Candida pneumonia is an extremely rare disease, associated with high mortality rates. A pulmonary infection caused by Candida spp. may exist in two forms: a very rare primary pneumonia due to aspiration of oropharyngeal material; and a relatively more common secondary pneumonia due to haematogenous seeding from a distant site of infection. The predominant origin of septic pulmonary embolism due to Candida spp. are right-sided fungal endocarditis, CVC infection, central venous thrombophlebitis and drug addiction.²

The presence of Candida in respiratory specimens may be due to contamination and there are no specific clinical and radiological pictures. The clinical syndrome is usually dominated by signs and symptoms of systemic inflammatory syndrome.³ while the radiographic features include a miliary nodular pattern, with feeding-vessel sign, ground-glass opacity, small nodules or multiple larger nodules with ill-defined borders randomly distributed in bilateral lungs. This pattern was prevalent in the two patients presented here. Other less common CT findings include air-space consolidation, pleural effusion, cavitation and thickening of the bronchial walls.⁴

Conclusive diagnosis requires demonstration of the organism in lung tissues. Our two cases were not confirmed by biopsy but certain points strongly favoured the diagnosis: (i) the patients were immunocompromised; (ii) Candida spp. were repeatedly isolated from bronchial samples; (iii) tracheal and bronchial specimen cultures and blood cultures were negative for pyogenic organisms; (iv) PAC cultures were positive for Candida spp; (v) patients failed to respond to ordinary antibiotics; and (vi) there was a good clinical as well as radiological response to antifungal therapy.

To date, this is the first report of pulmonary candidiasis treated with anidulafungin therapy. Recently, Crandon et al.⁵ studied the bronchopulmonary penetration of intravenous voriconazole and anidulafungin given in combination in healthy adults, and found good anidulafungin concentrations in alveolar macrophages and optimal lung distribution. Another study found the combination of anidulafungin and voriconazole synergistic at a dosage of 5 mg/kg/day in neutropenic rabbits with experimental invasive pulmonary aspergillosis.⁶ These data seem to support the clinical use of this drug alone or in combination with voriconazole for the treatment of Candida lung infections.

In conclusion, we have described two cases of bilateral septic pulmonary candidiasis successfully treated with anidulafungin therapy. This report suggests a potential role for anidulafungin in the treatment of pulmonary fungal infections.

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The use of linezolid in the treatment of paediatric patients with infections caused by enterococci including strains resistant to vancomycin

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Sir,

Linezolid has both in vitro and in vivo antibacterial activity against resistant Gram-positive bacteria, including vancomycin-resistant enterococci (VRE). However, efficacy and safety data in paediatric patients with VRE infections are limited. To address this gap we conducted a Phase III, prospective, open-label, non-comparator, multicentre study at six US study sites (ClinicalTrials.gov; #NCT00035854). After obtaining local institutional review board approval and written informed consent, the investigators enrolled 13 critically ill patients (six male and seven female) aged 4 days to 17 years [mean (± SD), 7 ± 6.4 years; median, 3.4 years], all of whom had infections initially diagnosed by the local microbiology laboratory as being caused by VRE alone or by a combination of VRE and Gram-negative bacteria (Table 1). Specimens (blood, wound, needle aspirate or urine) were collected within 24 h. Swabs of intact skin surfaces were not accepted. Linezolid susceptibility was initially determined at local laboratories using disc diffusion techniques (Kirby-Bauer) or Etest strips. Thereafter the isolates were sent to a central laboratory where MICs were determined according to CLSI guidelines. The findings from the central laboratory indicated that nine patients had vancomycin-resistant Enterococcus faecium, one had vancomycin-resistant Enterococcus faecalis and one had both vancomycin-intermediate E. faecium and vancomycin-intermediate Enterococcus gallinarum (MIC for both 8 mg/L). However, in two patients with E. faecium, the isolates were found to be susceptible to vancomycin (the second patient also having E. gallinarum for which susceptibility test results were not available).

Exclusion criteria included the following: >24 h treatment with an antibiotic other than linezolid that was effective against VRE within 48 h of enrolment unless there was treatment failure or the pathogen showed resistance to linezolid (resistance has been reported in Enterococcus); infections expected to be cured by surgical incision alone; decubitus and ischaemic ulcers without cellulitis; necrotizing fasciitis; gas gangrene; burns >20% of total body surface; infections related to a medical device that could not be removed; endocarditis; osteomyelitis; septic arthritis; CNS infections; known phaeochromocytoma; carcinoid syndrome; untreated hyperthyroidism; uncontrolled hypertension; and hypersensitivity to linezolid or vancomycin.

