

An Audit of Antifungal Stewardship in the Netherlands

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Antifungal stewardship

- Rare infections
- Occur at any department → Little personal expertise
- Difficult diagnosis
- Resistance often unknown → Predominantly empirical therapy
- High mortality (25-50%)
- Increasing resistance
- Rapidly changing 'evidence' and guidelines
- High drug costs – most expensive antimicrobials

ReGist



STICHTING WERKGROEP ANTIBIOTICABELEID

Radboudumc



ZonMw

National registry for the
evaluation of treatment patterns,
guideline adherence and
use of expensive antifungals

MSD
Pfizer
Gilead
Pharmo Institute
Pharmerit



STICHTING WERKGROEP ANTIBIOTICABELEID

ReGist

11 hospitals (7 university – 4 large regional) – within 3 years' study period (2010-2012)

976 prescriptions for *therapy* of *invasive* fungal infections

+ other applications (prophylaxis, superficial inf.) of *expensive* antifungals¹

Indications for antifungal treatment

Indication	Number of drug episodes	Number of patients
Invasive infection	976	484
Superficial infection (skin, mucosa)	4	4
Prophylaxis	59	47
Other	3	2
Total	1,042	537

ReGist

Numbers of drug episodes for invasive infections by organism and type of treatment

	Directed therapy	Empirical therapy	Pre-emptive therapy (diagnostic-driven)
	Drug episodes	Drug episodes	Drug episodes
Aspergillus	122	73	234
Candida	351	76	6
Cryptococcus	4	0	-
Zygomycete	0	5	9
Other*	59	9	4
Total	543	163	253

- ✓ Weinig emirisch therapie
- ✓ Candida: Voor gerichte therapie (kweek-postief)
- ✓ Aspergillus: Pre-emptieve (diagnostic-driven) & gerichte therapie

ReGist

Numbers of drug episodes for invasive infections by organism and type of treatment

	Directed therapy	Empirical therapy	Pre-emptive therapy (diagnostic-driven)
	Drug episodes	Drug episodes	Drug episodes
Aspergillus	122	73	234
Candida	351	76	6
Cryptococcus	4	-	-
Zygomycete	7	5	9
Other*	59	9	4
Total= 959	543	163	253

- ✓ Little empirical therapy
- ✓ *Candida*: mainly directed therapy (positive cultures)
- ✓ *Aspergillus*: Pre-emptive (diagnostic-driven) & directed therapy

Adherence to guidelines

ReGist – Drug choices

Drug use by indication	Aspergillus		Candida	
Including first/second line	n	%	n	%
Conventional amphot B	4	1%	1	0%
Lipid-associated AmB	41	11%	9	2%
Echinocandin	30	7%	197	46%
Fluconazole	4	1%	200	47%
Itraconazole	4	1%	0	0%
Posaconazole	10	2%	0	0%
Voriconazole	333	78%	17	4%
		First line: 86%		
Total	426		424	

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Outcomes – Invasive aspergillosis

Aspergillus First line Directed and Pre-emptive therapy	Voriconazole	
	N	%
First line treatment	95	
Treatment Success	50	52.6%
Treatment Failure		
- Lack of efficiency	31	32.6%
- Death	9	9.5%
- Adverse event		

Room for improvement:

- ✓ Diagnostics
- ✓ Dosing / therapeutic drug monitoring

Herbrecht et al, N Engl J Med 2002:

Voriconazole 52.8%

Amphotericin B 31.6%

The New England Journal of Medicine

VORICONAZOLE VERSUS AMPHOTERICIN B FOR PRIMARY THERAPY OF INVASIVE ASPERGILLOSIS

RAOUL HERBRECHT, M.D., DAVID W. DENNING, F.R.C.P., THOMAS F. PATTERSON, M.D., JOHN E. BENNETT, M.D., REGINALD E. GREENE, M.D., JÖRG-W. OESTMANN, M.D., WINFRIED V. KERN, M.D., KIEREN A. MARR, M.D., PATRICIA RIBAUD, M.D., OLIVIER LORTHOLARY, M.D., PH.D., RICHARD SYLVESTER, Sc.D., ROBERT H. RUBIN, M.D., JOHN R. WINGARD, M.D., PAUL STARK, M.D., CHRISTINE DURAND, M.D., DENIS CAILLOT, M.D., ECKHARD THIEL, M.D., PRANATHARTHI H. CHANDRASEKAR, M.D., MICHAEL R. HODGES, M.D., HARAN T. SCHLAMM, M.D., PETER F. TROKE, PH.D., AND BEN DE PAUW, M.D., FOR THE INVASIVE FUNGAL INFECTIONS GROUP OF THE EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER AND THE GLOBAL ASPERGILLUS STUDY GROUP*

