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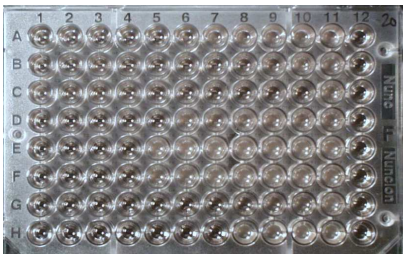
Emerging echinocandin resistance in *Candida*



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Disclosures:
Research grants & Speaker: Astellas, Basilea, Gilead, MSD & Pfizer;
Advisory board: MSD, Pcovery, Pfizer; Acted as consultant for: Alcimed, Astellas, Gilead & Pfizer
Chair(wo)man for EUCAST-AFST

Agenda

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- Echinocandins
  - mechanism of action
  - mechanisms of resistance
- Size of the problem
  - in general
  - specifically for *C. glabrata*
- What to do
  - detection
  - antifungal stewardship

Echinocandin-use: DK vs. Norway (total DDD)

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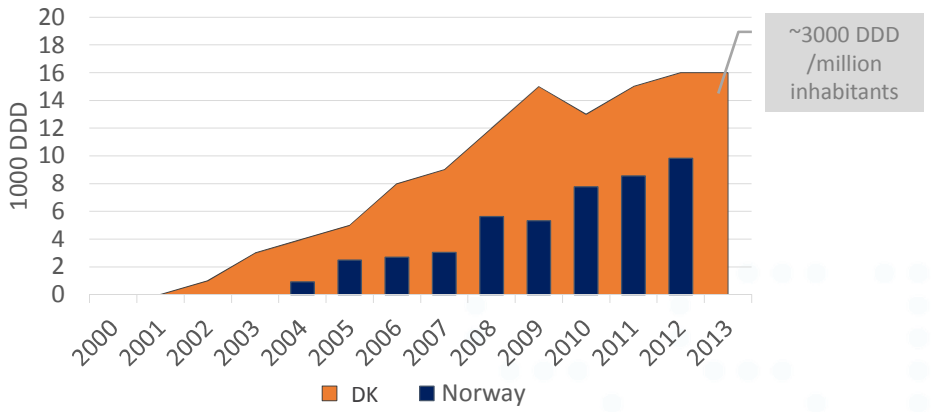

Note:
NO population is 9% smaller than the DK population

Arendrup JCM 2011, CMI 2013, www.medstat.dk & www.legemiddelforbruk.no/english/

M Cavling ARENDRUP

Echinocandins mode of action & resistance

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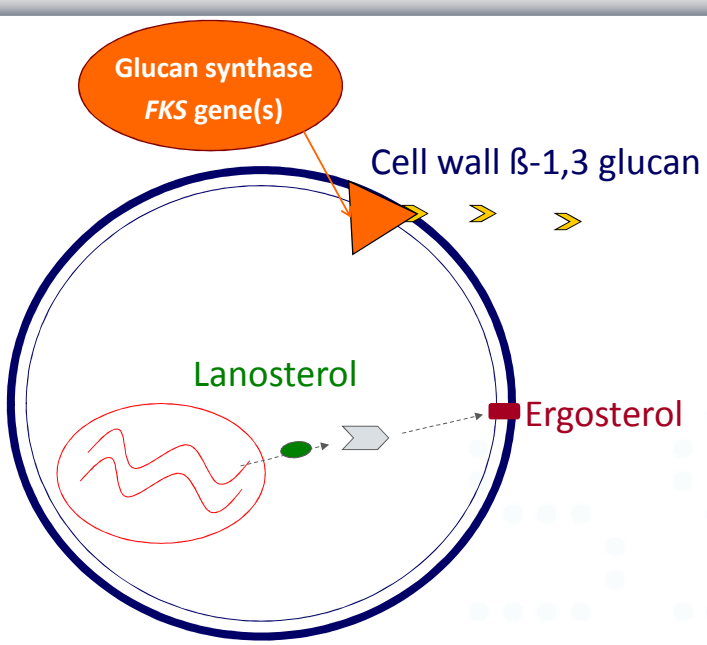

Echinocandins
- Anidulafungin
- Caspofungin
- Micafungin

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Echinocandins mode of action & resistance

