the isolate was now resistant to tigecycline (MIC 8 mg/L; Table 1). At the time of this episode the patient was on 50 mg of tigecycline twice daily iv, and had by that point received 53 days of tigecycline, indicating development of resistance during prolonged tigecycline therapy.

The patient was then commenced on colistin [4.5 million units (MU) twice daily iv]. After 10 days of this treatment, the dose was reduced to 3 MU twice daily in the light of rising serum creatinine and elevated colistin levels (trough 8.5 mg/L, peak 10.4 mg/L). On day 13 of colistin treatment, admission to the intensive care unit (ICU) was required for supportive treatment of sepsis. Meropenem and teicoplanin were added empirically to cover the previously isolated P. aeruginosa and MRSA. On day 15 of colistin therapy the patient developed generalized seizures. CT brain scan and CSF were normal. Colistin therapy was discontinued and the seizures stopped shortly afterwards, suggesting colistin-associated neurotoxicity, a recognized side effect.

The patient returned to a single room within a general ward after 10 days on the ICU. Subsequent blood cultures were negative. Six months after initial presentation, the patient remains clinically stable. Despite prolonged admission, contact isolation prevented onward transmission of the NDM-positive bacteria within the hospital.

This is the first carbapenemase-producing E. coli confirmed to be resistant to tigecycline by the national reference laboratory. An 8-fold reduction in the MIC of tigecycline for the resistant isolate when tested in the presence of the efflux inhibitor phenyl-arginine-β-naphthylamide (PAβN; at 40 mg/L) was observed (compared with only a 2-fold reduction for the susceptible isolate), which suggests up-regulated efflux as the resistance mechanism. Future studies will ascertain the specific pump(s) involved.

The isolates remained susceptible to colistin, as do most with NDM enzymes. 5,6 This case suggests that invasive infection with NDM producers can be successfully treated with colistin, albeit with the risk of significant toxicity, and further demonstrates the emerging threat of the NDM-type metallo-β-lactamases.

We received the patient’s verbal and written consent for their case to be published in a scientific journal for the purposes of medical education and research.

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Micafungin therapy in a critically ill, morbidly obese patient

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Sir,

Obesity continues to increase in prevalence throughout the world, reaching rates of nearly 30% in the USA.1 Physiological changes in obesity significantly alter medication distribution,
metabolism and elimination, making optimal dosing of antimi-
robials in this population challenging.2

Micafungin is an echinocandin antifungal with a spectrum of
activity that includes most Candida species. Current recommended
dosing for invasive candidiasis is 100 mg intravenously (iv) daily,
with no adjustment in renal or mild-to-moderate hepatic dysfunc-
tion.3 Limited data are available regarding the pharmacokinetics
and potential need for dose adjustment of micafungin in obese
patients.

We present the case of a 40-year-old African-American
female admitted with septic shock secondary to lower extremity
cellulitis and acute respiratory distress syndrome with respiratory
failure requiring mechanical ventilation. Her past medical history
was significant for metabolic syndrome and morbid obesity
(weight 230 kg and body mass index 102 kg/m²). She was
treated aggressively with fluid resuscitation and appropriate anti-
microbial therapy, and clinically improved. On hospital day 23,
she developed a fever to 38.9°C. Urinalysis showed a white
blood cell count of 30/high-power field (hpf) (normal=0–3/
hpf) and a red blood cell count of 221/hpf (normal=0–5/hpf);
in addition, nitrite was negative. A complete blood count showed
a significant leucocytosis of 16 000 cells/mm³
(normal = 3700–9100 cells/mm³), with 66% neutrophils. Urine
culture was positive for Candida glabrata. Micafungin at a dose
of 100 mg iv daily was initiated secondary to her compromised
clinical status, with the possibility of disseminated disease and
urinary tract infection diagnosis. All blood and respiratory cul-
tures were negative. Due to her morbid obesity, the appropriateness
of standard-dose micafungin was in question. Serum
concentrations obtained on treatment day 5 at 4, 13 and 23 h
from the start of the infusion were 2.93, 1.96 and 1.36 mg/L,
respectively (Figure 1). She completed 2 weeks of micafungin
therapy, resulting in clinical resolution and urine sterilization.
The micafungin dose remained unchanged during therapy,
because serum concentration data were not available until
therapy was completed.

