alter after correction for difference in the baseline eGFR. Mean increases in serum creatinine were 13.3 nmol/mL for gentamicin and 0.1 nmol/mL for tobramycin (P=0.02). The relative decrease in eGFR between the groups showed a trend of a higher loss of eGFR for patients given gentamicin (4.8% versus 1%, P=0.07).

This large retrospective study shows that ODD gentamicin is more nephrotoxic than ODD tobramycin in infected patients treated with an aminoglycoside for ≥3 days. To our knowledge, this is the first study directly comparing the nephrotoxic potential of these two most frequently used aminoglycosides. Despite the retrospective design with consecutive cohorts, the risks of both selection and time bias appear low since, per criterion, similar numbers of patients were excluded and there were no significant differences between characteristics of both included and eligible patients (data not shown for the latter). The validity of our outcomes is strengthened by the large cohort investigated and the hospital-wide switch to tobramycin in all aminoglycoside indications. Nevertheless, future prospective randomized studies remain warranted to confirm these results. In conclusion, our data suggest that in the once-daily dosing era, a further reduction of the incidence of nephrotoxicity may be obtained by preferring tobramycin over gentamicin as first-line aminoglycoside in infected patients.

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Transparency declarations
None to declare.

References

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Sepedonum intra-abdominal infection: a case report and review of an emerging fungal infection
Norihiro Yogo1*, Leland Shapiro1,2 and Kristine M. Erlandson1

1 Division of Infectious Diseases, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; 2Division of Infectious Diseases, Department of Medicine, Denver Veterans Affairs Medical Center, Denver, CO, USA

*Corresponding author. Tel: +1-303-724-4941; Fax: +1-303-724-4926; E-mail: norihiro.yogo@ucdenver.edu

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Sir, Sepedonum is an environmental fungus that is not considered to be a cause of human disease. We present, along with a review of the literature, a unique case of a man with localized, recalcitrant, intra-abdominal Sepedonum infection.

A man in his 60s with congestive heart failure, poorly controlled diabetes mellitus type I and end-stage renal disease on peritoneal dialysis presented to our institution with abdominal pain and a cloudy peritoneal dialysate. Peritoneal dialysate analysis revealed 4000 white blood cells/μL with 80% neutrophils and a negative Gram stain. A CT scan of the abdomen and pelvis showed a 6.6 × 6.8 cm fluid collection near the tip of the peritoneal dialysis catheter. The catheter was removed on hospital Day 5, and on Day 7 a colony of mould grew from catheter tip and peritoneal fluid specimens.

Early growth on fungal medium (Sabouraud Dextrose Agar pH 5.6; Thermo Fischer Scientific, Lenexa, KS, USA) raised a suggestion of Scedosporium spp. and oral voriconazole was initiated. However, the patient developed delirium and visual hallucinations, prompting a change to 5 mg/kg liposomal amphotericin B intravenously daily on hospital Day 11. Upon maturation, the mould was woolly white with a light brown underside (Figure 1a). Microscopy revealed septated hyphae with spherical, thick-walled conidia consistent with Sepedonum (Figure 1b). A DNA probe for Histoplasma capsulatum was negative and Sepedonum was confirmed by a reference laboratory.

On hospital Day 13, the right lower quadrant fluid collection was drained percutaneously and a drainage catheter was placed, with cultures again yielding Sepedonum. The percutaneous catheter was removed after 1 week due to a low output. However, 3 days after catheter removal, the patient had recurrent abdominal pain and a repeat CT showed a reaccumulation of fluid measuring 5.7 × 4.2 cm. Repeat fluid drainage and fungal cultures revealed Sepedonum despite 2 weeks of liposomal amphotericin B treatment.

Since comorbidities precluded surgical debridement, five percutaneous drainage procedures were performed to remove fluid.
that reaccumulated within a thick-walled cavity after each attempt at catheter removal. After 5 weeks of amphotericin B, fluid cultures were sterile, although 15 weeks of therapy was required for clinical resolution.

*Sepedonium* is an environmental organism that is considered a contaminant in clinical microbiological specimens and not considered a cause of human disease. Morphologically, *Sepedonium* resembles *H. capsulatum* but *Sepedonium* is not dimorphic. Diagnosis is based on morphology and a negative DNA probe for *H. capsulatum*.