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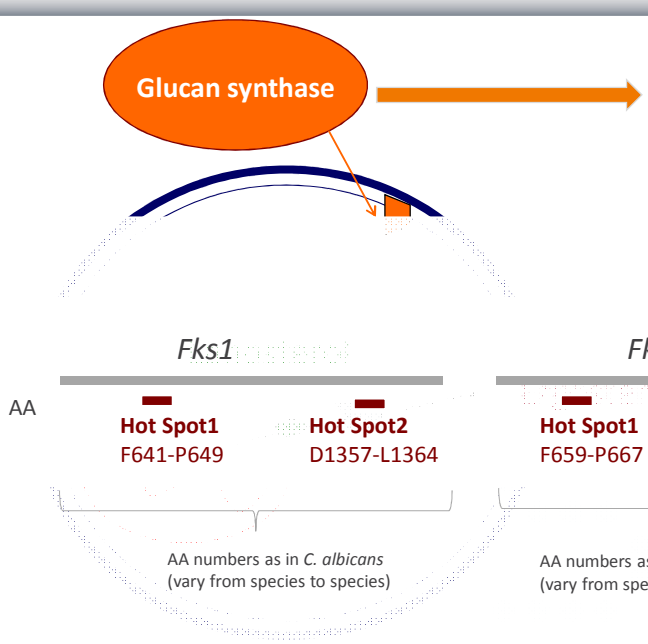

Target gene mutations
Two hot spot regions in:
→ *FKS1*
…but in *C. glabrata* also
→ *FKS2*

Candida Echinocandin resistance: *FKS*

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	AFG EUCAST ECOFF (mg/L)	FKS1p Hot spot 1 1st AA no.	FKS1p Hot spot 1 AA sequence	FKS1p Hot spot 2 1st AA no.	FKS1p Hot spot 2 AA sequence	FKS2p Hot spot 1 1st AA no.	FKS2p Hot spot 1 AA sequence	FKS2p Hot spot 2 1st AA no.	FKS2p Hot spot 2 AA sequence
C. albicans	0.03	641	FLTLSLRDP	1357	DWIRRYTL				
C. dubliniensis	0.03	641	FLTLSLRDP	1357	DWIRRYTL				
C. glabrata	0.06	625	FLILSLRDP	1340	DWVRRYTL	659	FLILSLRDP	1374	DWIRRYTL
C. kefyr	(0.03)	54*	FLTLSLRDP	769*	DWVRRYTL				
C. krusei	0.06#	655	FLILSIRDP	1364	DWIRRYTL				
C. lusitaniae	(0.06)	634*	FLTLSLRDP	**	DWIRRYTL				
C. tropicalis	0.06	76*	FLTLSLRDP	792*	DWIRRYTL				
C. parapsilosis	4	652	FLTLSLRDA	1369	DWIRRYTL				
C. metapsilosis	(4)	104*	FLTLSLRDA	821*	DWIRRYTL				
C. orthopsilosis	(4)	39*	FLTLSLRDA	756*	DWVRRYTL				
C. guilliermondii	(4)	632	FMALSLRDP	1347	DWIRRYTL				
C. lipolytica	NA	662	FLILSLRDP	1387	DWIRRCVL				
S. cerevisiae	(1)	639	FLVLSLRDP	1353	DWVRRYTL	658	FLILSLRDP	1372	DWVRRYTL

X "strong R" mutation, low letters indicate the codon involves a mutation or deletion; high letters indicate the codon involves a mutation or stop codon;
X "weak R" mutation;
X "silent" mutation, acquired or naturally occurring;
X naturally occurring mutation proven or possibly related to the intrinsic lower susceptibility;
X naturally occurring mutation of unknown impact; * Inaccurate annotation, sequencing of entire gene-sequence required;
Micafungin ECOFF elevated for *C. krusei* compared to *C. albicans* and *C. glabrata*, but not the anidulafungin ECOFF.

