Different bile concentration of micafungin and itraconazole in a patient with candidal cholecystitis

Candidal cholecystitis is a rare infection that occurs in patients with disseminated candidal infections during post operative recovery or in the immunocompromised host.[1–6] Micafungin or itraconazole are effective for the treatment of superficial and disseminated candidasis,[2] however, their efficacy in candidal cholecystitis is unknown. The therapeutic efficacy of micafungin and itraconazole in treatment of candidal cholecystitis may depend on their biliary excretion rate but so far there are no reports.

Here, we report a case of candidal cholecystitis in a 90-year old man who was receiving systemic chemotherapy and radiation therapy for esophageal cancer. The infectious complications were treated with percutaneous drainage and systemic antifungal therapy. The patient had high fever and upper abdominal pain. Physical and laboratory examination showed findings consistent with the diagnosis of cholecystitis. Culture of two blood samples from the patient were positive for *Candida albicans* without other pathogens. Eye examination presented characteristic findings of candidal retinopathy. Abdominal CT showed gallbladder swelling with irregular hypertrophy of the walls and gallstones. He underwent percutaneous transhepatic gallbladder drainage. Culture of bile samples obtained from the patients were positive for *C. albicans* without other pathogens. A diagnosis of disseminated candidasis with candidal cholecystitis was made. He had been managed with percutaneous transhepatic gallbladder drainage and combination therapy with intravenous micafungin (150 mg every 24 h) and itraconazole (100 mg every 12 h). His condition gradually improved. However the clinical course of the patient deteriorated during monotherapy with oral itraconazole without intravenous micafungin. The clinical condition of the patient improved when both drugs were administered for 58 days. He was discharged on the 60th hospital day and the subsequent clinical course of the patient was stable. No adverse events were caused by the combination therapy. *C. albicans* isolated from the bile samples of the patient was susceptible to micafungin (minimal inhibitory concentrations (MIC): 0.06 μg/ml) and itraconazole (MIC: 0.06 μg/ml). Biliary excretion of micafungin and itraconazole was measured by determining the concentration of micafungin (BLM Corp, Tokyo, Japan) and itraconazole (SLR Corp, Tokyo, Japan) in both serum and bile samples using high performance liquid chromatography. The minimal concentrations of the antifungal agents in serum and bile samples were measured 24 h after infusion of 150 mg of micafungin and 12 h after ingestion of 100 mg of oral itraconazole. The minimal concentration of the antifungal agents in serum was: micafungin: 1.537 μg/ml, itraconazole: 0.1216 μg/ml and hydroxyitraconazole: 0.2485 μg/ml while in bile it was: micafungin: 1.925 μg/ml, itraconazole: $<$0.01 μg/ml and hydroxyitraconazole: $<$0.01 μg/ml. To our knowledge this is the first report of the biliary concentration of micafungin and itraconazole in a patient with systemic candidiasis with cholecystitis.

The use of micafungin and itraconazole in the clinic depends on several factors, such as whether there is chronic renal insufficiency which is a contraindication for the use of amphotericin B. The clinical course of our patient improved with administration of micafungin, whereas oral itraconazole therapy alone was ineffective. In a patient with a liver transplant, candidal cholangitis was successfully treated with caspofungin as the peak level of caspofungin in serum and bile was greater than the in vitro MIC of caspofungin for *C. albicans*.[4] Ketoconazole, however, was ineffective in candidal cholecystitis, probably because the drug was not significantly excreted in bile.[5]

In our patient, the minimum concentrations of both micafungin and itraconazole in serum were greater than the MIC of *C. albicans* isolated from the bile. However, micafungin was significantly excreted in bile and its concentration was greater than the MIC but itraconazole was not significantly secreted into the bile and did not reach the MIC. Similarly in a previous study in rats; the biliary excretion of micafungin was about 10% of the micafungin dose after intravenous administration, whereas biliary excretion of itraconazole and hydroxyitraconazole were less than 0.5% of the itraconazole dose after intravenous administration.[7,8] This difference in biliary excretion rate shown in the present report supports the idea that micafungin is useful for treating candidal biliary infection and that itraconazole is not. It appears that the pharmacokinetics of other echinocandins (e.g. caspofungin) is similar to that of micafungin.[5,9] However, the pharmacokinetics of itraconazole is different from other triazoles.[2] The excretory mechanism is not clear but a previous study in rats suggested that multidrug resistance-associated protein-2 is involved in the hepatobiliary excretion of micafungin.[7]

Conflict of interest

None of the authors declare a conflict of interest.

