Is pre-emptive therapy a realistic approach?

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Is pre-emptive therapy a realistic approach?

YES

NO

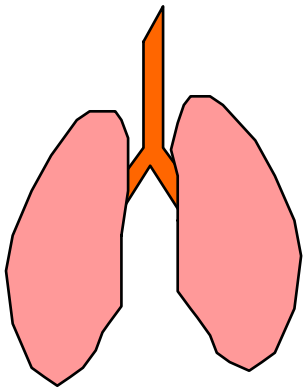
Contents

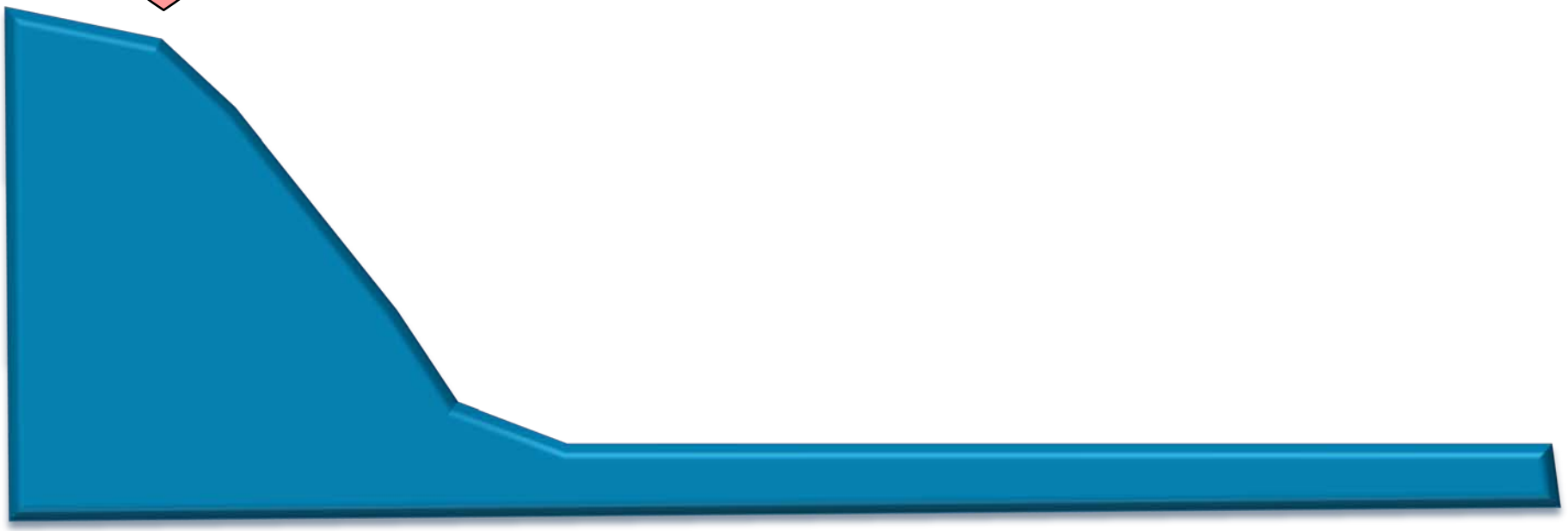
- Evolution of pulmonary IFD
- Treatment strategies
- Evidence for preemptive approach
- Future initiatives