C. glabrata in mice "S >< I >< R

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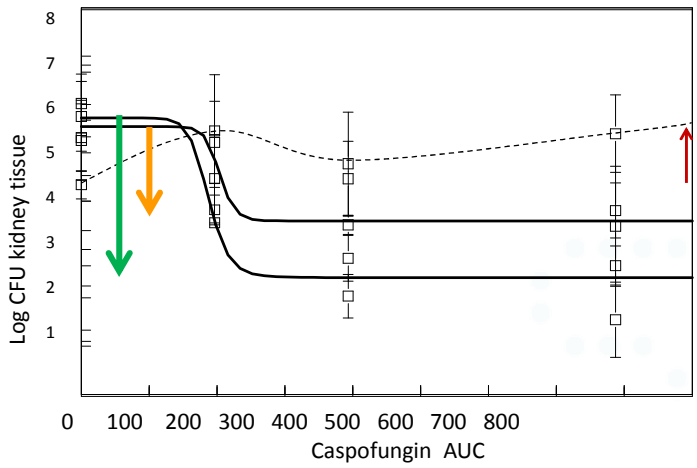
Mice challenged iv with 3 strains: caspofungin MIC 0.25, MIC 1 & MIC 16
Treated ip with caspofungin



RR#24 Fks1p S629P
+1.139 log growth

R#83 Fks2p S663F
-1.850 log reduction

S#3 wild type
-2.728 log reduction

Arendrup AAC 2012

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Same *Fks1* mutation D → Y …. different impact

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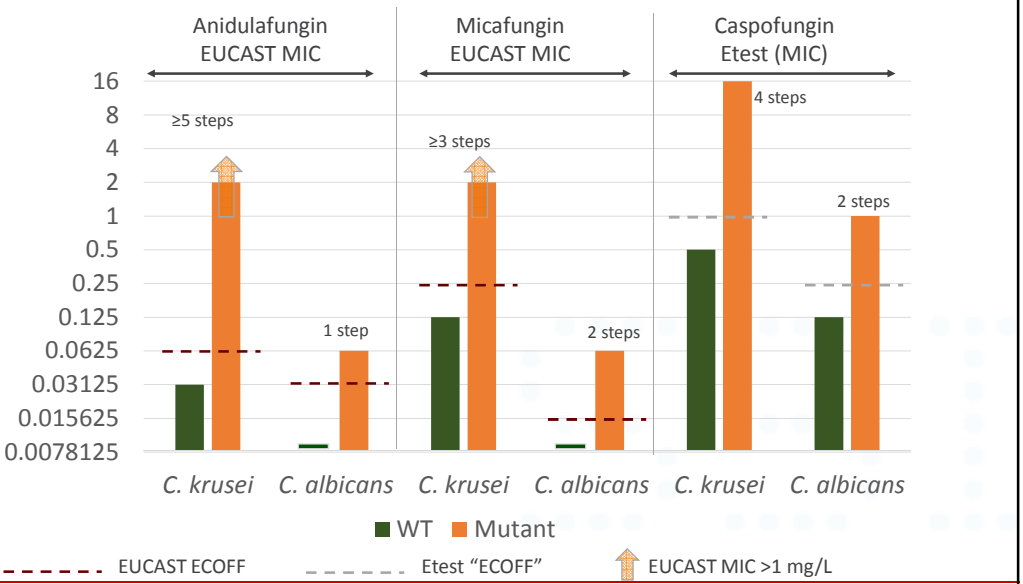
- MIC elevation greater in *C. krusei* D662Y than in *C. albicans* D648Y



Jensen AAC 2014

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France: 20 cases 5.5 years (2004-10)

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- Incidence among *C. albicans*, *C. glabrata* & *C. krusei*
  - 0.4% in the Paris area
- Caspofungin exposure
  - One naïve !
  - Median 26 days (10 days → >8 months)

2004-5: 2 isolates
2006-10: 18 isolates

- Species involved
  - 10 *C. glabrata* – 8 w Fks2p Δ, 1 w Fks1p Δ, 1 w both
  - 8 *C. albicans* – all Fks1p; 7 hot spot 1 Δ, 1 hot spot 2 Δ
  - 2 *C. krusei* – all Fks1p hot spot 1 Δ
- 11/20 were blood isolates
  - 55% Mortality among candidaemia cases

Dannaoui Emerg Inf Dis 2012

US cancer centre: Caspofungin ≥4 mg/L

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- Incidence
  - 1% (7/582 patients)
- Caspofungin exposure preceding 3 months
  - Three naïve ! (but no Fks sequence data)
- Species involved
  - 2 *C. glabrata*
  - 2 *C. albicans*
  - 3 *C. tropicalis*
- 5/7 were blood isolates
  - 1/5 died among candidaemia cases

