

# Treatment of bladder fungal balls in a premature infant with a combination of three antifungal agents

By Afia Manaf, MRPharmS

Bladder fungal balls are a recognised complication of septic fungal infections. This article describes an example of this complication and discusses the antifungal and antibacterial treatments that were used

**C**andidal infections are a significant cause of mortality (10 to 54 per cent) and morbidity (25 per cent) in neonatal intensive care units (NICUs).<sup>1</sup> Invasive candidiasis in NICUs is one condition that is becoming increasingly difficult to treat, due to the emergence of resistance to antifungal drugs.

Bladder fungal balls are an unusual but recognised complication of invasive candidiasis. They can be difficult to eradicate using standard antifungal drugs and can cause urinary tract obstruction, leading to acute renal failure.<sup>2</sup> The causative pathogens are *Candida* spp, which produce clinical manifestations such as asymptomatic candiduria, cystitis, systemic candidiasis, primary renal candidiasis and bezoar (fungal ball) formation.<sup>2</sup> Risk factors for bladder fungal balls include premature birth, treatment with broad-spectrum antibiotics or immunosuppressant drugs (eg, steroids), prolonged hospital stay, intravenous catheterisation and endotracheal intubation.<sup>1</sup>

## Case report

A male infant, born at 27-week gestation in a district general hospital (birth weight 1.2kg), was intubated, given surfactant and put on ventilatory support. Enteral feeding via a nasogastric tube was started at day two of life and gradually increased. By day seven, he was fully enterally fed.

**Initial presentation** At three weeks of age, the infant developed abdominal distension, increased oxygen requirements and respiratory distress. His C-reactive protein (CRP) concentration was 230mg/L (normal <5mg/L) and he was transferred to the neonatal surgical unit (NNSU) at St Mary's Hospital, Manchester.

An abdominal X-ray showed evidence of necrotising enterocolitis (NEC) and proximal bowel dilation. Feeds were stopped and he was started on intravenous antibiotics (benzylpenicillin, gentamicin, metronidazole), morphine and maintenance fluids. His renal function

appeared to be normal. A right hemicolectomy (right side of the colon removed) was performed to treat the NEC, which had secondarily caused ileal perforation.

A central venous catheter was inserted so that total parenteral nutrition (TPN) could be started. Two days after surgery, the morphine infusion was stopped and the infant was extubated. TPN was started at 130ml/kg/day (this is less than the normal rate of 180ml/kg/day, because the infant had patent ductus arteriosus, so was at risk of fluid overload). At this point, the infant's abdomen was soft and his bowels had started to function. After seven days, the antibiotics were stopped because samples taken from blood cultures showed no evidence of bacterial or fungal growth and the CRP concentration had returned to normal.

Ten days after the operation, central venous access was lost, meaning that TPN could not be continued (normally, it would continue for two to three weeks, or until a regular feeding pattern had been established). Therefore, enteral feeds were restarted.

**First relapse** Four days later, the infant became unwell, experiencing frequent episodes of bradycardia, apnoeic attacks, increased oxygen requirements and abdominal distension. His CRP concentration rose to 84mg/L. In view of his abdominal distension and the possibility that NEC would recur, enteral feeds were stopped and maintenance fluids were restarted, along with intravenous antibiotics (meropenem, vancomycin and metronidazole).

Over the next two days, the clinical condition of the infant improved and there was no evidence of bacterial or fungal growth (including meningococcal disease) in either blood or urine cultures. The surgical team decided to reintroduce enteral feeds, at a rate of 1ml per hour. The infant was transferred back to the district general hospital.

**Second relapse** Five days after transfer, the infant's condition deteriorated. He experienced frequent episodes of blood-

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oxygen desaturation and had an abdominal distension, bile-stained aspirates and a CRP concentration of 187mg/L.

Enteral feeds were stopped again and the antibiotics were changed to cefotaxime, metronidazole and flucloxacillin (although no rationale was documented). The infant was transferred back to the NNSU.

At day 48 of life, he underwent a second abdominal operation as a result of perforated NEC, and a further ileal resection was performed.

Following this surgery, the infant became extremely unwell and haemodynamically unstable. He required ventilatory and inotropic support, therefore dopamine was started, along with morphine for sedation and pain relief. He became acidotic and anuric, for which he was given furosemide.

Two days later, blood cultures indicated the presence of coagulase-negative staphylococci. His antibiotics were changed to meropenem and vancomycin. However, there was evidence that vancomycin was accumulating (trough level of 19mg/L before the third dose), so it was withheld and the meropenem dose was reduced by half — a precautionary measure, in case the infant's kidney function was compromised.

After 48 hours of this antibiotic treatment, the infant began to pass urine. Inotropic requirements were reduced and his mean arterial pressure stabilised. The following day, inotropic support was discontinued. This acute episode of renal failure gradually improved and by day 55 of life, the infant's urine output was 3.6ml/kg/h (normal = 2ml/kg/h). He was still oedematous, so TPN was started at a reduced rate of 100ml/kg/day.

Cultures grown from an abdominal wound swab showed the presence of enterobacter, resistant to meropenem but sensitive to gentamicin, amikacin and chloramphenicol. Therefore, gentamicin was added to the regimen of meropenem and vancomycin. TPN was gradually increased to 150ml/kg/day over the next few days.

At day 59 of life, *Candida albicans* was isolated from a skin axillary swab. The following day, *Candida* spp were isolated from urine, so fluconazole was started.