Evolution of invasive mould disease

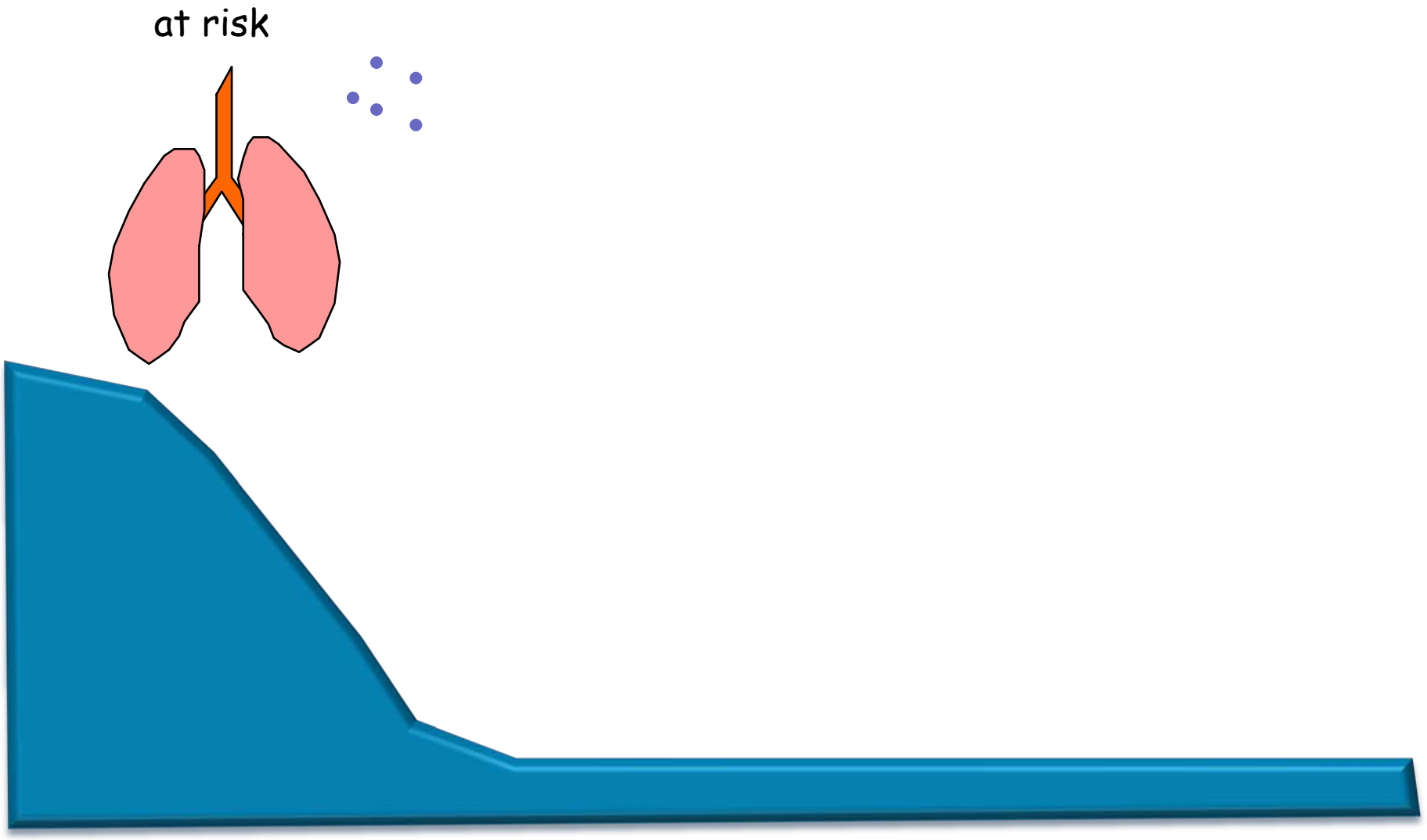
What if invasive mould disease...