ReGist

Outcomes – Invasive candidiasis

First-line directed therapy of culture-proven invasive candidiasis

	Caspofungin		Anidulafungin		Fluconazole		Voriconazole	
	N	%	N	%	N	%	N	%
	33		46		66		2	
Treatment Success	28	85%	34	74%	39	59%	2	100%

ReGist

Outcomes – Invasive candidiasis

First-line directed therapy of culture-proven invasive candidiasis

	Caspofungin		Anidulafungin		Fluconazole		Voriconazole	
	N	%	N	%	N	%	N	%
	33		46		66		2	
Treatment Success	28	85%	34	74%	39	59% (p<0.01)	2	100%

ReGist

Outcomes – Invasive candidiasis

First-line directed therapy of culture-proven invasive candidiasis

	Caspofungin		Anidulafungin		Fluconazole		Voriconazole	
	N	%	N	%	N	%	N	%
	33		46		66		2	
Treatment Success	28	85%	34	74%	39	59%	2	100%
Treatment Failure:								
- Lack of efficiency	4	3%	4	9%	24	36%	0	0%
- Death	1	12%	7	15%	2	3%	0	0%
- Adverse event	0	0%	1	2%	1	2%	0	0%

ReGist

Severity of illness – Invasive candidiasis

Directed therapy of culture-proven invasive candidiasis

Characteristic	Caspofungin	Anidulafungin	Fluconazole	Voriconazole
No. of patients	37	54	74	3
Baseline Karnofsky score (100 → 0) (SD)	43.5 (23.1)	27.8 (18.5)	46.4 (24.4)	23.3 (5.77)
APACHE II score (0 → >30)	13.6 (7.0)	17.3 (9.9)	13.3 (8.1)	8.0 (n/a)

Each point increase:
Mortality OR +1.11;
Success OR - 0.94

ReGist

Severity of illness – Invasive candidiasis

Directed therapy of culture-proven invasive candidiasis

Characteristic	Caspofungin	Anidulafungin	Fluconazole	Voriconazole
No. of patients	37	54	74	3
Baseline Karnofsky score (100 = 0)	43.5	27.8	46.4	23.3
APAC Hematology ↔ (0 → caspofungin)	13.6	17.3	13.3	8.0
Comorbidities	N (%)			
- Hematologic malignancy	8 (22)	3 (6)	1 (1)	1(33)
- Chemotherapy	7 (19)	4 (7)		1(33)
- Organ transplant	5 (14)	6 (11)		1(33)
- Invasive surgical procedure	17 (46)	44 (82)	44 (60)	2(67)
Admitted to ICU (%)	32%	89%	43%	100%

Prescription bias:
APAC Hematology ↔ caspofungin

Prescription bias:
ICU ↔ anidulafungin

ReGist

Outcomes – Invasive candidiasis

First-line directed therapy of culture-proven invasive candidiasis

	Caspofungin		Anidulafungin		Fluconazole		Voriconazole	
	N	%	N	%	N	%	N	%
	33		46		66		2	
Treatment Success	28	85%	34	74%	39	59%	2	100%
APACHE II score	22	13.6	41	17.3	48	13.3	1	8.0
Admitted to ICU (%)		32%		89%		43%		100%

Reboli et al, N Engl J Med 2007:

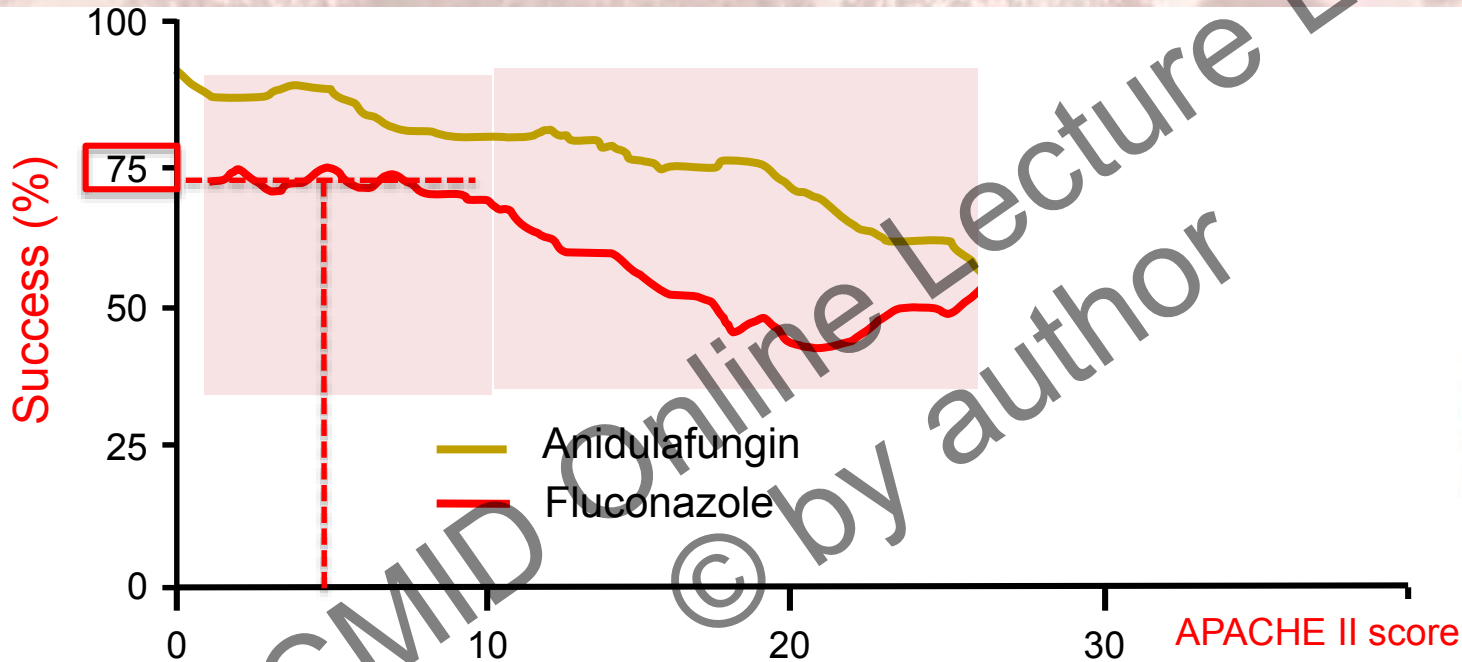
Anidulafungin 75.6%

Fluconazole 60.2%

Anidulafungin versus Fluconazole for Invasive Candidiasis

Annette C. Reboli, M.D., Coleman Rotstein, M.D., Peter G. Pappas, M.D., Stanley W. Chapman, M.D., Daniel H. Kett, M.D., Deepali Kumar, M.D., Robert Betts, M.D., Michele Wible, M.S., Beth P. Goldstein, Ph.D., Jennifer Schranz, M.D., David S. Krause, M.D., and Thomas J. Walsh, M.D., for the Anidulafungin Study Group

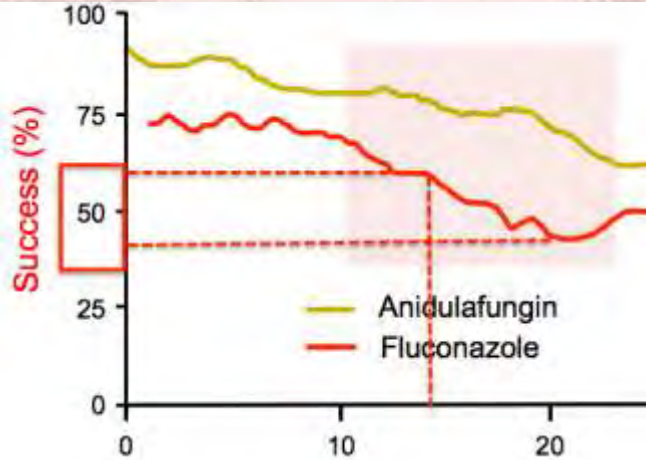
Echinocandin vs. fluconazole for candidemia



IDSA 2009 Guidelines (and SWAB 2008)

The Expert Panel favors an echinocandin for patients with moderately severe to severe illness (...).

Fluconazole is recommended for patients who are less critically ill (...)



ReGist es – Invasive candidiasis

of culture-proven invasive candidiasis

	Caspofungin		Anidulafungin		Fluconazole		Voriconazole	
	N	%	N	%	N	%	N	%
	33		46		66			
Treatment Success	28	85%	34	74%	39	59%		
APACHE II score	22	13.6	41	17.3	48	13.3		
Admitted to ICU (%)		32%		89%		43%		



IDSA 2009 Guidelines (and SWAB 2008)

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Fluconazole is recommended for patients who are less critically ill (...)