A literature review revealed only two previous cases of *Sepedonium* implicated in human disease. The first reported case, in 1934, described a middle-aged man with a progressive ulcerative dermatitis and lymphadenitis. Post mortem analysis revealed yeast-like organisms in the lung and caseating granulomas in the adrenal glands. In retrospect, this clinical presentation along with the presence of yeast within the phagocytes suggested a diagnosis of *H. capsulatum* as opposed to *Sepedonium*.

The second reported case, in 2003, was in a 43-year-old man with a new diagnosis of AIDS. He presented with a CD4 lymphocyte count of 31 cells/μL and erythematous papular skin lesions. Skin biopsy and blood cultures were positive for *Sepedonium*. The patient was treated with oral itraconazole and initiation of antiretroviral therapy, with resolution of his skin lesions.

The limited clinical literature and extremely rare occurrence of *Sepedonium* infections strongly suggest this is an opportunistic organism affecting persons with impaired immunity. Our patient had uncontrolled diabetes mellitus and end-stage renal disease requiring peritoneal dialysis. The peritoneal dialysis catheter was a likely portal of entry and enabled a persistent localized infection. Although the fungus was considered to be a true pathogen early in the clinical presentation, contamination of the specimen was also considered. However, the recovery of this organism from repeated fluid aspirations and the exchange of catheters between samples made contamination during specimen collection unlikely. Contamination at the laboratory level was also considered, but the absence of other reports of *Sepedonium* at our institution during this time made this unlikely.

There are no established antifungal susceptibility breakpoints for *Sepedonium*. Given microbiological similarities to *Histoplasma* and underlying congestive heart failure precluding the use of itraconazole, our patient was treated with liposomal amphotericin B. The duration of therapy was based on the patient’s clinical response and extrapolated from treatment guidelines for histoplasmosis.

In summary, we describe a case of persistent intra-abdominal infection due to *Sepedonium*, an environmental fungus not considered to cause human disease. Opportunities for environmental organisms to become emerging pathogens are enhanced by the increasing prevalence of immunosuppressing conditions such as AIDS and diabetes mellitus, and by the more widespread use of invasive and semi-invasive procedures (exemplified by the recent outbreak of *Exserohilum* related to contaminated steroid injections). Clinicians should be aware of the potential for infections caused by *Sepedonium* in susceptible hosts.

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This study was carried out as part of our routine work.

**Transparency declarations**

None to declare.

**References**

To our knowledge, no data on intra-abdominal fluconazole exposure in LTx patients have been published. Here we report on the intra-abdominal penetration and pharmacodynamic exposure in three LTx patients who had documented intra-abdominal candidiasis (cholangitis in Patients 1 and 2; peritonitis in Patient 3) treated with fluconazole. Informed consent for bile or ascites and blood sampling was obtained from the patients. Single bile samples (from a T-tube that was used for splinting the biliary anastomosis between the donor’s and the recipient’s bile ducts) or ascites samples (during diagnostic paracentesis) and simultaneous blood samples (from the antecubital vein) were collected at steady-state just before the daily fluconazole administration for assay of trough concentrations ($C_{\text{min}}$). Plasma, ascites and bile fluconazole concentrations were measured by means of a validated HPLC technique, with some modifications.

At the Institute of Clinical Pharmacology fluconazole dosages are routinely adjusted in real time by therapeutic drug monitoring (TDM) in LTx patients, with the intent of maintaining plasma $C_{\text{min}}$ at around 10–15 mg/L. This approach should ensure an AUC/MIC ratio of >100,5,6 against all fluconazole-susceptible strains of *Candida* (MIC ≤2 mg/L).7

Briefly, Patient 1 (60–70 years, 60–70 kg and serum creatinine 1.2 mg/dL) and Patient 2 (60–70 years, 60–70 kg and serum creatinine 1.18 mg/dL) had a diagnosis of *Candida* cholangitis at 14 days and 30 months post-transplant, respectively. *Candida albicans* strains susceptible to fluconazole (MIC 0.25 mg/L; Sensititre YeastOne colorimetric MIC procedure) were isolated from the biliary drainage of both patients. Intravenous fluconazole was started with a 400 mg loading dose, followed by TDM-guided maintenance dosages (200 mg daily reduced to 100 mg daily from day 10 for Patient 1; 200 mg daily for the whole treatment period for Patient 2). Fluconazole bile and plasma $C_{\text{min}}$ (Table 1) were 9.04 and 17.81 mg/L, respectively at therapy day 9 for Patient 1, and 6.29 and 12.61 mg/L at therapy day 5 for Patient 2.