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Misidentification of ampicillin–sulbactam heteroresistance in *Acinetobacter baumannii* strains from ICU patients

Dear Editor,

Acinetobacter baumannii is a ubiquitous organism, that commonly behaves as an opportunistic pathogen causing nosocomial outbreaks among burn or intensive care units' (ICUs) patients. Ventilator-associated pneumonias (VAPs), catheter-related, urinary tract infections, bone, soft tissue and abdominal infections, bacteremias and meningitis caused by this organism have been described in the literature. Nosocomial spread of this pathogen is due to its ability to both survive on wet surfaces and to tolerate desication; also, its tendency to easily acquire resistance determinants against antimicrobials is of worrisome concern. Treatment of *A. baumannii* is frequently limited to ampicillin–sulbactam, carbapenems, aminoglycosides, tigecycline and colistin, due to the common expression of Class A extended-spectrum betalactamases or ESBLs (conferring resistance to all betalactams except for cephamycins, betalactamase inhibitors, and carbapenems), class B metallo-carbapenemases (which hydrolyze all betalactams, with the exception of aztreonam), chromosomally encoded constitutive or inducible class C betalactamases (responsible for resistance to cephalosporins and betalactamase inhibitors), and class D chromosome- or plasmid-mediated OXA-type penicillinases (making producing strains resistant to all betalactams). In addition, efflux pumps, loss of outer membrane porins (OMPs) and reduced expression of penicillin-binding proteins (PBP)-2 may cause multidrug resistance (MDR). Tigecycline-resistance by organisms of this species has also been reported by several authors and has been supposed to be due to an efflux pump, mostly expressed by MDR strains. Resistance to this new glycilglycine by *A. baumannii* has been also found to occur during drug administration, whereas strains initially appeared as fully susceptible. Colistin should finally represent the last line of defense, but resistant strains have recently appeared.[1–5]

Twenty MDR *A. baumannii* strains were isolated from ICU patients' bronchoalveolar lavages over a 2-year period (January 2007–December 2008). These were initially identified and screened for antimicrobial susceptibilities by the Vitek2 (bioMérieux, France). Identifications were then confirmed by rRNA sequencing. Also, they appeared to be genotypically unrelated. All of the strains showed resistance to ampicillin (MIC $\geq$32 mg/L), amoxicillin/clavulanate (MIC $\geq$32 mg/L), piperacillin/tazobactam (MIC $\geq$256 mg/L), cefoxitin (MIC $\geq$32 mg/L), ceftazidime (MIC $\geq$32 mg/L), cefotaxime (MIC $\geq$64 mg/L), cefepime (MIC $\geq$32 mg/L), aztreonam (MIC $\geq$64 mg/L), imipenem (MIC $\geq$16 mg/L), meropenem (MIC $\geq$16 mg/L), ciprofloxacin (MIC $\geq$4 mg/L), tetracycline (MIC $\geq$16 mg/L), gentamicin (MIC $\geq$16 mg/L), tobramycin (MIC $\geq$16 mg/L), cotrimoxazole (MIC $\geq$320 mg/L). 50% of the isolates also exerted tigecycline-resistance, while all of them exhibited susceptibility to ampicillin/sulbactam- and colistin (MICs $\leq$4 mg/L and $\leq$0.5 mg/L, respectively). Sensitivities were confirmed by a CLSI agar disk method,[6] whereas Vitek2 MIC for tigecycline (MIC 0.5 mg/L) was compared with an E-test method (AB BIODISK), results of which appeared as confirmatory.

Given the common expression of AmpC enzymes by *A. baumannii*, we supposed ampicillin/sulbactam-resistance to be inducible by prolonged exposure to the drug. Hence, plates were incubated for 48 h (rather than 24 h). Interestingly, $\leq$5 colonies were observed inside each of the ampicillin/sulbactam inhibition zones; this was documented only in five tigecycline-resistant strains. Mutant colonies inside were subcultured and screened for antibiotic resistance (both by Vitek2 and by CLSI disk method), showing full ampicillin/sulbactam-resistance, whereas colistin-susceptibility remained unchanged. As an explanation for that, we thought than a slightly prolonged exposure to the drug had been able to determine resistance, by inducing AmpC enzyme-expression (sulbactam has been known to act as a weaker AmpC inducer than clavulanate, so that ampicillin/sulbactam sensitivity