Echinocandin versus fluconazole for candidemia

Mycoses Study Group 02 Study – Pooled analysis

- ✓ 1915 patients - Individual patient-level pooled analysis of 7 candidemia trials
- ✓ Logistic regression using 30-day mortality as primary outcome:

✓ Increased mortality:

	OR	p
✓ Age	1.01	0.02
✓ APACHE II score	1.11	0.0001

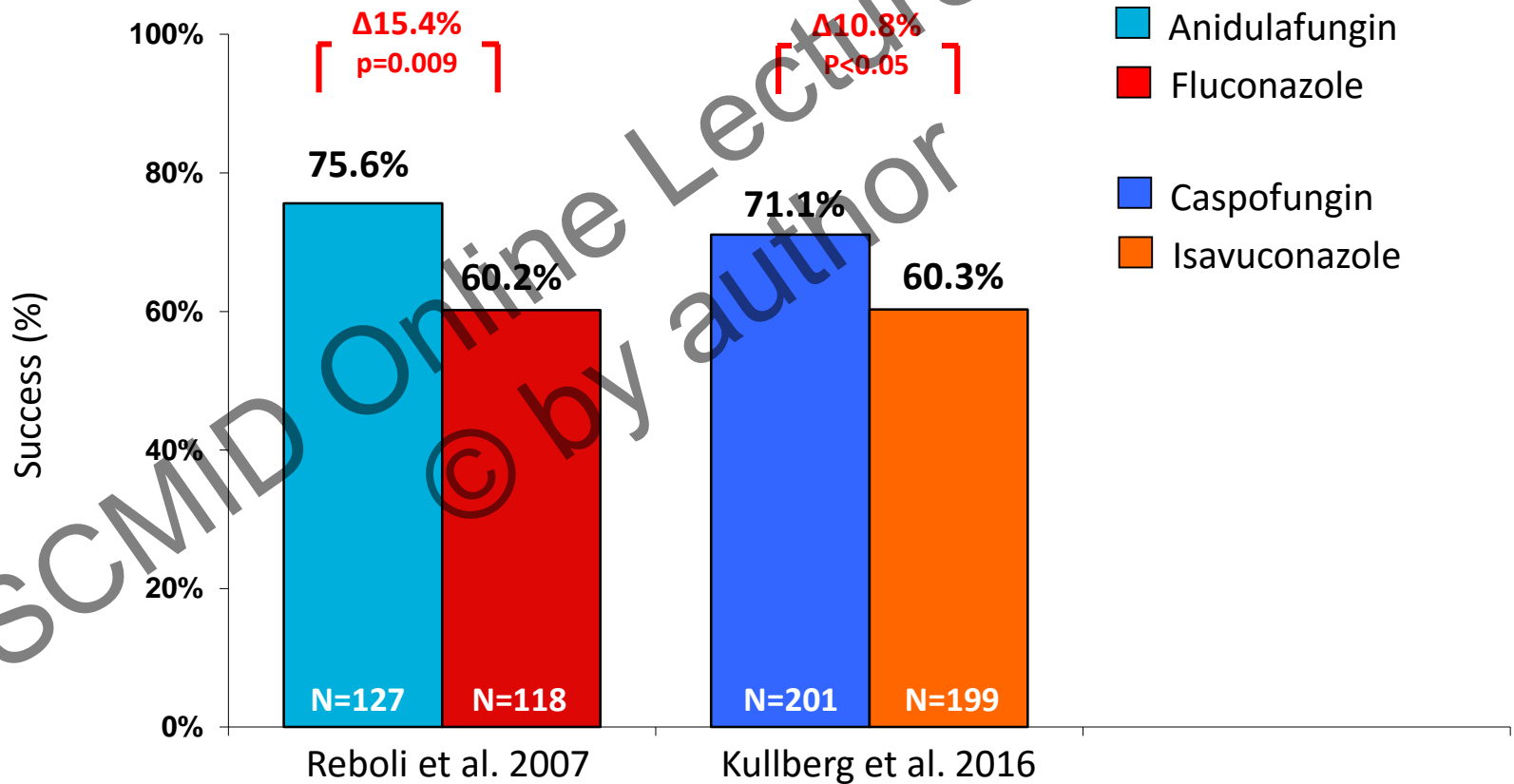
✓ Decreased mortality:

✓ Echinocandin antifungal	0.65	0.02
✓ CVC removal during therapy	0.50	0.0001

✓ Success:

✓ APACHE II score	0.94	0.0001
✓ Echinocandin antifungal	2.33	0.01
✓ CVC removal during therapy	1.69	0.002

Echinocandin versus fluconazole for candidemia



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Conclusions

- ✓ Very restrictive use of empirical therapy
- ✓ Treatment choice for invasive aspergillosis according to guidelines (86%)
- ✓ Patient outcomes similar to those in pivotal randomized trial
- ✓ Treatment choice for candidemia/invasive candidiasis not according to 2008 guidelines
- ✓ Patient outcomes similar to those in 2007 pre-guidelines randomized trial
- ✓ Excess failure rates associated with inappropriate fluconazole prescriptions

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