Kofteridis JAC 2010

C. glabrata echinocandin MIC & outcome

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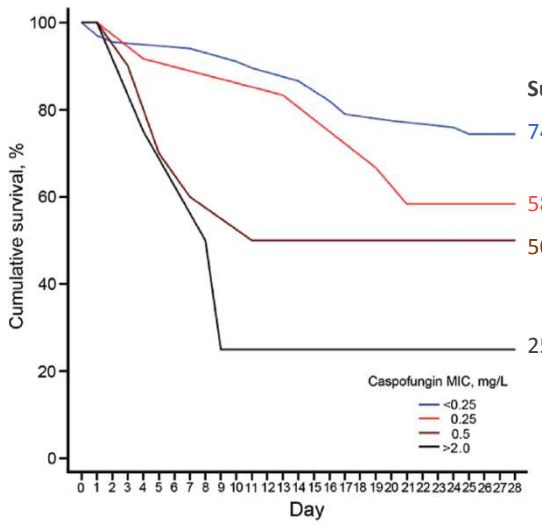
- Cancer patients w 93 blood isolates (2005-13)



Survival day 28

74.6% (50/67) caspofungin MIC<0.25 mg/L

58.3% (7/12) caspofungin MIC 0.25 mg/L

50% (5/10) caspofungin MIC 0.5 mg/L

25% (1/4) caspofungin MIC >2 mg/L

log-rank p = 0.001 for linear trend

Farmakiotis Emerg Inf Dis 2014

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Echinocandin resistance in abdominal candidiasis

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- Echinocandin resistant isolates w *fks* mutations
  - 24% (6/25) patients w intraabdominal candidiasis

- Patient characteristics
  - 25 Pts w echinocandin exposure (median 42 d, 4-438 d)
    - 100% (GI) diseases
    - 92% (23/25) GI surgery ≤ 30 days
    - 44% solid-organ transplant recipients
- Presentation
    - abdominal abscesses (13)
    - peritonitis (8)
    - abscesses & peritonitis (2)
    - cholangitis or cholangitis+peritonitis (1 each).
    - 40% (10/25) were echinocandin breakthrough infections
      - caspofungin (9)
      - micafungin (1)

Shields AAC 2014

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Case

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- 59 year-old ♀, 5 days Abdominal pain & Fever

- X-ray: Intra-peritoneal gas
- GI surgery:
  - Perforation, faecal peritonitis, necrosis of sigmoid colon
  - Resection of sigmoid colon & small bowel
  - Salpingo-oophorectomy
  - Ileostomy and colostomy

- ICU
  - Mechanical ventilation
  - Haemodialysis
  - Broad spectrum ABs

Arendrup AAC 2009

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Case continued

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- Day 4: Antifungal Prophylaxis Fluconazole 400 mg/day
- Day 8: yeast in blood culture, flu→ Caspofungin
- GI surgery due to perforation
  - Day 11: Small bowel resection
  - Day 27: Small bowel resection

Case continued

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- Imaging
  - Day 31: leakage
  - Day 35: mesenteric oedema, liver abscesses, abd abscesses
- GI surgery
  - Surgical debridement, drainage of liver abscesses and rinsing. Day 41, 42 and 43
- Death due to multi-organ failure day 45

Case cont. Mycology & Treatment

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Sample day	Sample type	Result	Treatment
Day 0	Abdominal Pus:	Faecal flora	-
Day 4	Blood, trachea:	*C. albicans* **S**	Flu
Day 7	Blood:	*C. albicans* **S**	Caspo
Day 17	Trachea	*C. albicans* **S**	Caspo
Day 21	Urine	*C. albicans* **S**	Caspo
Day 22	Wound, trachea:	*C. albicans* ND + yeast	Caspo
Day 24	Trachea:	*C. albicans* **S**	Caspo
Day 29	Urine & pus	*C. albicans* **S** & ND	Caspo
Day 35	Catheter tip:	*C. albicans* Caspo **R**	Caspo
Day 38	Urine/Tracheal suction:	*C. albicans* Caspo **R** / Mould	Caspo
Day 39	Peritoneal cavity	*C. albicans* ND	Caspo
Day 40	Tracheal suction:	*C. albicans* / Mould	Caspo+Flu
Day 43	K-Urine/Tracheal suction:	*C. albicans* / Mould	Caspo+Flu
Day 45	Death		

