Serum Galactomannan Index for the Rapid Diagnosis of Fungal Peritonitis in Patients With Peritoneal Dialysis

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Fungal peritonitis, a relatively uncommon but serious complication of peritoneal dialysis (PD), is associated with high rates of technique failure (40%) and mortality (15%–50%).\textsuperscript{1,2} Therefore, immediate PD catheter removal followed by antifungal agent administration for a minimum period of 2 weeks is strongly recommended by the International Society for Peritoneal Dialysis 2016 peritonitis guideline.\textsuperscript{3} Despite treatment according to this guideline, only one-third of patients with fungal peritonitis are able to resume PD.\textsuperscript{4} The poor treatment outcomes of fungal peritonitis are hampered by the lack of a sensitive biomarker that can facilitate timely diagnosis and treatment. Serum levels of the fungal cell wall component galactomannan (GM), which is shed by fungi during their growth and death,\textsuperscript{5} may help address this gap in clinical care. This biomarker has been used to aid in the diagnosis of systemic and invasive fungal infections, as well as in monitoring the treatment response and relapse of fungal infections, particularly of the respiratory system.\textsuperscript{5} A serum GM index (GMI) of ≥0.5 has previously been used to diagnose suspected fungal pulmonary infections.\textsuperscript{6,7} As a proof of concept, the potential value of serum and PD effluent GMI in diagnosing and risk-stratifying patients with fungal peritonitis on PD was assessed in the present study.

RESULTS

Patient Demographics and Characteristics

Participant flow is shown in Figure 1. There were no significant differences among patients with fungal peritonitis (n = 23), bacterial peritonitis (n = 21), and no peritonitis (n = 19) with respect to age, sex, PD vintage, residual kidney function, and comorbidities (Table 1, Supplementary Table S1). As expected, controls without peritonitis had no peritonitis symptoms, higher serum albumin concentrations, and lower PD effluent cell counts than did the other groups. The most common fungal pathogen was Candida spp. followed by Trichosporon spp., Aspergillus spp., and Fusarium spp. (Table 2).
Serum GMI Values

Serum GMI in patients with fungal peritonitis was significantly higher than that in patients with bacterial peritonitis and controls without peritonitis (median, 0.85 [interquartile range, 0.43–1.75] vs 0.45 [interquartile range, 0.35–0.79] vs. 0.43 [interquartile range, 0.34–0.47], respectively; \( P = 0.036 \)) (Figure 2a). To differentiate fungal peritonitis from non–fungal peritonitis (including bacterial peritonitis and non-peritonitis), a serum GMI cutoff value of \( \geq 0.56 \) (Supplementary Table S2) provided the best diagnostic accuracy with 65.2% sensitivity, 85.0% specificity, 4.35 positive likelihood ratio, and 0.41 negative likelihood ratio. At this cutoff point, the calculated area under the curve from receiver operating characteristic curve analysis for serum GMI was 0.73 (95% confidence interval, 0.58–0.87) (Table 3 and Figure 2b).

Six patients with bacterial peritonitis (patients 2, 7, 13, 16, 19, and 20) had a positive GMI result. On the basis of polymerase chain reaction–based diagnosis of fungal peritonitis, the GMI was positive in patients 10, 12, 15, and 17.

Table 1. Clinical characteristics of patients on PD in this study

| Characteristic            | Fungal peritonitis (n = 23) | Bacterial peritonitis (n = 21) | Nonperitonitis (n = 19) |
|---------------------------|----------------------------|--------------------------------|-------------------------|
| Male sex                  | 10 (43)                    | 10 (48)                        | 11 (58)                 |
| Age (yr)                  | 51.3 ± 13.3                | 55.4 ± 16.0                    | 68.1 ± 7.1              |
| Diabetes mellitus         | 12 (52)                    | 9 (43)                         | 10 (53)                 |
| Hypertension              | 18 (78)                    | 17 (81)                        | 14 (74)                 |
| Serum hemoglobin level (g/dl) | 10.2 ± 3.2               | 10.7 ± 2.7                     | 11.9 ± 1.3              |
| Serum albumin level (g/dl) | 2.7 ± 0.9                  | 2.8 ± 0.5                      | 3.4 ± 0.4               |
| Serum potassium level (mEq/l) | 3.4 ± 0.9                 | 3.1 ± 0.9                      | 3.5 ± 0.7               |
| Urine volume (ml)         | 458.3 ± 264.4              | 283.3 ± 132.9                  | 615.5 ± 418.4           |

Table 2. Organisms cultured in cases of bacterial and fungal peritonitis in this study

| Identified bacteria (21)      | Identified fungi (23)       |
|------------------------------|-----------------------------|
| Pseudomonas aeruginosa (6)   | Candida spp. (6)\(^a\)      |
| Escherichia coli (5)         | Trichosporon spp. (3)\(^a\) |
| CoNS (3)                     | Aspergillus spp. (3)        |
| Streptococcus mitis (2)      | Fusarium spp. (2)           |
| Staphylococcus aureus (1)    | Unidentified mold (2)       |
| Enterobacter aerobacteriae (1)| Exophiala spp. (1)\(^a\)    |
| Proteus mirabilis (1)        | Aeromunium spp. (1)         |
| Stenotrophomonas maltophilia (1)| Alternaria spp. (1)       |
| Bacillus spp. (1)\(^b\)      | Paecilomyces spp. (1)       |
| Penicillium spp. (1)         | Stachybotrys spp. (1)       |

