, CFTX, AMK</td>
<td>2</td>
</tr>
<tr>
<td>A6</td>
<td>28</td>
<td>Endometritis</td>
<td></td>
<td>Group B Streptococcus Enterococcus faecium</td>
<td>AMOX-CLAV</td>
<td>2</td>
</tr>
<tr>
<td>A7</td>
<td>57</td>
<td>MDS</td>
<td>Platelets</td>
<td></td>
<td>PIP-TZ</td>
<td>1</td>
</tr>
<tr>
<td>A8</td>
<td>44</td>
<td>HIV/RT</td>
<td></td>
<td>Veillonella parvula + Pseudomonas aeruginosa Acinetobacter ursingii</td>
<td>CFTX, PHOS</td>
<td>4</td>
</tr>
<tr>
<td>A9</td>
<td>28</td>
<td>Meningoencephalitis</td>
<td></td>
<td></td>
<td>TIM, CPM</td>
<td>AMOX</td>
</tr>
</tbody>
</table>
Table 1. (continued.)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (year)</th>
<th>Current medical condition(s)</th>
<th>Bacteria(s) in blood cultures</th>
<th>Antibacterial therapy</th>
<th>Time between BC and BG sampling (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A10</td>
<td>35</td>
<td>Chorioamnionitis</td>
<td>Escherichia coli</td>
<td>AMOX-CLAV</td>
<td>&lt; 1 mo before BG sampling</td>
</tr>
<tr>
<td>A11</td>
<td>33</td>
<td>AML</td>
<td>Pseudomonas aeruginosa</td>
<td>PIP-TZ, AMK, AMK</td>
<td>3</td>
</tr>
<tr>
<td>A12</td>
<td>21</td>
<td>MA</td>
<td>Escherichia coli</td>
<td>PIP-TZ, CFTX, VA, AMI, AMK</td>
<td>4</td>
</tr>
<tr>
<td>A13</td>
<td>20</td>
<td>GI epithelium dysplasia</td>
<td>Klebsiella pneumoniae</td>
<td>PIP-TZ, VA, PIP-TZ, VA, AMK</td>
<td>3</td>
</tr>
<tr>
<td>A14</td>
<td>41</td>
<td>AML</td>
<td>Pseudomonas aeruginosa</td>
<td>PIP-TZ, VA, AMK</td>
<td>2</td>
</tr>
<tr>
<td>A15</td>
<td>64</td>
<td>RT</td>
<td>Klebsiella oxytoca</td>
<td>PIP-TZ</td>
<td>2</td>
</tr>
<tr>
<td>A16</td>
<td>77</td>
<td>Diabetes chronic prostatitis</td>
<td>Enterobacter spp.</td>
<td>MPM</td>
<td></td>
</tr>
<tr>
<td>A17</td>
<td>71</td>
<td>Polycystic kidney disease</td>
<td>Hafnia alvei</td>
<td>AMK</td>
<td></td>
</tr>
<tr>
<td>A18</td>
<td>69</td>
<td>HIV/MM</td>
<td>Salmonella spp</td>
<td>AMOX-CLAV</td>
<td></td>
</tr>
<tr>
<td>A19</td>
<td>35</td>
<td>None</td>
<td>Salmonella typhi</td>
<td>PIP-TZ, AMK</td>
<td></td>
</tr>
<tr>
<td>A20</td>
<td>26</td>
<td>None</td>
<td>Salmonella paratyphi</td>
<td>CFTX</td>
<td></td>
</tr>
<tr>
<td>A21</td>
<td>21</td>
<td>Aplasia</td>
<td>C.difficile colitis</td>
<td>VA, IMI, AMK</td>
<td></td>
</tr>
</tbody>
</table>

ALL, Acute Lymphoid Leukemia; NHL, AML, acute myeloid leukemia; Non-Hodgkin’s Lymphoma; MM, Multiple Myeloma; AutoSCT, autologous stem cell transplant; AlloSCT, allogeneic stem cell transplant; VA, vancomycin; CEFT, ceftazidime; GTM, gentamicin; AMK, amikacin; IMI, imipenem; AMOX-CLAV, amoxicillin-clavulanate; AMP, ampicillin; CFTX, cefotaxime; MPM, meropenem; PIP-TZ, piperacillin-tazobactam; TMP-SMX, trimethoprim-sulfamethoxazole; BG, 1–3 β-D-glucan

1 Enterococcus and 1 Corynebacterium jeikeium. Eleven patients had Gram-negative bacteraemia and three had polymicrobial bacteraemia. All patients (n = 21) had negative BG results.

Discussion

This is the first systematic study that examines prospectively the reactivity of BG in consecutively recruited adults with various underlying conditions (haematological and non-haematological) while excluding patients with any known major cause of false positive results.

It is possible that the sampling for the BG assay being done, on average, 2.8 days after the blood cultures were drawn prevented the detection of some initially low positive BG results. The data from our studies differ from the retrospective investigation of Albert et al. [21] in which 3/17 samples were positive for BG in patients with Gram positive bacteraemia and in 13/22 patients who had Gram negative bacteraemia. However, 2/3 patients from the former group and 11/13 patients from the latter also had other conditions (surgery, haemodialysis, hypertriglyceridemic sample, ICU stay) which are associated with false positive or difficult to interpret results [19,20].

Our results are in accordance with the most recent studies by Racil et al. [18] and Metan et al. [25] who showed that bacteremia was not associated with a higher rate of false positive BG in patients with haematological malignancies.

Many antibiotics [12] have been associated with false positive BG results in vitro but only two, cefepime [13] and intravenous amoxicillin-clavulanate [27], have been reported in vivo. In our study, only two patients received IV amoxicillin-clavulanate at the time of enrolment and both had a negative BG test.

In conclusion, our prospective systematic study evidences that bacteremia per se is not associated with elevated BG in adults.

Declaration of Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the article.

References


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