



Leiden University
Medical Center

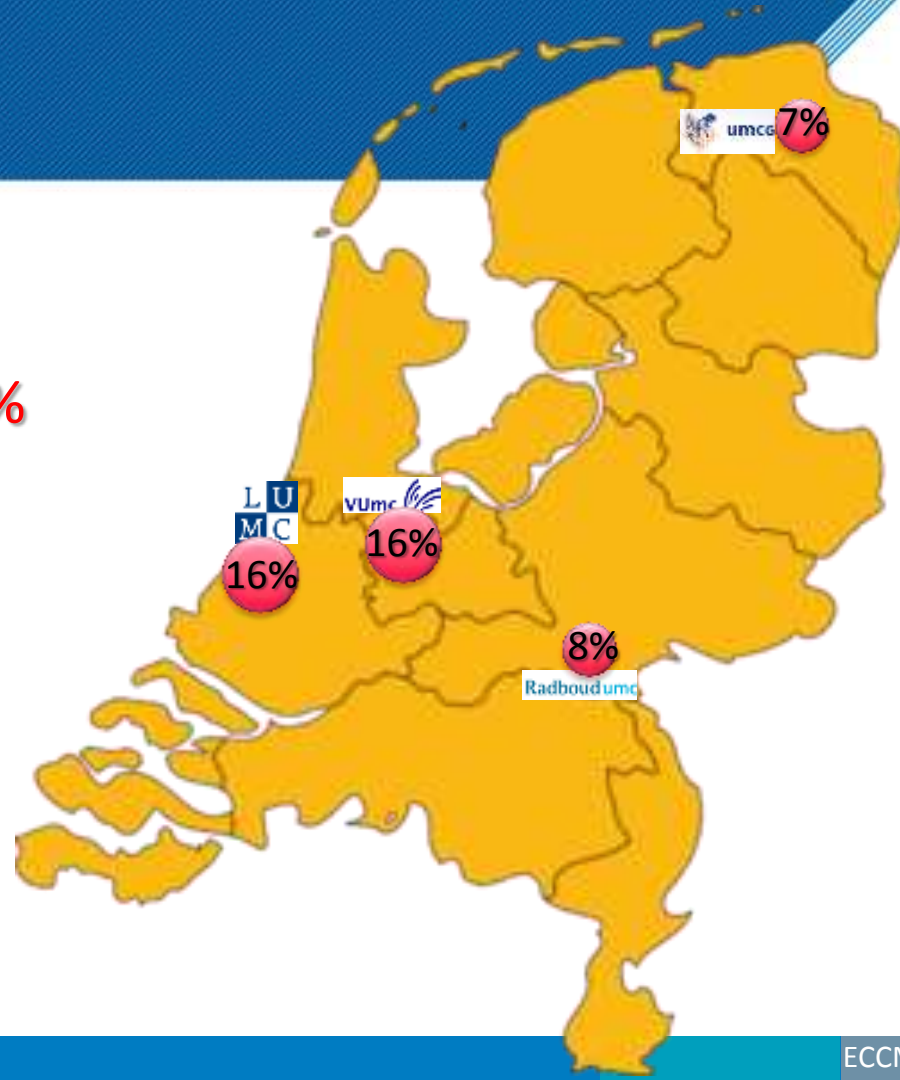
Management and outcome of invasive aspergillosis and voriconazole resistance

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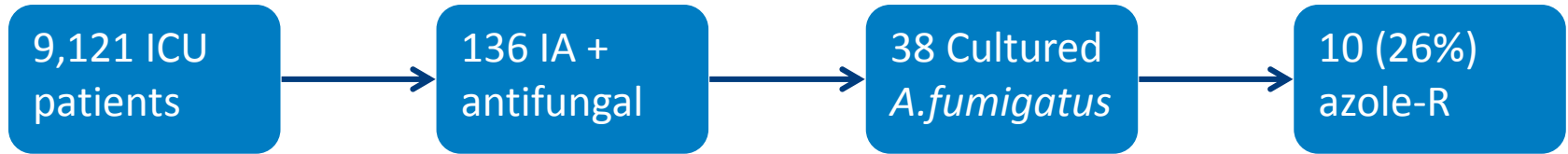
Background