Acquired Resistance

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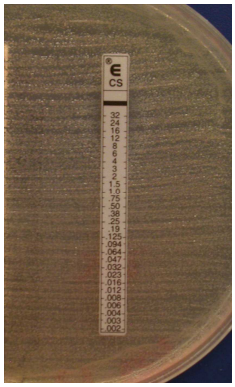
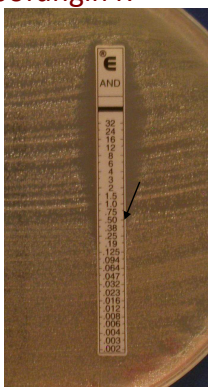
C. albicans Caspofungin R





CAS: >32 µg/ml Anid: 0.5 µg/ml

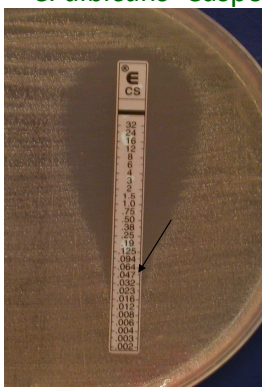
EUCAST:

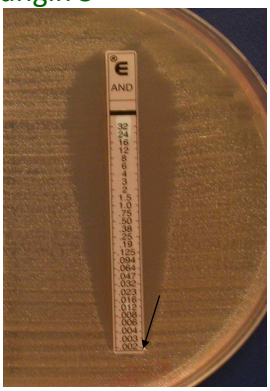
CAS: 2 µg/ml Anid: 0.125 µg/ml

CLSI:

CAS: 1 µg/ml Anid: 0.5 µg/ml

C. albicans Caspofungin S





CAS: 0.06 µg/ml Anid: ≤ 0.002 µg/ml

EUCAST:

CAS: 0.25 µg/ml Anid: ≤ 0.03 µg/ml

CLSI:

CAS: ≤0.06 µg/ml Anid: 0.015 µg/ml

In vivo susceptibility - IV mouse model

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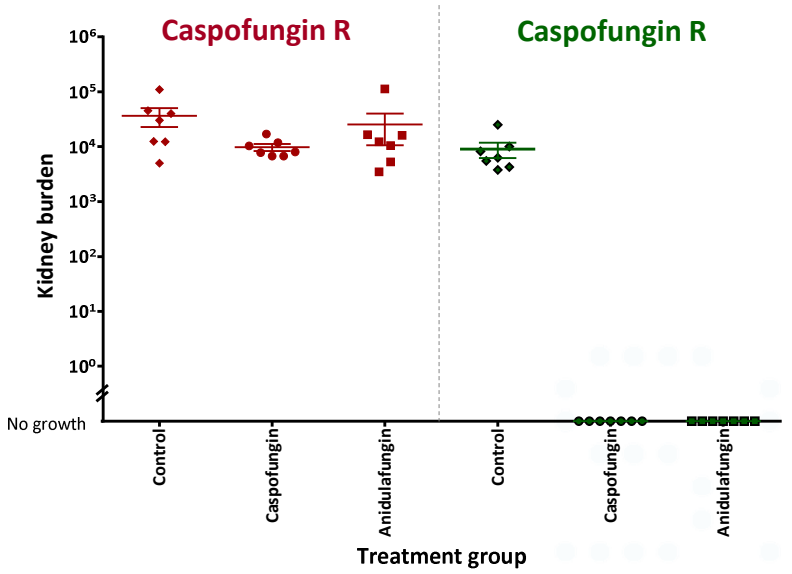

Sequencing of *FSK1*

S645P mutation

Arendrup AAC 2009

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Echinocandin R in *C. glabrata*

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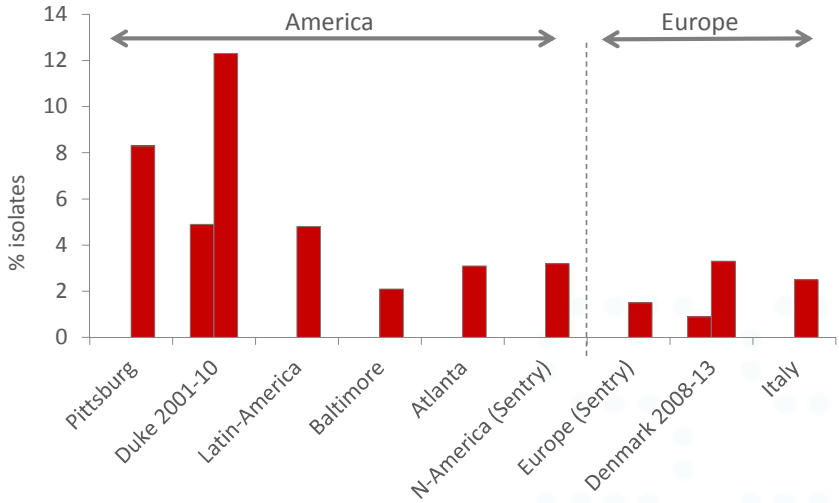