CoNS, coagulase-negative Staphylococcus.
\(^a\)Yeast-form fungi (others are mold-form).
\(^b\)Gram-positive bacteria (others are gram negative).
Number of cases is given in parentheses.
fungal infections, 2 patients (patients 16 and 19) had a positive polymerase chain reaction result, indicating a true-positive GMI result. In other words, an occult infection with fungus likely explained the positive GMI result in these 2 cases of bacterial peritonitis. The results of the polymerase chain reaction of the remaining cases were negative, although 2 cases (patients 2 and 13) had positive serum dipstick test results for heme, suggesting a possible explanation for a false-positive GMI result. Of note, there were 2 cases (patients 7 and 20) in which the isolated organism, *Pseudomonas aeruginosa* (1 case) and *Escherichia coli* (1 case), was known to cause a false-positive GMI result.

In contrast, 8 patients with fungal peritonitis had a negative serum GMI, including patient 25 (*Candida parapsilosis*), patient 29 (*Exserohilum rostratum*), patient 30 (*Fusarium solani*), patient 31 (*Candida guilliermondii*), patient 33 (*Trichosporon spp.*), patient 38 (*Aspergillus flavus*), patient 42 (*Alternaria spp.*), and patient 43 (*Exophiala spp.*). Possible reasons for these false-negative serum GMI results were the presence of a serum inhibitor or a lack of peripheral blood translocation in either the fungal whole cell or the cell wall. Of note, the follow-up serum titer of patient 29 increased to a level above the cutoff value at 1.88 during amphotericin B treatment.

### DISCUSSION

Our case-cohort study demonstrated that serum GMI may be useful for the timely diagnosis of fungal peritonitis. Because GMI measurement is less time-consuming than the conventional culture method (6 hours vs. 3–6 days), the more rapid diagnosis of fungal peritonitis by GMI offers a potential clinical advantage to patients on PD. The International Society for Peritoneal Dialysis 2016 peritonitis guideline recommended that an immediate catheter removal should be considered when fungi are identified in PD effluent. Earlier catheter removal is associated with improved outcomes, including mortality.³

Optimal serum GMI cutoff values ≥0.5 have been used for the diagnosis of invasive fungal infections.⁸,⁹,¹¹ However, in the present study, a slight increase in the cutoff to ≥0.56 provided the most optimal diagnostic accuracy for fungal peritonitis. This finding implies that there is a translocation of GM from the peritoneal fluid into the circulation in patients with fungal peritonitis. We demonstrated that serum GMI could be used for the diagnosis of fungal peritonitis with >65% sensitivity and 83% specificity. After excluding false positive from hemolytic serum (2 cases) and true positive from occult
fungal infection (2 cases), there were 2 cases (10%) with bacterial peritonitis and false-positive serum GMI above the 0.56 cutoff. These cases involved specific bacterial pathogens known to produce false-positive GMI results, namely, *Pseudomonas aeruginosa* (1 case) and *Escherichia coli* (1 case). The false positivity in these cases possibly occurred because of (i) the high concentration of these organisms in the blood, causing a cross-reactivity in the Platelia Aspergillus enzyme immunoassay (Bio-Rad, Marnes-la-Coquette, France), and (ii) transient fungal antigenemia from cow’s milk products or fungal overgrowth in the compromised gut during the episode of severe gram-negative peritonitis and prolonged antibiotic treatment. Dietary factors must therefore be taken into account when interpreting the cause of false-positive results in young children and patients with an impaired intestinal barrier.

In contrast, the false-negative GMI in 4 patients with *Candida parapsilosis*, *Candida guilliermondii*, *Trichosporon* spp., and *Alternaria* spp. might be related to fungal burden or the cell wall GM compositions of these fungi, leading to decreased sensitivity. GM detection is not possible in patients with *Pneumocystis jiroveci*, *Candida* spp. (some strains), and *Acremonium* spp. because of the absence of GM content in the cell walls of these fungi. Meanwhile, the false-negative GMI occurred only in the serum of 4 patients who were infected with *Aspergillus flavus*, *Exophiala* spp., *Exserohilum rostratum*, and *Fusarium solani*. It is possible that fungal pathogens in all these cases did not invade into the bloodstream.

This study has some limitations. First, the number of patients in our proof-of-concept study was relatively small, such that a much larger study would be required to confidently establish the utility of serum GMI as a diagnostic biomarker for fungal peritonitis. Second, the results of this study may not generalize to populations on PD outside Thailand in whom the incidence of fungal peritonitis is appreciably lower.

In conclusion, serum GMI is a promising biomarker for the diagnosis of fungal peritonitis in patients on PD, particularly in conjunction with other parameters such as potassium hydroxide stain, culture, and polymerase chain reaction.

**APPENDIX**

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**DISCLOSURE**

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)
Supplementary References.
Supplementary Methods.
Table S1. Patient characteristics, previous peritonitis, laboratories, and outcome.
Table S2. Accuracy of serum galactomannan index for differentiating fungal peritonitis at different cutoff points.

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Genetic Kidney Disease in Southern Tasmania

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Evidence suggests that 1.7 million persons (10% of the Australian adult population) are living with chronic kidney disease (CKD).1 Within the Australian CKD population, around 10% of individuals are found to have a genetic cause for their kidney disease.2 As genomic sequencing technology becomes more mainstreamed, the identification of genetic kidney disease (GKD) is expected to increase. The CKD population experiences an excess of...