Total resistance in 2015
in the Netherlands 10,7%

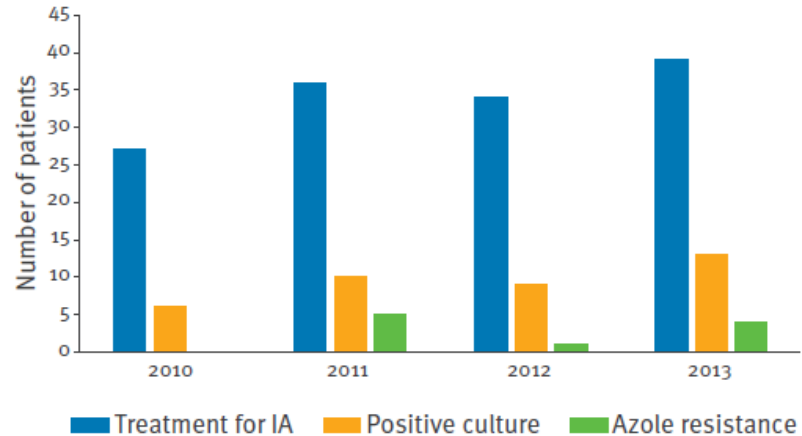


Background

Emerging azole-resistant *Aspergillus fumigatus* in Leiden the Netherlands



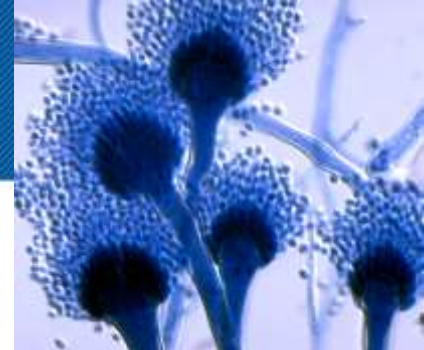
- Overall 90-day mortality:
azole-resistant 100% (10/10)
azole-susceptible 82% (23/28)
- Most IA cases no susceptibility info →



Management and outcome of invasive aspergillosis in high prevalence of voriconazole resistance

Inclusion: all culture positive IA, LUMC cases from 2011 till 2015

- Classification probable, proven or putative
 - EORTC/MSG and Blot (ICU)
- Voriconazole-susceptible (VS) and resistant (VR)
 - Phenotypical and molecular testing Nijmegen
- 1) overall- 2) attributable mortality at 90 days