Shields AAC 2013; Alexander CID 2013; Nucci PlosOne 2013; Lockhardt JCM 2012; Pfaller JCM 2011; Arendrup ECCMID 2015; Tortorano Infection 2009.

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Echinocandin-R *C. glabrata* Duke Hosp

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- 2001-10: 274 pt; 293 episodes; 313 *C. glabrata*

Resistance to	2001-2	2009-10	Overall
Echinocandin	4.9%	12.3%	6.7%
Fluconazole	18%	30.1%	24.9%
Echinocandin res in fluconazole res isolates			14.1%

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Echinocandin breakpoints for *Candida* spp

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Breakpoints (BPs): S: ≤X; R: >Y **Revised BPs**

	CLSI M27-S3	CLSI Revised 2011 (M27-S4)	EUCAST
ANF	≤2	≤0.25; >0.5 (alb, krus, trop) ≤0.125; >0.25 (glab) ≤2; >4 (para, guillier)	≤0.032; >0.032 (alb) ≤0.06; >0.06 (glab, krus, trop) ≤0.002; >4 (para) (guillier IE)
CSF	≤2		-
MFG	≤2	≤0.25; >0.5 (alb, krus, trop) ≤0.06; >0.125 (glab) ≤2; >4 (para, guillier)	≤0.016; >0.016 (alb) ≤0.03; >0.03 (glab, krus, trop) ≤0.002; >2 (para) (guillier IE)

www.eucast.org; Pfaller Drug Resist Updat. 2010 & 2011; www.clsi.org

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Etest: Caspofungin and CLSI BP

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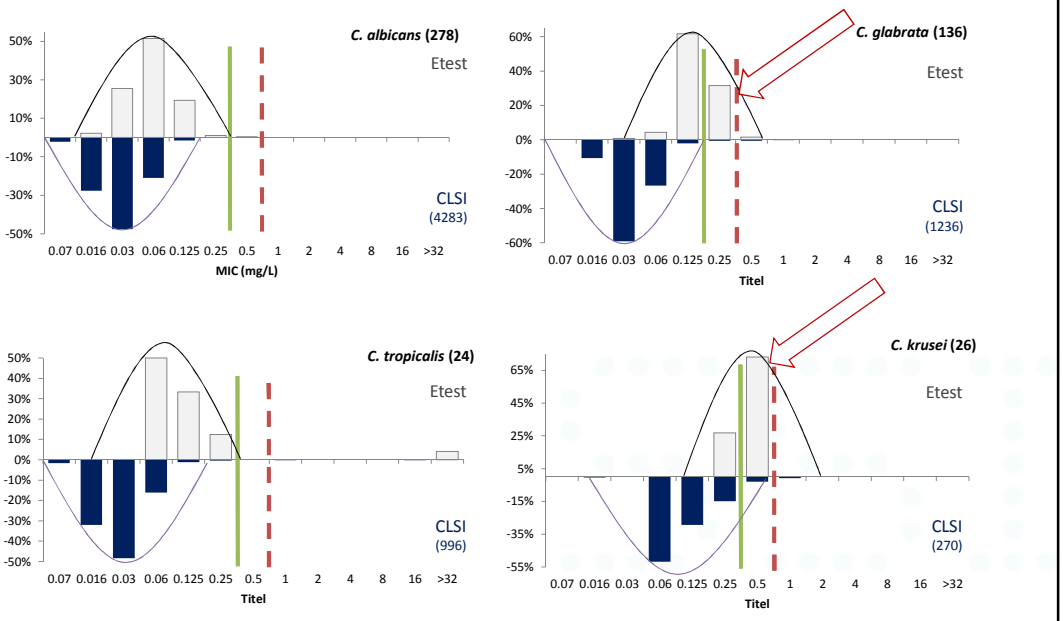

