National Essential Medicine List
Tertiary Level Medication Review Process
Component: ECHINOCANDINS, antimycotics for systemic use

MEDICINE MOTIVATION:

1. **Executive Summary**

Date: July 2017
Medicine (INN): Caspofungin, Micafungin, Anidulafungin - Echinocandins
Medicine (ATC): J02AX04/05/06
Indication (ICD10 code): B37; Invasive Candidiasis (resistant to fluconazole/amphotericin B, and/or where renal dysfunction is present and amphotericin B cannot be used)
Patient population: Hospitalised patients, intensive care
Prevalence of condition: Candidaemia: 3.6 episodes per 10 000 hospitalisations[i]
Level of Care: Tertiary
Prescriber Level: Specialist/consultant
Current standard of Care: Fluconazole/Amphotericin B
Efficacy estimates: (preferably NNT): NNT = 6 (Anidulafungin vs Fluconazole, Global Response), NNT = 12 (Anidulafungin vs Fluconazole, all-cause mortality)[ii]
Motivator/reviewer name(s): G Richards lead for Tertiary ERC

2. **Name of author(s):** Prof Guy Richards (lead) and Tertiary ERC

3. **Author affiliation and conflict of interest details:**

• MSD, Pfizer, Aspen, Cipla, Dr Reddy's, BMS, Fresenius, Boehringer, Pharmacare, Takeda, Novartis, Sanofi, Astra Zeneca, Pharmadynamics, and others. • Aspen Shares - R60 000 (195 shares).	Honoraria/Advisory Boards and Sponsorships to Congresses.	Potentially Significant.

4. **Introduction/ Background**

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 therapy[iii] and is considered to be the 5th to 10th most likely cause of bloodstream infection in these patients.

Species currently cultured include Candida auris and parapsilosis as leading causes of candidaemia in South Africa, with an estimated prevalence of 30% for each.[iv] These organisms are generally resistant to the azoles and often to amphotericin B. Additionally patients with fungaemia may have renal dysfunction where amphotericin B should be avoided.

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.

5. **Purpose/Objective i.e. PICO question** [comparison to current standard of care for a specific indication]: automated

-P *(patient/population):* Fungaemia and renal dysfunction
-I *(intervention):* Echinocandin (caspofungin, micafungin, anadulafungin)
-C *(comparator):* Azoles and amphotericin B
-O *(outcome): global response rates, all -cause mortality, adverse events*

6. Methods:

a. Search Strategy:

((("Echinocandins"[Mesh]) OR "caspofungin" [Supplementary Concept]) OR "micafungin" [Supplementary Concept]) OR "anidulafungin" [Supplementary Concept] AND candidaemia

Limits: Randomised Controlled Trials - 17

Meta-analysis – 15

b. Selection of studies

Randomised controlled trials/Meta-analyses evaluating an echinocandin vs current standard of care (fluconazole or amphotericin B)

c. Evidence synthesis

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes
Mills et.al, 2009.[v]	Meta-analysis	11 studies 965 patients	Confirmed invasive candidiasis, predominantly adults	Amphotericin B Azoles	Primary: Global response rates Secondary: all-cause mortality, Adverse effects	**Global response rates** • Echinocandins vs amphotericin B (2 trials): RR of 1.10 (95% CI, 0.99–1.23, P = 0.08). • Anidulafungin vs fluconazole (1 trial): RR of 1.26 (95% CI, 1.06–1.51). **All cause mortality** • Echinocandins vs amphotericin B (2 trials): RR of 1.01 (95% CI, 0.84–1.20, P = 0.93). • Anidulafungin vs Fluconazole (1 trial): RR of 0.73 (95% CI, 0.48–1.10, P = 0.34). **Serious adverse effects** • Echinocandins vs amphotericin B (2 trials): RR of 0.49 (95% CI, 0.37–0.66, P = <0.0001) in favour of the echinocandins. • Anidulafungin vs fluconazole (RR 0.90, 95% CI, 0.60–1.36, P = 0.66).