Patient 3 (60–70 years, 60–70 kg and serum creatinine 1.7 mg/dL) developed *Candida* peritonitis at day 62 post-transplant, after a history of recurrent, refractory ascites. Cultures from ascites yielded *C. albicans* susceptible to fluconazole (MIC 0.25 mg/L; Sensititre YeastOne colorimetric MIC procedure). Intravenous fluconazole was started with a 400 mg loading dose followed by a maintenance dose of 150 mg daily, then reduced to 100 mg daily from day 8. *Candida* $C_{\text{min}}$ in ascites and plasma at therapy day 5 was 9.60 and 11.30 mg/L, respectively (Table 2). The fluconazole bile-to-plasma ratios of $C_{\text{min}}$ in the two LTx patients with cholangitis (0.50 and 0.51) were lower than previously observed in a non-LTx patient with *Candida* cholecystitis (around 1.2 at therapy day 5 by visual inspection).8 Conversely, the ascites-to-plasma ratio of $C_{\text{min}}$ in the LTx patient with peritonitis (0.85) was similar to that observed in a non-LTx cirrhotic patient with *Candida* peritonitis (0.81 at 3 h post-dose at therapy day 5).8

Interestingly, 14 days of fluconazole treatment with maintenance of plasma $C_{\text{min}}$ at around 15 mg/L resulted in clinical resolution of intra-abdominal candidiasis in all three LTx patients with no evidence of recurrence at 30 days of follow-up. It should be noticed that, thanks to TDM, in these particular patients successful treatment was based on doses of fluconazole much lower (100–200 mg/day) than those usually administered for systemic infections (400–800 mg/day).8 Previous studies showed that the AUC/MIC ratio is the pharmacodynamic parameter that best correlates with fluconazole efficacy,9,10 and the recent

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**Intra-abdominal penetration and pharmacodynamic exposure to fluconazole in three liver transplant patients with deep-seated candidiasis**

Federico Pea1,2*, Elda Righi3, Piergiorgio Cojiuti1,2, Alessia Carmelutti4, Umberto Baccarani5, Giorgio Soardo6 and Matteo Bassetti3

1Institute of Clinical Pharmacology, Azienda Ospedaliero-Universitaria Santa Maria della Misericordia, Udine, Italy; 2Department of Experimental and Clinical Medical Sciences, University of Udine, Udine, Italy; 3Clinic of Infectious Diseases, Azienda Ospedaliero-Universitaria Santa Maria della Misericordia, Udine, Italy; 4Clinic of Internal Medicine-Liver Unit, Department of Experimental and Clinical Medical Sciences, University of Udine, Udine, Italy; 5Department of Medical and Biological Sciences, University of Udine, Udine, Italy

*Corresponding author. Institute of Clinical Pharmacology, Azienda Ospedaliero-Universitaria Santa Maria della Misericordia, Udine, Italy. Tel: +39-0432-559833; E-mail: pea.federico@aoud.sanita.fvg.it

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Sir, Invasive candidiasis is a major cause of mortality and morbidity after liver transplantation (LTx).1 Immunosuppression may predispose transplant patients to infections, and in the specific context of LTx recipients the surgically reconstructed biliary tract may represent a primary site for infectious complications. It has been shown that the impairment of bile excretion, a frequent condition in LTx patients, may increase the likelihood of developing invasive fungal cholangitis.2 Additionally, invasive candidiasis may be commonly associated with peritonitis in these patients.1

Fluconazole is presently the drug of first choice for the treatment of intra-abdominal candidiasis in those patients who are not critically ill and who have no specific risk factors or previous azole exposure.3

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**References**

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