All patients were started on intravenous (iv) linezolid. Patients aged 0–11 years received 10 mg/kg (up to 600 mg per dose) every 8 h and patients aged 12–17 years received 600 mg every 12 h. Patients with Gram-negative or anaerobic infections due to organisms other than enterococci were allowed to continue in the study as long as the additional therapy had no activity against enterococci.

The primary infections were vascular catheter-associated bacteraemia (n=4), bacteraemia of unknown source (n=3), urinary tract infection (UTI; n=3), skin and skin structure infection (SSSI; n=1), pyelonephritis (n=1) and intra-abdominal abscess (IAA; n=1) as defined previously. All patients had normal baseline physical examinations. Infected catheters were removed in patients with bacteraemia. Total mean (± SD) duration of iv and oral linezolid treatment was 17.1 ± 7.2 days (range, 7–33 days; median, 15 days) (iv, 14.2 ± 9 days (range, 3–33 days; median, 13 days); oral, 10.5 ± 6.9 days (range, 5–20 days; median, 8.5 days)).

The follow-up microbiological eradication rate was 5/7 (71.4%) and the clinical cure rate was 8/12 (66.7%) (Table 2).

### Table 1. Patient characteristics, duration of treatment and outcome at TOC

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Treatment (days)</th>
<th>Culture source</th>
<th>Organism</th>
<th>Vancomycin susceptibility</th>
<th>Clinical outcome</th>
<th>Microbiological outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>M</td>
<td>10</td>
<td>blood</td>
<td>E. faecium</td>
<td>susceptible</td>
<td>cured</td>
<td>eradication</td>
</tr>
<tr>
<td>2</td>
<td>0.6</td>
<td>F</td>
<td>19</td>
<td>blood</td>
<td>E. faecium</td>
<td>resistant</td>
<td>cured</td>
<td>eradication</td>
</tr>
<tr>
<td>3</td>
<td>1.6</td>
<td>F</td>
<td>7</td>
<td>blood</td>
<td>E. faecium</td>
<td>resistant</td>
<td>failed</td>
<td>persistence</td>
</tr>
<tr>
<td>4</td>
<td>11.9</td>
<td>M</td>
<td>14</td>
<td>SSSI</td>
<td>E. faecium</td>
<td>resistant</td>
<td>cured</td>
<td>eradication</td>
</tr>
<tr>
<td>5</td>
<td>16.3</td>
<td>M</td>
<td>33</td>
<td>urine</td>
<td>E. faecium</td>
<td>resistant</td>
<td>failed</td>
<td>persistence</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>F</td>
<td>13</td>
<td>urine</td>
<td>E. faecium</td>
<td>resistant</td>
<td>cured</td>
<td>eradication</td>
</tr>
<tr>
<td>7</td>
<td>3.4</td>
<td>M</td>
<td>18</td>
<td>blood</td>
<td>E. faecium</td>
<td>resistant</td>
<td>failed</td>
<td>persistence</td>
</tr>
<tr>
<td>8</td>
<td>3.2</td>
<td>M</td>
<td>22</td>
<td>urine</td>
<td>E. faecium</td>
<td>intermediate</td>
<td>cured</td>
<td>eradication</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td>M</td>
<td>15</td>
<td>blood</td>
<td>E. faecium</td>
<td>intermediate</td>
<td>cured</td>
<td>eradication</td>
</tr>
<tr>
<td>10</td>
<td>15.4</td>
<td>F</td>
<td>28</td>
<td>IAA</td>
<td>E. faecium</td>
<td>resistant</td>
<td>failed</td>
<td>persistence</td>
</tr>
<tr>
<td>11</td>
<td>1.4</td>
<td>F</td>
<td>15</td>
<td>blood</td>
<td>E. faecium</td>
<td>susceptible</td>
<td>cured</td>
<td>eradication</td>
</tr>
<tr>
<td>12</td>
<td>12.2</td>
<td>F</td>
<td>12</td>
<td>urine</td>
<td>E. faecium</td>
<td>resistant</td>
<td>cured</td>
<td>eradication</td>
</tr>
<tr>
<td>13</td>
<td>0.3</td>
<td>F</td>
<td>16</td>
<td>blood</td>
<td>E. faecalis</td>
<td>resistant</td>
<td>cured</td>
<td>indeterminate</td>
</tr>
</tbody>
</table>

M, male; F, female.

Patient no. 3 had a history of end-stage liver disease and multiple liver transplants, experienced an event of multi-organ failure and died on study day 7. Death was not considered related to linezolid.