Ortega et.al.[vi]

In a study by Ortega et. al. which assessed the influence of new antifungal treatments on candidaemia outcome. The study was divided into two time periods (1994-2003 and 2004 – 2008) according to the introduction of echinocandins. Four hundred and thirty-three candidaemias were analysed. There were 94 deaths in the period without echinocandins, and 38 in the period with echinocandins (p = 0.03). Echinocandins, alone or in combination showed to be associated with better outcomes (OR 0.22, 95% CI 0.06 to 0.81; p = 0.02).

Andes et.al.[vii]

A review of randomised trials by Andes et.al.1, looking at patient-level quantitative treatment of invasive candidiasis assessed the impact of host-, organism-, and treatment-related factors on mortality and clinical cure. This review included 1915 patients. The predictors of mortality were found to be increasing age (p = 0.02), APACHE II score (p = 0.0001), immunosuppressive therapy (p = 0.001) and infection with candida tropicalis (p = 0.01). Conversely the predictors of decreased mortality were the removal of central venous catheter (OR 0.5, 95% CI 0.35 to 0.72, p = 0.0001); and treatment with echinocandins (OR 0.65, 95% CI 0.45 – 0.94, p = 0.02).

d. Evidence quality: *Fair quality. Mills et.al. Meta-analysis conducted search independently and in duplicate, with methodologically advanced approaches to pool and conduct sensitively analyses across a priori defined covariates. Limitations included: no inclusion of unpublished trials, only 3 major clinical outcomes assessed, other outcomes may yield different effects, timing of assessing outcomes varied, and certain studies were industry funded.*

Guideline recommendations:

The Infectious Diseases Society of America, Clinical Practice Guidelines for the Management of Candidiasis[viii] recommends the following:

- Candidaemia in non-neutropenic patients – Echinocandin as initial therapy (strong recommendation, high-quality evidence). Fluconazole can be used as an alternative in select patients - those not critically ill and not considered fluconazole resistant.
- Testing for azole susceptibility is recommended for all blood-stream and other clinically relevant Candida isolates.
- Transition from an echinocandin to fluconazole (usually within 5 – 7 days) recommended for patients who are clinically stable, have isolates that are susceptible to fluconazole (eg. C. albicans), and have negative repeat blood cultures following initiation of antifungal therapy (strong recommendation; moderate-quality evidence).
- Candidaemia in neutropaenic patients – echinocandin as initial therapy (strong recommendation, moderate-quality evidence).

Cultured Species:

The cultured species at Charlotte Maxeke Hospital between January 2017 to April 2017 are displayed below. Two hundred and four candida spp. were isolated from all specimen types that were cultured. The species were identified as follows:

Candida spp.	Number
C.albicans	107
C.auris	14
C.gabrata	13
C.parapsilosis	10
C. krusei	6
C.tropicalis	6
Other species	9

Private Sector, Ampath 2016 data shows that C.parapsilosis is the most common candida species being cultured, followed by C.auris then C. albicans. In the GERM SA Annual Report 2015[ix] the most commonly cultured candida was C. albicans, followed by C.parapsilosis. It was additionally shown in this report that only 46 % of the cultured C.parapsilosis were susceptible to fluconazole. *(see below tables from GERM SA report)*

Table 9. *Candida* species distribution for cases of candidaemia with a viable bloodstream isolate by province, 2014 and 2015, n=659

Species	n (%)								
	EC	FS	GA*	KZ	LP	MP	NC	NW	Overall
Candida albicans	11 (46)	65 (42)	74 (34)	85 (44)	7 (58)	17 (71)	4 (29)	11 (50)	274 (42)
Candida parapsilosis	8 (33)	62 (41)	18 (8)	63 (32)	2 (17)	3 (13)	6 (43)	8 (37)	170 (26)
Candida glabrata	4 (17)	13 (8)	24 (11)	24 (12)	2 (17)	2 (8)	1 (7)	2 (9)	72 (11)
Candida tropicalis	1 (4)	4 (3)	4 (2)	11 (6)	0 (0)	2 (8)	1 (7)	0 (0)	23 (3)
Candida krusei	0 (0)	4 (3)	93 (43)	7 (4)	1 (8)	0 (0)	0 (0)	0 (0)	105 (16)
Other *Candida* species	0 (0)	4 (3)	5 (2)	3 (2)	0 (0)	0 (0)	2 (14)	1 (5)	15 (2)
Total	**24**	**152**	**218**	**193**	**12**	**24**	**14**	**22**	**659**