Obesity leads to multiple physiological changes in a patient,
significantly altering antimicrobial pharmacokinetics. Morbidly
obese patients have an increased body mass, both lean mass
and adipose tissue, and increased cardiac output and blood
volume, which may influence drug distribution. Changes in
serum protein levels, increased renal clearance and altered
hepatic metabolism impact protein binding and drug elimin-
ation.3,4 Micafungin is a highly protein bound, hydrophilic agent
that is heptatically metabolized and excreted primarily via the
faeces.5 Micafungin is >99% bound to circulating albumin and
α-1-acid-glycoprotein. In obese patients, a higher amount of
micafungin may be tightly bound to serum proteins and distrib-
uted to tissues, including adipose tissue, which is ~30% water,
thus decreasing the micafungin exposure. Because micafungin
is not highly excreted in the urine, concentrations are expected
to be <15% of serum concentrations.5

Micafungin exhibits fungicidal activity against most Candida
species in a linear dose-dependent relationship, as predicted by
the AUC/MIC ratio. Pharmacokinetic analyses have demonstrated
linearity in doses up to 8 mg/kg.5 Adult subjects of normal body
weight with invasive candidiasis receiving 100 mg of micafungin
iv daily had average (+SD) maximum serum concentrations fol-
lowing a single dose and at steady-state of 5.7 ± 2.2 and
10.1 ± 4.4 mg/L, respectively.5 In stem cell transplant (SCT) recip-
ients, Hiemenz et al.6 reported maximum serum concentrations
on day 1 and day 7 to be 7.1 and 22.0 mg/L, respectively. Serum
concentrations at 4 h post-dose on day 7 (steady-state) were
~5.5 mg/L, significantly higher than the comparable concentra-
tion (2.93 mg/L) obtained in our patient on day 5 of therapy
(Figure 1).6 Pharmacokinetic data from an SCT population may
not be generalizable to our case patient, although comparable
steady-state AUC0–24 has been observed in HIV-infected
patients with oesophageal candidiasis and other hosts with
invasive candidiasis.3

In an analysis performed by Gumbo et al.,7 investiga-
tors found a divergence in the micafungin kinetic profile with an
infection point at a weight of 66.3 kg. Subjects with a body
weight >66.3 kg had an ~50% increased clearance and signifi-
cantly lower AUC0–24, compared with subjects below this
weight threshold.7 The authors concluded that an increase in
dose may be warranted to achieve a comparable AUC/MIC
ratio. Although dosing recommendations for micafungin are
not weight based, our patient received a dose of 0.4 mg/kg/
day, compared with an average of >1 mg/kg for the normal
weight patient; translating to a 300 mg dose in our patient.
Safety has been demonstrated in doses up to 8 mg/kg, with
subjects receiving an average of 600 mg per dose.8

Despite a significantly lower AUC as compared with a patient
of normal weight and presumably subtherapeutic urine concen-
trations, our patient had favourable microbiological and clinical
outcomes. This may be due to the relatively low MIC90
(0.06 mg/L) of non-resistant C. glabrata species and, in part, to
the potential for micafungin to disassociate from serum proteins
and exert its antifungal activity in vivo.9,10

In our morbidly obese patient, serum micafungin concen-
trations were significantly lower than previously published
steady-state concentrations in normal body weight hosts. In
lieu of available micafungin serum concentrations, the enhanced
clearance and significantly decreased exposure observed in
obesity may prompt clinicians to consider a dosage increase in

Figure 1. Micafungin serum concentrations in a morbidly obese patient
compared with published data. *Serum micafungin concentrations were
measured by the Fungus Testing Laboratory in San Antonio, TX, USA
using HPLC methods. SCT = SCT recipients; concentrations are estimates
from graphical representation of data (Hiemenz et al.6).
obese patients with invasive disease. Further studies are warranted to establish the optimal dose, and to assess the safety and efficacy of higher micafungin doses in an obese population with invasive candidiasis.

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