Patient no. 5 was awaiting a heart transplant and had a history of congenital heart disease, renal insufficiency and renal transplant, had an event of Pseudomonas sepsis and died on study day 45. Death was not considered related to linezolid.

Patient no. 7 was enrolled with a culture-confirmed VRE bacteraemia of unknown source and completed 17 days of study treatment; it was then determined that the patient had VRE endocarditis (an exclusionary condition per protocol). The patient was withdrawn from the study and classified as failed/persistence. The patient was switched to non-study linezolid, completed 42 days of treatment and was classified as cured.
At test of cure (TOC), which took place 12–28 days after the completion of treatment, 2/3 (66.7%) patients with bacteraemia and 2/3 (66.7%) patients with UTI were cured. Both the patient with pyelonephritis and the patient with SSSI were cured. The patient with IAA had an outcome of failed at end of treatment (EOT) and TOC.

Adverse events (AEs) reported during the study were abdominal pain (n=1), headache (n=1), decreased cyclosporin level (n=1), monilial rash (n=2), diarrhoea (n=2), nausea (n=1), vomiting (n=1) and tongue discoloration (n=1). Except for diarrhoea, which resolved upon discontinuation of linezolid, these AEs resolved while receiving linezolid. Two patients died during the study; neither death was considered related to linezolid (one patient with a history of end-stage liver and renal disease experienced multi-organ failure; another patient with a history of renal transplant developed Pseudomonas aeruginosa sepsis).

Anaemia was observed in one patient in whom linezolid was discontinued due to multiple AEs of abdominal distension, abdominal pain and diarrhoea. These AEs eventually resolved. This patient had an outcome of cured at EOT and TOC visits. No patient experienced a neurological AE attributed to linezolid.

Changes in laboratory values were assessed using modified AIDS Clinical Trials Group grading criteria to fit the age groups used in the study. Platelet count decreased transiently in 5/13 patients (39%); four of them had abnormal baseline values. No patient experienced bleeding. The lowest platelet count (29x10^3/μL, on day 17) was observed in a patient who received linezolid for 33 days. The baseline platelet count was 87x10^3/μL (normal range, 140–440x10^3/μL). At EOT the platelet count was 68x10^3/μL, and it improved to 91x10^3/μL 10 days later.

Linezolid has been reported to be effective in children with VRE infections. However, there are no reports from prospective paediatric studies with which to compare these results. Although limited by the small sample size, these results provide further evidence that linezolid is clinically and microbiologically effective in treating infections caused by VRE in paediatric patients. Decreased platelet count, a known complication of linezolid, was the most common laboratory AE; it was transient and resulted neither in bleeding nor in study drug discontinuation.

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**Transparency declarations**

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**Author contributions**

All authors were involved in all stages of the development of this manuscript.

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### Table 2. Assessment of clinical outcome in the ITT, clinically evaluable (CE) and microbiologically evaluable (ME) populations

<table>
<thead>
<tr>
<th>Visit</th>
<th>Assessment</th>
<th>ITT (n=13), no. (%)</th>
<th>CE (n=10), no. (%)</th>
<th>ME (n=7), no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOT</td>
<td>cured or improved</td>
<td>9 (69.2)</td>
<td>8 (80)</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td></td>
<td>failed</td>
<td>4 (30.8)</td>
<td>2 (20)</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td></td>
<td>number assessed</td>
<td>13</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>TOC</td>
<td>cured</td>
<td>8 (66.7)</td>
<td>8 (80)</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td></td>
<td>failed</td>
<td>4 (33.3)</td>
<td>2 (20)</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td></td>
<td>number assessed</td>
<td>12</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>indeterminate</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

a Intent-to-treat (ITT) population: all enrolled patients who received ≥1 dose of study medication and had a culture-positive infection caused by Enterococcus spp. at study entry. One patient died at day 7 of therapy and two patients were excluded (one had endocarditis and one was enrolled for catheter-related bacteraemia and treated for 16 days, but was restarted on a non-study regimen of linezolid for pyelonephritis caused by VRE on day 18).

b CE population: all ITT patients who received ≥80% of the prescribed study medication for ≥7 days, did not receive prior or concomitant antibiotic therapy for intercurrent illness (except for lack of efficacy) and who had a follow-up (TOC) assessment.

c ME population: all patients who had a culture positive for VRE identified by the central laboratory at baseline.

d All percentages are based on the number of patients assessed.

e EOT visit; took place within 4 days after completion of last dose of linezolid.

f Patients with indeterminate or missing outcomes were excluded.

g TOC visit; took place 12–28 days after EOT.
References