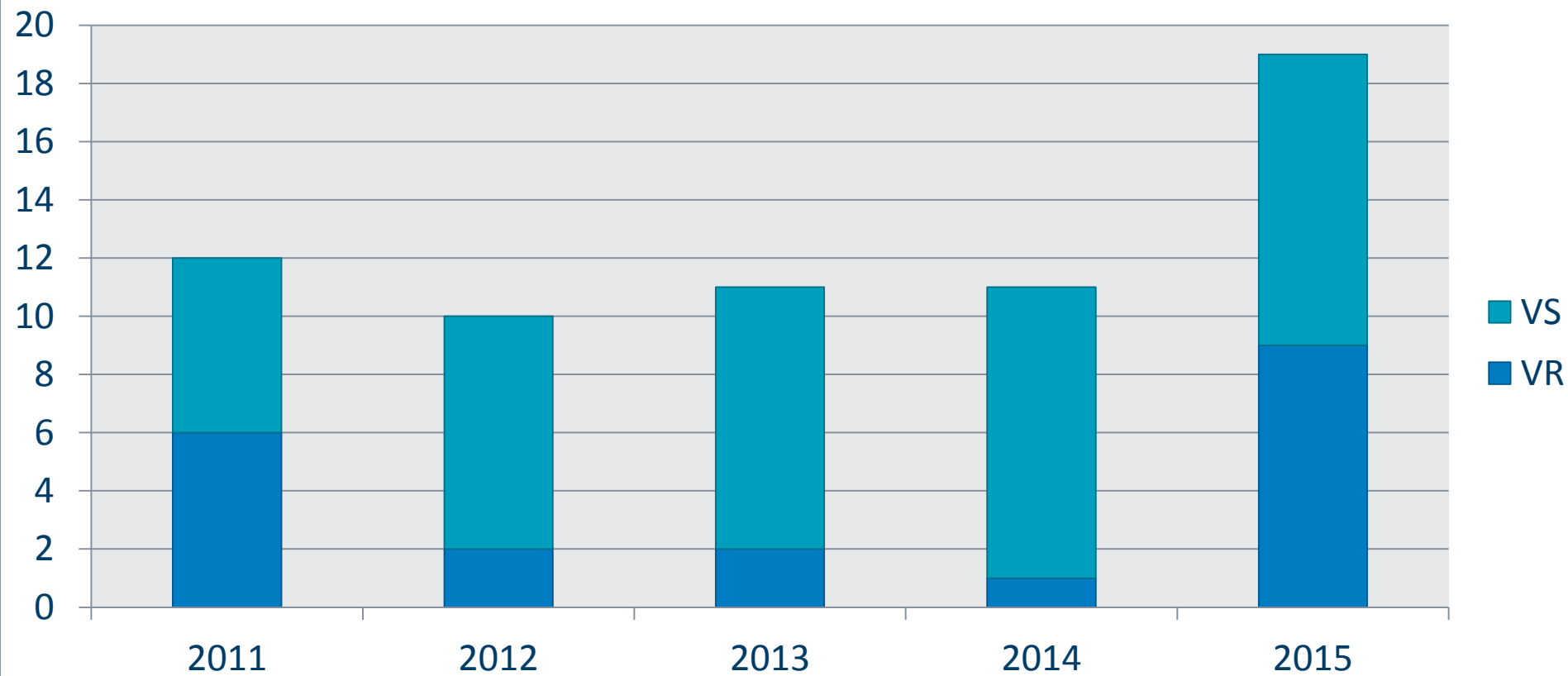
Attributable mortality in invasive aspergillosis

- Attributable to invasive aspergillosis
 - (1) did not respond to therapy (stable or disease progression);
 - (2) partial response who died involving any of the sites of infection;
 - ~~(3) result of the toxicity of antifungal therapy.~~
- Attributable to underlying disease
- Both
- Unknown

Demographics and classification of culture positive IA

Characteristics n=63		VR cohort 20 (32%)	VS cohort 43 (68%)	p-value
Age, mean years (range)		52 (5–71)	60 (19–80)	
Male sex (percentage)		12 (60)	27 (63)	
ICU stay		12 (60)	28 (65)	
Prophylaxis		8 (40)	13 (30)	
Underlying condition	Hematologic malignancy	14 (70)	21 (49)	p 0.1735
	Stem cell transplantation	7 (35)	14 (33)	
	Structural lung disease	2 (10)	4 (9)	
Solid organ transplantation		1 (5)	4 (9)	
Neutropenic episode		9 (45)	10 (23)	p 0.1387
Site of infection	Pulmonary only	17 (85)	37 (86)	
	Disseminated	1 (5)	3 (7)	
	Other	2 (10)	4 (9)	
Classification of IA:	Putative	5 (25)	10 (23)	p 0.4176
	Probable	14 (70)	26 (60)	
	Proven	1 (5)	7 (16)	

