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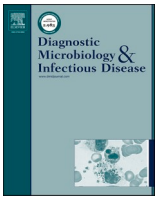

(1-3)-ß-D-glucan for the diagnosis of *Nocardia* infection in solid organ transplant recipients☆

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Dear Editors,

Bacteria belonging to the genus *Nocardia* spp. can cause severe opportunistic infections called nocardiosis [1,2]. The microbiological diagnosis of nocardiosis is difficult [3] and recent studies have suggested that (1-3)-ß-D-glucan (BDG) may be useful to diagnose *Nocardia* infection [4–6]. Our objective was to evaluate the diagnostic performance of BDG in solid organ transplant (SOT) recipients with nocardiosis and control SOT recipients without nocardiosis.

We took advantage of a previously published retrospective European case-control study including 117 SOT recipients with nocardiosis and 234 matched control SOT recipients [1]. To evaluate the performance of the BDG assay, we retrieved serum samples collected around the time of diagnosis of *Nocardia* infection (± 6 months), or around a corresponding time point for control SOT recipients. Serum samples (stored at -80°C [7]) were shipped in dry ice to the Parasitology-Mycology Department of the Necker Hospital (Paris, France). BDG levels were measured using the Fungitell ® assay (Associates of Cape Cod, Inc., Falmouth, MA, USA). BDG positivity was defined at the manufacturer cutoff of 80 pg/mL.

Most cases and controls were kidney transplant recipients (80%) (**Supplementary Table 1**). We focused on 39 serum samples collected around the date of nocardiosis (for 15 SOT recipients who developed nocardiosis) or around a corresponding time post-transplant (for 24 control SOT recipients without nocardiosis). A known cause of BDG cross-reactivity was present in the month prior to serum sampling in 11% of these patients (4/37, including three hemodialysis and one invasive fungal disease) [8–10]. Serum BDG was positive in 93% of SOT recipients with nocardiosis (14/15), as compared to 83% of control SOT recipients who did not develop nocardiosis (20/24, p=0.6). When focusing on patients without any known cause of BDG cross reactivity (12 cases and 21 controls), median BDG concentrations were not statistically different between SOT recipients with and without nocardiosis (179 [77-403] versus 178 [70-523] pg/mL, respectively, p=0.9, Fig. 1**A and 1B**). We obtained similar results when focusing on the 13/39 serum samples which were obtained close to the date of nocardiosis (*i.e.*, ± 40 days) (Fig. 1**C**).

In this study, we observed that BDG was frequently positive in SOT recipients with nocardiosis, but that BDG positivity was similarly common among control SOT recipients without nocardiosis. We also observed frequent serum BDG positivity in control SOT recipients who did not have nocardiosis, as well as in SOT recipients who were at time of transplantation, but not in control blood donors. A known cause of BDG assay reactivity was noted in only a limited proportion of these patients, suggesting the potential presence of unidentified sources of BDG reactivity in these patients.

Our study has several limitations. Firstly, we allowed the inclusion of serum samples that were relatively distant to the date of nocardiosis (± 6 months). Last, serum BDG testing was retrospective; serum samples from blood donors were however used as negative controls to verify that there was no contamination of the samples (**Supplementary Data**).

In conclusion, our retrospective study suggests that BDG should not be used for the diagnosis of nocardiosis among SOT recipients, mostly due to a low clinical specificity.

Author contributions statement

- MP, JC, MEB and DL participated in research design.
- All authors participated in the writing of the paper.
- All authors participated in the performance of the research.
- MP, JC, MEB and DL participated in data analysis.

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Ethics statement

In France, the study was approved by the CPP Ile-de-France I Ethical board (March 7, 2014). In other countries, the participating centers obtained approval from their respective Ethics Committees before joining the study.