Arendrup & Pfaller AAC 2012

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Echinocandin-R *C. glabrata*

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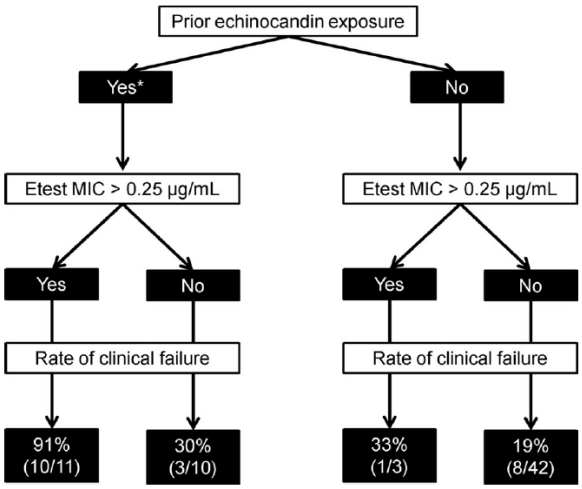
Caspofungin BP proposal for Etest and *C. glabrata*

S ≤ 0.25 mg/L



Shields AAC 2013

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Echinocandin use and resistance

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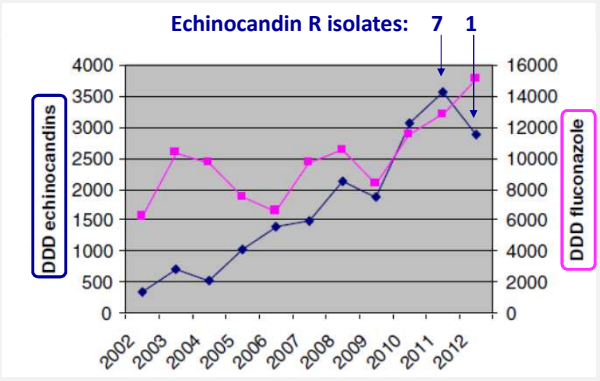
- Fluconazole & Echinocandin use (a Paris tertiary centre)

Year	Patients on echinocandins	DDD/patient	Breakthrough rate
2011	213	16.7	3.3%
2012	216	13.3	0.5%

P: 0.03



Mean exposure for patients with "R" isolates:

33 days
(8-58 days)

Week 1: 0
Week 2: 2
Week 4: 1
Week 5: 1
Week 8: 1
Week 9: 1

Treatment choice after species ID (ESCMID guidelines)

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- *C. parapsilosis*
  - Change to Fluconazole

- *C. glabrata, C. krusei* or another Fluconazole "I/R" strains
  - Continue echinocandin treatment

But avoid >3 weeks whenever possible

- *C. albicans*, *C. tropicalis* and other fluconazole "S" strains
  - Consider Step down to fluconazole
    - If clinically stable and responding
    - After 10 days (ECCMID – based on the Reboli study)
    - Earlier?

Acknowledgements

(in alphabetic order):

The EUCAST Steering Committee

M Cuenca-Estrella
SJ Howard
C Lass-Flörl
J Meletiadis
J Mouton

The EUCAST General Committee

Other collaborators

Jensen RH
Astvad K
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BJ Kullberg
DS Perlin
M Pfaller
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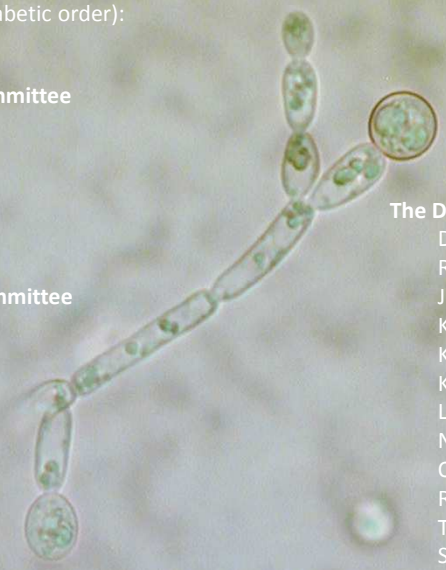
Lemming LE
Nielsen L
Olesen B
Røder B
Thøger Gorm
Schønheyder HC



Thank you for your attention