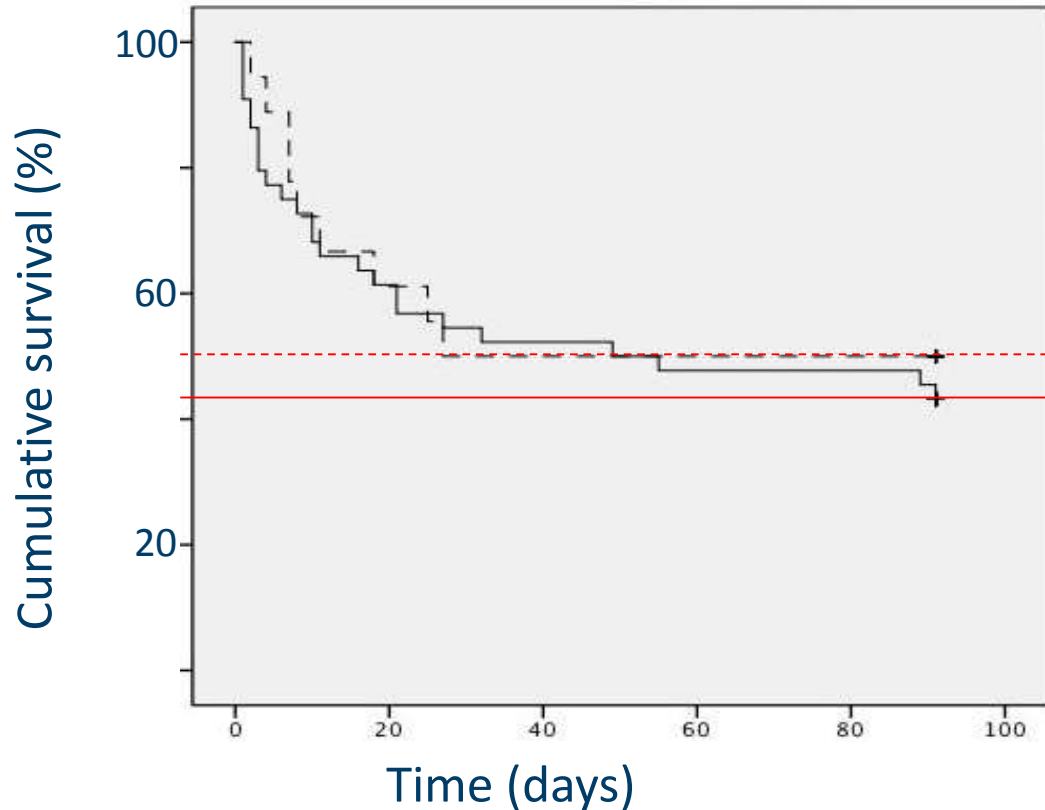
Prevalance of culture positive IA



Outcome of culture positive IA

Mortality	VR cohort 20 (32%)	VS cohort 43 (68%)	p-value
All cause	53% (10/19)	58% (25/43)	ns

Outcome of culture positive IA



Cumulative 90-day survival

— Voriconazole susceptible

-- Voriconazole resistant

Outcome of culture positive IA

Mortality	VR cohort 20 (32%)	VS cohort 43 (68%)	p-value	
All cause	53% (10/19)	58% (25/43)	ns	
2011-2013	8/10 (80%)	14/23 (61%)	p = 0.4300	VR: 2011-13 versus 2014-15 p = 0.0230
2014-2015	2/9 (22%)	11/20 (55%)	p = 0.1296	
Attributable	42% (8/19)	36% (15/42)	ns	
2011-2013	7/10 (70%)	9/23 (39%)	p = 0.1411	VR: 2011-13 versus 2014-15 p = 0.0198
2014-2015	1/9 (11%)	6/19 (32%)	p = 0.3715	
Hematologic patients	5/13 (38%)	9/21 (43%)	ns	ICU versus non-ICU stay 30/39 – 5/23 p < 0.0001
Delay	7/15 (47%)	n.a.	n.a.	
Prophylaxis	5/8 (63%)	5/13 (38%)	ns	
ICU stay	8/11 (72%)	22/28 (79%)	ns	

Conclusion

All cause and attributable mortality was not significantly different in azole resistant or azole susceptible IA cases.

Delay in appropriate treatment was not found to contribute to mortality.

ICU stay was significantly related to mortality.

A new IA management algorithm to target azole resistance **coincides** with a **decrease of overall mortality**.

Discussion

Attributable mortality for IA is complex and needs standardization.

A possible limitation is the evaluation of **culture positive** cases only.

Susceptibility testing needs further improvement, i.e. with **molecular methods**.

New treatment algorithms are vital in areas with high prevalence of **voriconazole resistance***.

LUMC - Invasive Fungal Infection

Severely ill patients

1. Respiratory insufficiency by Aspergillosis
2. Haemoptysis
3. Neutropenia > 2 weeks
4. Post-SCT Recurrence of malignancy
5. GvHD immunosuppressives
6. Azole pretreatment

None of the criteria :

Voriconazole

400 mg bid per os followed by 200 mg bid;
TDM

One or more criteria:

Liposomal Amphotericin B

3 mg/kg od iv;

De-escalation based on clinical evaluation after 2 weeks or susceptibility-guided



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