Table 10. Number and percentage of *Candida* bloodstream isolates (five commonest species only) susceptible* to fluconazole, voriconazole and anidulafungin by broth microdilution testing, 2014 and 2015, n=644

Antifungal agent	Number (%) of isolates susceptible				
	C. albicans	*C. parapsilosis*	*C. glabrata*	*C. tropicalis*	*C. krusei*
Fluconazole	273/274 (99)	78†/170 (46)	N/A**	23/23 (100)	N/A
Voriconazole	273/274 (99)	128†/170 (75)	N/A	23/23 (100)	105/105 (100)
Anidulafungin	274/274 (100)	170/170 (100)	72/72 (100)	23/23 (100)	105/105 (100)

Cost:

Adult costs	Vial strength		Product	Supplier	SEP per vial	Cost per Loading dose	Cost per dose (daily)
Anidulafungin	100	mg	Eraxis	Pfizer	R2,419.49	**R4,838.98**	**R2,419.49**
Caspofungin	50	mg	Cancidas	MSD	R2,888.60		**R2,888.60**
Caspofungin	70	mg	Cancidas	MSD	R2,888.60	**R2,888.60**	
Micafungin	100	mg	Mycamine	Astellas	R1,960.80	**R1,960.80**	**R1,960.80**
Micafungin	50	mg	Mycamine	Astellas	R980.40	**R1,960.80**	**R1,960.80**

**Single exit price (SEP) database May 2017*

	Vial strength		Product	Supplier	Price		Cost/ loading dose	Cost/daily dose (70kg adult)	Cost per/ daily dose incl. vial wastage
Amphotericin B	50	mg	Fungizone	BMS	R44.53	*		**R62.34**	**R89.06**
Liposomal Amphotericin B	50	mg	AmBisome	Key Oncologics	R2,506.97	**		**R3,509.76**	**R5,013.94**
Fluconazole	200	mg	Bio-Fluconazole	Biotech	R15.87	**	**R63.48**	**R31.74**	**R31.74**

**SEP, December 2017*

***National contract price, 2017*

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?

Confident [x] Not confident [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?

Benefits outweigh harms [x] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]</td><td>Needs to be managed as part of Antimicrobial Stewardship efforts.</td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [x] Major [ ] Uncertain [ ]

Is the option acceptable to key stakeholders?
Yes [x] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [ ]</td><td>Cost of medicines/ month:
<table><tr><th>Medicine</th><th>Cost/daily dose (ZAR)</th></tr><tr><td>Anidulafungin</td><td>R2419.49</td></tr><tr><td>Caspofungin</td><td>R2888.60</td></tr><tr><td>Micagungin</td><td>R1960.80</td></tr></table></td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?

Yes [x] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?
Yes [x] No [ ] Uncertain [ ]</td><td></td></tr>
</table>

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	☐	☒

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
- New evidence

References:

[i] Kreusch A, Karstaedt AS. Candidaemia amoung adults in Soweto, South Africa, 1990-2007. International Journal of Infectious Diseases. 2013, 17:e621-e623.

[ii] Reboli AC, et. al. Anidulafungin versus fluconazole for invasive candidemia. NEJM. 2007, 356:2472-2482.

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

[iv] Magobo, R., et.al. Emerging infectious diseases. July 2014.

[v] Mills EJ, Perri D, Cooper C, Nachega JB, Wu P, Tleyjeh I, Phillips P. Antifungal treatment for invasive candida infections: a mixed treatment comparison meta-analysis. Annals of Clinical Microbiology and Antimicrobials. 2009, 8(23):1-11.

[vi] Andes DR, et.al. Impact of treatment strategy on outcomes in patients with candidaemia and other forms of invasivie candidiasis: A patient-level quantitative review of randomized trials. Clinical Infectious Diseases. 2012: 54 (8): 1110-1112.

[vii] Andes DR, et.al. Impact on treatment strategy on outcomes in patients with candidaemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin Infect Dis. 2012, 54(8): 1110 – 1122.

[viii] Pappas, PG, et.al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Infectious Diseases Society of America. 2016. 62(4): e1-50.

[ix] National Institute for Communicable Diseases, division of the National Health Laboratory Services. GERMS South Africa, Annual Report 2015.