

## Correspondence

procedure, the patient developed fever (38°C), lethargy and neck stiffness. Analysis of ventricular CSF revealed 105 white cells/mm<sup>3</sup> (90% of the white cells were neutrophils), a glucose level of 23 mg/dL (glucose level in the blood: 106 mg/dL) and protein of 119 mg/dL. Microscopic examination of the Gram staining showed yeast and no other microorganisms. Cultures were positive for *C. albicans* in three separate samples. The blood culture was sterile. The patient had been treated with fluconazole 400 mg intravenously (iv) daily, oxacillin 12 g iv daily, rifampicin 600 mg iv daily, but meningitis persisted. Twenty days after the stroke, the patient was admitted to our Infectious Diseases unit. The external shunt was removed and replaced immediately, and therapy with AmBisome (3 mg/kg/day) and flucytosine (150 mg/kg/day) was started. In addition, on days 7–9 of the new treatment, intraventricular amphotericin B deoxycholate was injected into the shunt at a dose of 4 mg daily (the shunt was closed for 4 h). Despite this therapy, the patient had a torpid clinical course; his fluids and clinical condition improved but without complete resolution. CSF culture was positive until the 7th day of therapy and after this was negative. Following 23 days of this drug regimen, serial CSF and serum samples were taken to check amphotericin B levels. Some samples were also taken during intraventricular infusion. All samples were stored at –80°C until assay. After 30 days, the patient died as a result of a second haemorrhagic stroke. Amphotericin B concentrations in the patient's CSF and serum samples were analysed by HPLC, as described by Bekersky *et al.*<sup>1</sup> We performed standard curves for amphotericin B by regression analysis. The peak serum level of amphotericin B was 15.61 mg/L and the area under the concentration–time curve (AUC) was 115.5 mg·h/L. Amphotericin B concentrations in ventricular CSF were between 0.09 and 0.24 mg/L (AUC 3.7 mg·h/L). Concentrations of ventricular amphotericin B taken after intrathecal administration (range +7, +24 h after intra-shunt infusion) were between 100.5 and 1.75 mg/L. The concentration of amphotericin B in lumbar fluid was 0.59 mg/L (the fluid sample was obtained by single lumbar puncture, 48 h after intra-shunt infusion of amphotericin B and 22 h after AmBisome iv).

One major concern, for therapy of fungal shunt infections, is CSF penetration of systemically administered amphotericin B. Currently, *C. albicans* is considered susceptible to amphotericin B at a concentration of 1 mg/L (MIC < 1 mg/L).<sup>2</sup> The minimal drug concentration achieved at the infection site should be at least equal to the MIC for the infecting organism, and *in vivo*, the ratio between the maximum concentration of the drug ( $C_{max}$ ) and the MIC value is the best predictor for outcome.<sup>3</sup> Conventional amphotericin B deoxycholate is notorious for its inability to achieve consistently measurable concentrations in CSF; it ranges from undetectable to no more than 4% of serum concentrations.<sup>4</sup>

A potential strategy for reducing the toxicity and increasing the therapeutic index of amphotericin B is the use of lipid formulations of this drug, which allow the administration of a much higher dose.<sup>5</sup> In our case, administration of AmBisome at 3 mg/kg/day did not result in significantly enhanced amphotericin B concentration in CSF; in fact a fluid  $C_{max}$  of 0.24 is a sub-MIC concentration, and limited clinical results were obtained. These data show the poor penetration into CSF of liposomal amphotericin B at a dose of 3 mg/kg/day (CSF AUC was equivalent to 3.2% of serum AUC). The intrathecal amphotericin B therapy, administered only for 3 days in this case, achieved a temporary elevated concentration in ventricular CSF, but this did not contribute to the clinical outcome. If CNS penetration is based on  $C_{max}$ , an increased intravenous liposomal amphotericin dosage can be advocated to treat CNS *Candida* infections. In clinical situations, the administration, at maximal tolerable dosage, of AmBisome (5–10 mg/kg/day)

may provide more effective therapeutic results.<sup>5</sup> In addition, although a post-antifungal effect on *Candida* species was disregarded, it may have been attributable to amphotericin B and flucytosine,<sup>6</sup> and it should be the aim of antimicrobial therapy to increase CSF drug concentration above the MIC so that there is a greater possibility of completely eradicating infection.

There exists a direct relationship between peak concentrations of amphotericin B in plasma, AUCs and cerebral tissue concentrations. This correlates directly with greater antifungal efficacy.<sup>5</sup> Thus, if azole-resistant *Candida* shunt infections occur, a high dose of AmBisome (5–10 mg/kg/day) may be a reasonable option.

## References

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## Vitamin C and SARS coronavirus

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Sir,

Recently, a new coronavirus was identified as the cause of the severe acute respiratory syndrome (SARS).<sup>1</sup> In the absence of a specific treatment for SARS, the possibility that vitamin C may show non-specific effects on severe viral respiratory tract infections should be considered. There are numerous reports indicating that vitamin C may affect the immune system,<sup>2,3</sup> for example the function of phagocytes, transformation of T lymphocytes and production of interferon.

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In particular, vitamin C increased the resistance of chick embryo tracheal organ cultures to infection caused by an avian coronavirus.<sup>4</sup> Studies in animals found that vitamin C modifies susceptibility to various bacterial and viral infections,<sup>3</sup> for example protecting broiler chicks against an avian coronavirus.<sup>5</sup> Placebo-controlled trials have shown quite consistently that the duration and severity of common cold episodes are reduced in the vitamin C groups,<sup>3</sup> indicating that viral respiratory infections in humans are affected by vitamin C levels. There is also evidence indicating that vitamin C may affect pneumonia.<sup>3</sup> In particular, three controlled trials with human subjects reported a significantly lower incidence of pneumonia in vitamin C-supplemented groups,<sup>6</sup> suggesting that vitamin C may affect susceptibility to lower respiratory tract infections under certain conditions. The possibility that vitamin C affects severe viral respiratory tract infections would seem to warrant further study, especially in light of the recent SARS epidemic.

## References

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