

National Essential Medicines List Tertiary/Quaternary Medication Review Process

Medication: Echinocandins (e.g. caspofungin, micafungin, anidulafungin)

Date: April 2018

Indication: Invasive Candidiasis (resistant to fluconazole/amphotericin B, and/or where renal dysfunction is present and amphotericin B cannot be used)

Introduction and contextualization: Candidaemia is one of the major causes of morbidity and mortality in seriously ill patients in Intensive Care Units, particularly when the onset of therapy is delayed. Mortality is as high as 30%-60% even with effective antifungal therapy¹ and is considered to be the 5th to 10th most likely cause of bloodstream infection in these patients. *Candida albicans* followed by *C.parapsilosis* are the leading causes of candidaemia in South Africa, with an estimated prevalence of 30% for each.² These organisms are generally resistant to the azoles and often to amphotericin B. Recent epidemiological data has also shown a mycological shift from *Candida albicans* to other non-*albicans* species (NAC) species such as *Candida glabrata*, *tropicalis* and *krusei*. Whereas it is uncertain as to why South Africa in particular has had such an increase in resistant organisms, it is likely that overuse of azoles as prophylaxis and excessive use in immunocompromised patients has contributed to this.

Evidence

- A meta-analysis³ evaluating antifungal treatments for invasive candida infections identified 11 randomised trials. For global response rates, 2 trials looking at echinocandins versus amphotericin B were pooled, with the relative risk (RR) = 1.10 (95% CI, 0.99 to 1.23, p = 0.08). One study compared anidulafungin to fluconazole, which found an RR of 1.26 (95% CI, 1.06 – 1.51) in favour of anidulafungin. For all-cause mortality, for echinocandins versus amphotericin B, 2 pooled trials showed a RR of 1.01 (95% CI, 0.84 to 1.20, p = 0.93); and anidulafungin versus fluconazole resulted in a RR of 0.73 (95% CI 0.48 to 1.10, p = 0.34). For serious adverse effects (2 trials), more severe adverse effects occurred in the amphotericin B patients compared to the echinocandins patients, RR of 0.49 (95% CI, 0.37–0.66, P = <0.0001).

Evidence quality: Reasonable quality randomized controlled trials and meta-analyses

Cost:

	Anidulafungin*	Caspofungin*	Micafungin*	Amphotericin B**	Ampho B liposomal*	Fluconazole**
Cost per daily dose	R2,419.49	R2,888.60	R1,960.80	R89.06	R5,013.94	R31.74

*Single exit price (SEP) database May 2017 ** National Contract, 2018

Recommendation

It is recommended that echinocandins be approved as an essential medicine for specialist use in invasive candidiasis resistant to fluconazole and amphotericin B, and/or where renal dysfunction is present and amphotericin B should be avoided

It is recommended that echinocandins be approved as a class, with the most affordable agent to be procured. (This should take into consideration the availability of a smaller and cheaper ampoule with one of the products) The use of echinocandins should be managed through motivation/appropriate restrictions at facilities, as part of Antimicrobial Stewardship activities. (See addendum – clinical criteria for use)

Review indicators:

- *Availability of amphotericin B, changing resistance patterns, or new evidence.*

¹ Gupta, A., et.al. Indian J Crit Care Med 2015;19:1514.

² Magobo, R., et.al. Emerging infectious diseases. July 2014.

³ Mills EJ, et. al. Annals of Clinical Microbiology and Antimicrobials. 2009, 8(23):1-11.