A day later, the infant was gradually weaned off morphine and extubated. His CRP concentration remained raised at 61mg/L, therefore the microbiology department advised to continue vancomycin to treat coagulase-negative *Staphylococcus* spp, but to replace meropenem and gentamicin with amikacin and Tazocin (piperacillin and tazobactam). Fluconazole was continued.

**Third relapse** The infant remained oedematous, for which he continued to

receive furosemide bolus doses daily (with additional doses as needed). His respiratory gas deteriorated (carbon dioxide saturation increased, oxygen saturation decreased, blood pH decreased) over the next 24 hours and he became acidotic again. He was reintubated and ventilated. His CRP concentration remained high and he was pyrexial, so the medical team decided to add metronidazole for anaerobic cover.

At this point, severe fungal sepsis was a distinct possibility and an ultrasound scan of the bladder revealed the presence of a fungal ball mass that was 5mm in diameter. Fluconazole was stopped and liposomal amphotericin (Ambisome) and flucytosine were started.

Two days later, *Candida albicans* was grown from peripheral blood cultures. CRP concentration was now 97mg/L. Vancomycin was stopped, because blood samples showed no evidence of coagulase-negative staphylococci growth.

After one week of antifungal treatment, cultures were still positive for *Candida albicans*. The infant continued to have respiratory acidosis and require high ventilatory pressures to maintain adequate blood-oxygen saturations. He also needed regular fluid boluses and furosemide to maintain urine output. Although he remained oedematous, his urea and creatinine concentrations remained normal. His CRP concentration remained high, despite continued treatment with metronidazole, Tazocin, amikacin, flucytosine and amphotericin.

**Caspofungin treatment** At this point, it was decided that the infant was not responding adequately to the antifungal therapy, and the consultant microbiologist recommended the addition of intravenous caspofungin, at a dose of 1mg/kg/day (1.7mg daily). Amikacin was stopped. Four days into treatment, Tazocin was stopped

because the infant's white cell count and CRP concentration began to reduce. Generalised oedema persisted, despite regular furosemide, but urea and creatinine concentrations remained within normal ranges. No adverse effects associated with caspofungin were observed.

After 14 days of treatment with caspofungin, flucytosine and amphotericin, the infant's CRP concentration reduced to 14mg/L and no fungal growth was evident in blood and urine cultures.

Two days later, an ultrasound of the bladder and kidneys indicated that fungal balls were no longer present and there was no kidney obstruction. After a three-week course of caspofungin and four weeks of amphotericin and flucytosine, all three antifungals were stopped. Prophylactic fluconazole was started at a dose of 3mg/kg/day and continued until all peripheral lines were removed. Fungal sepsis had now resolved.

## Discussion

**Use of antibiotics** A total of 10 antibiotics were used to treat this infant, however a general consensus for an appropriate antibiotic combination was not apparent. Several combinations of antibiotics were used for lengthy periods, which may have increased the risk of opportunistic fungal infection and antibiotic resistance.

**Use of antifungals** Fungal balls are often difficult to eradicate and require prolonged treatment with antifungal drugs. Traditionally, fluconazole or amphotericin (with or without flucytosine) have been used to treat invasive fungal infections in neonates. Fluconazole has the most data regarding the treatment of neonates and remains the azole of choice in many neonatal intensive care units.

Caspofungin offers potential as an alternative, having shown *in vitro* activity against *Candida* spp resistant to azoles and amphotericin, and synergistic activity with amphotericin against *Fusarium* spp and *Aspergillus* spp *in vitro*.<sup>3</sup> There is limited evidence for using caspofungin in neonates, especially premature neonates. However, a number of case reports describe the use of caspofungin alone or in combination with other antifungals in the treatment of refractory fungal infections in children and babies.<sup>4-14</sup>

In this case, flucytosine and amphotericin were used for one week before caspofungin was started. It could be argued that this was not adequate time to determine whether these two antifungals were effective, but the decision to add caspofungin was justified because the infant's condition was deteriorating.

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**Dose of caspofungin** The optimum dose of caspofungin in neonates is unknown. We used a weight-based dose (1mg/kg daily) in line with published literature.<sup>7,8</sup> Another study suggests that the dose for paediatric patients can be calculated from body surface area, at a dose of 50mg/m<sup>2</sup> daily.<sup>15</sup> However, this study does not include neonates, for whom it is difficult to estimate surface area. Therefore we justify our decision to calculate the dose from body weight.

**Development of NEC** Although the cause of NEC is not understood fully, it is associated with the early introduction of enteral feeds. Normally, a premature infant who is not breast-fed would have their level of enteral feeding built up over two to three weeks, according to his or her ability to tolerate the feeds. This may have been a factor in this case, as the infant was fully established on enteral feeds by day seven of life.

**Development of fungal balls** The fungal balls in this infant may have formed during the periods of anuria or oligouria, due to urinary stasis.

## — Conclusion

It is important to rationalise antibiotic use at all stages of NEC treatment. It is also important to work closely with microbiology staff and consider the possibility of fungal sepsis if a neonate presents with the clinical signs of sepsis, but responds poorly to antibiotics or those for whom bacterial cultures display negative growth.

Treatment with caspofungin proved successful in this case, but because it was used in combination with amphotericin and flucytosine, it is difficult to conclude

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whether caspofungin alone would have eradicated the infection. The limited published evidence for caspofungin use in neonates, prevents its routine use from being recommended. However, it may be an appropriate alternative to treat invasive fungal infections that are unresponsive or resistant to conventional antifungals.

The weight-based dose given in this case was successful in treating the infection and no side effects were observed. However, further pharmacokinetic studies are needed to determine an optimum effective dose and long-term safety.

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