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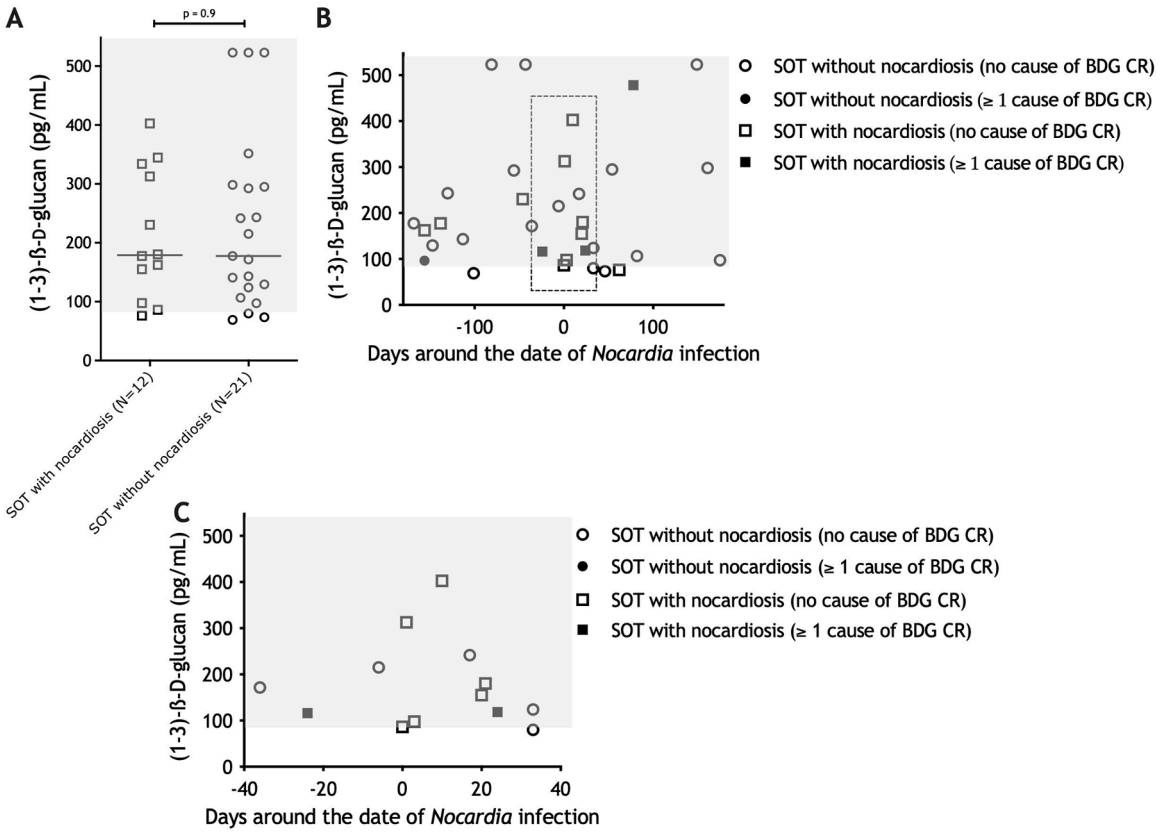

Fig. 1. (1-3) -ß-D-glucan (BDG) values (pg/mL) around the date of the diagnosis of nocardiosis (-180 to +180 days) among a cohort of solid organ transplant recipients with or without nocardiosis. A. BDG values in SOT recipients with and without nocardiosis but without any cause of BDG cross reactivity. B and C. BDG values in SOT recipients (with or without nocardiosis) with or without any cause for BDG cross reactivity around the date of the diagnosis of *Nocardia* infection within 2 times periods: [-180 to +180 days] (panel B) and [-40 to +40 days] (panel C). Comparisons between groups were performed using Mann-Whitney-Wilcoxon test in Prism® (Graphpad). NOTE: BDG: (1-3)-ß-D-glucan; CR: cross reactivity. Grey zone denotes a positive BDG result (≥ 80pg/mL), white zone a negative result (<80pg/mL).

CRediT authorship contribution statement

Margot Paumier: Writing – original draft, Investigation, Formal analysis, Conceptualization. **Julien Coussement:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Marie Matignon:** Writing – review & editing, Writing – original draft, Investigation. **Cécile Chauvet:** Writing – review & editing, Writing – original draft, Investigation. **Nicolas Bouvier:** Writing – review & editing, Writing – original draft, Investigation. **Arthur Poncelet:** Writing – review & editing, Writing – original draft, Investigation. **Jacques Dantal:** Writing – review & editing, Writing – original draft, Investigation. **Anne Scemla:** Writing – review & editing, Writing – original draft, Investigation. **Helga Ceunen:** Writing – review & editing, Writing – original draft, Investigation. **Eric Van Wijngaerden:** Writing – review & editing, Writing – original draft, Investigation. **Nassim Kamar:** Writing – review & editing, Writing – original draft, Investigation. **Martha T. van der Beek:** Writing – review & editing, Writing – original draft, Investigation. **Herman F. Wunderink:** Writing – review & editing, Writing – original draft, Investigation. **Julien De Greef:** Writing – review & editing, Writing – original draft, Investigation. **Sophie Candon:** Writing – review & editing, Writing – original draft, Investigation. **Marie-Elisabeth Bougnoux:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **David Lebeaux:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no conflicts of interest.

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None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diagmicrobio.2024.116184.

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