at risk

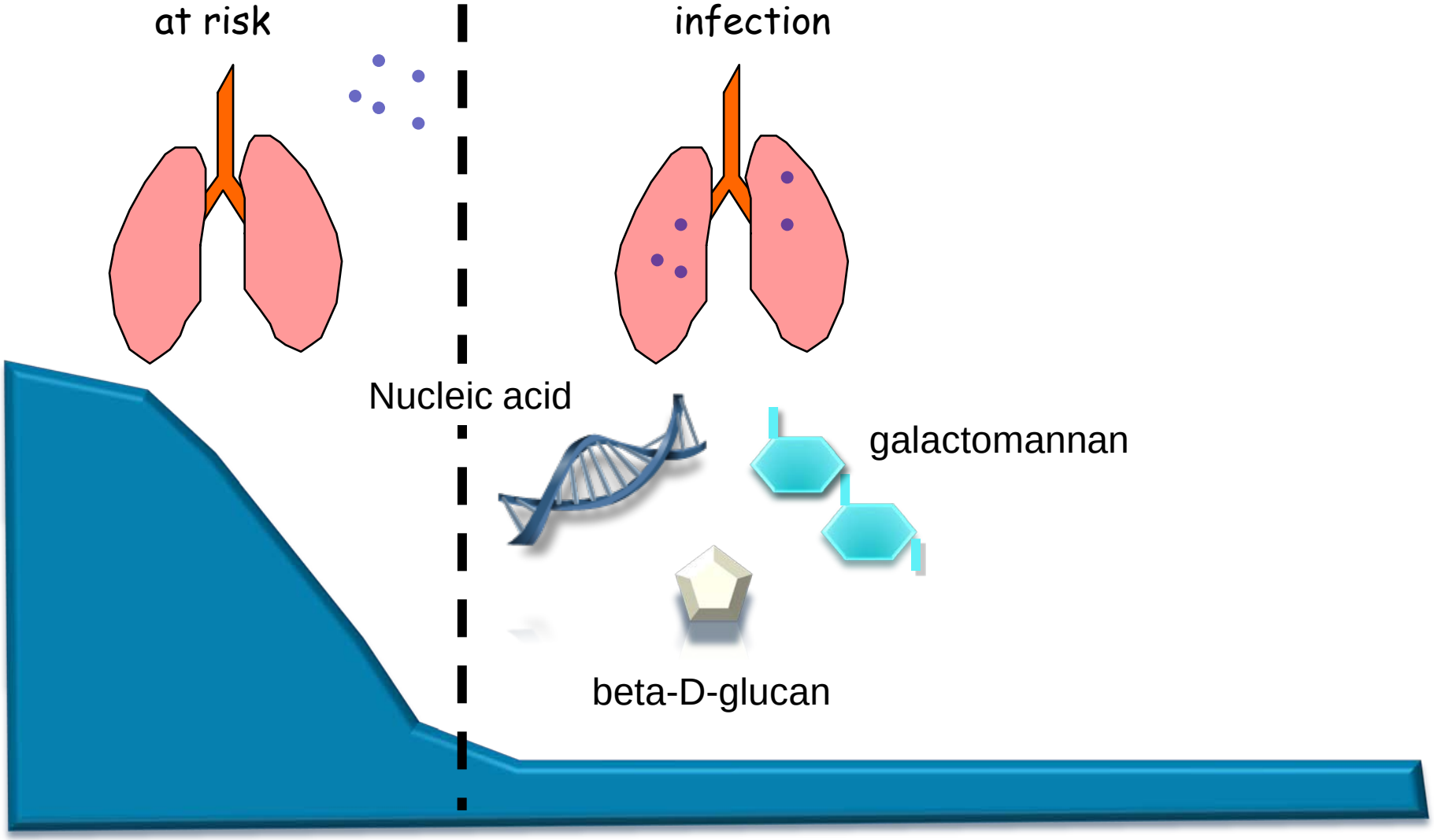




... begins with colonisation ...



... then progresses to infection ...



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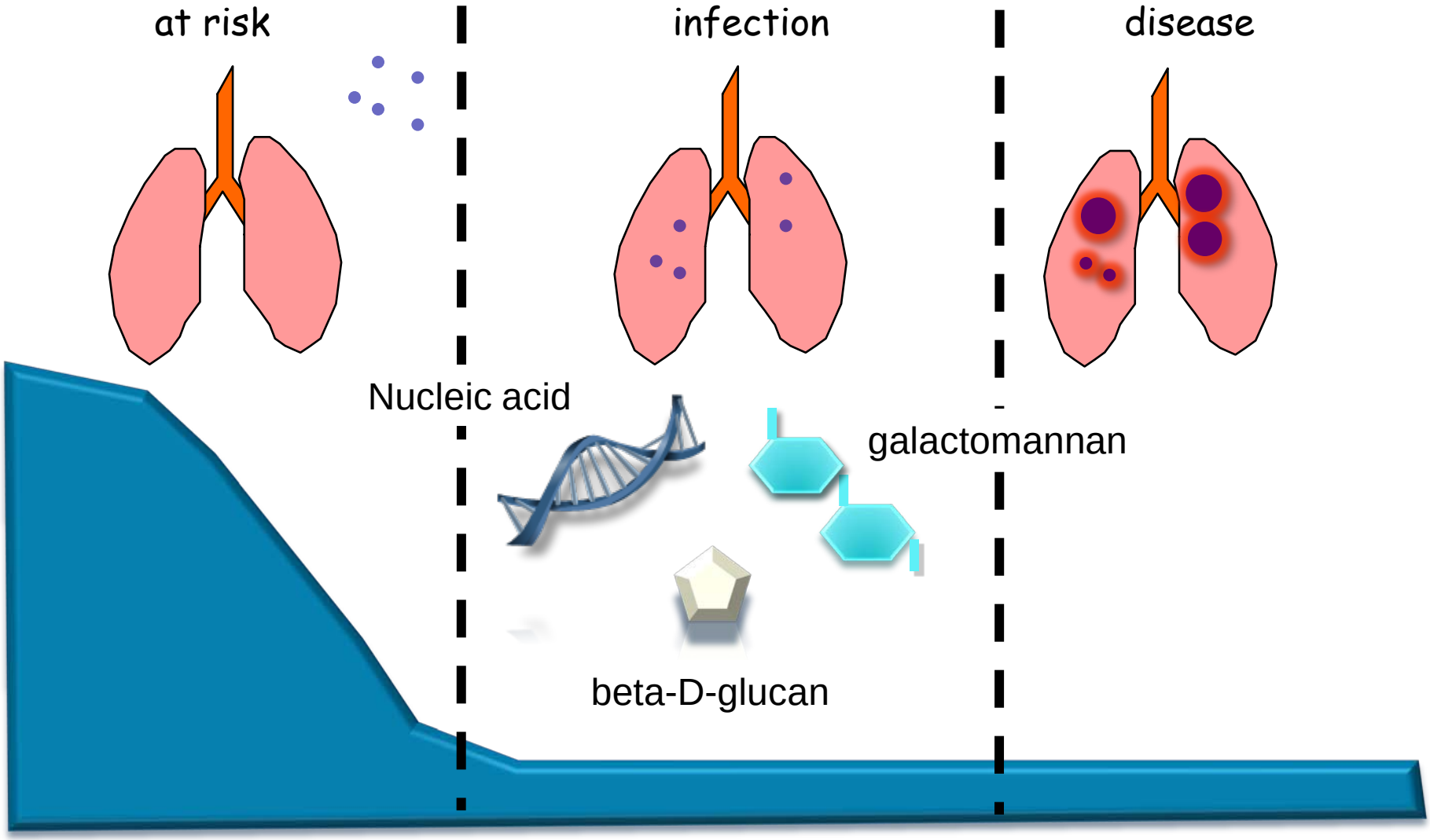
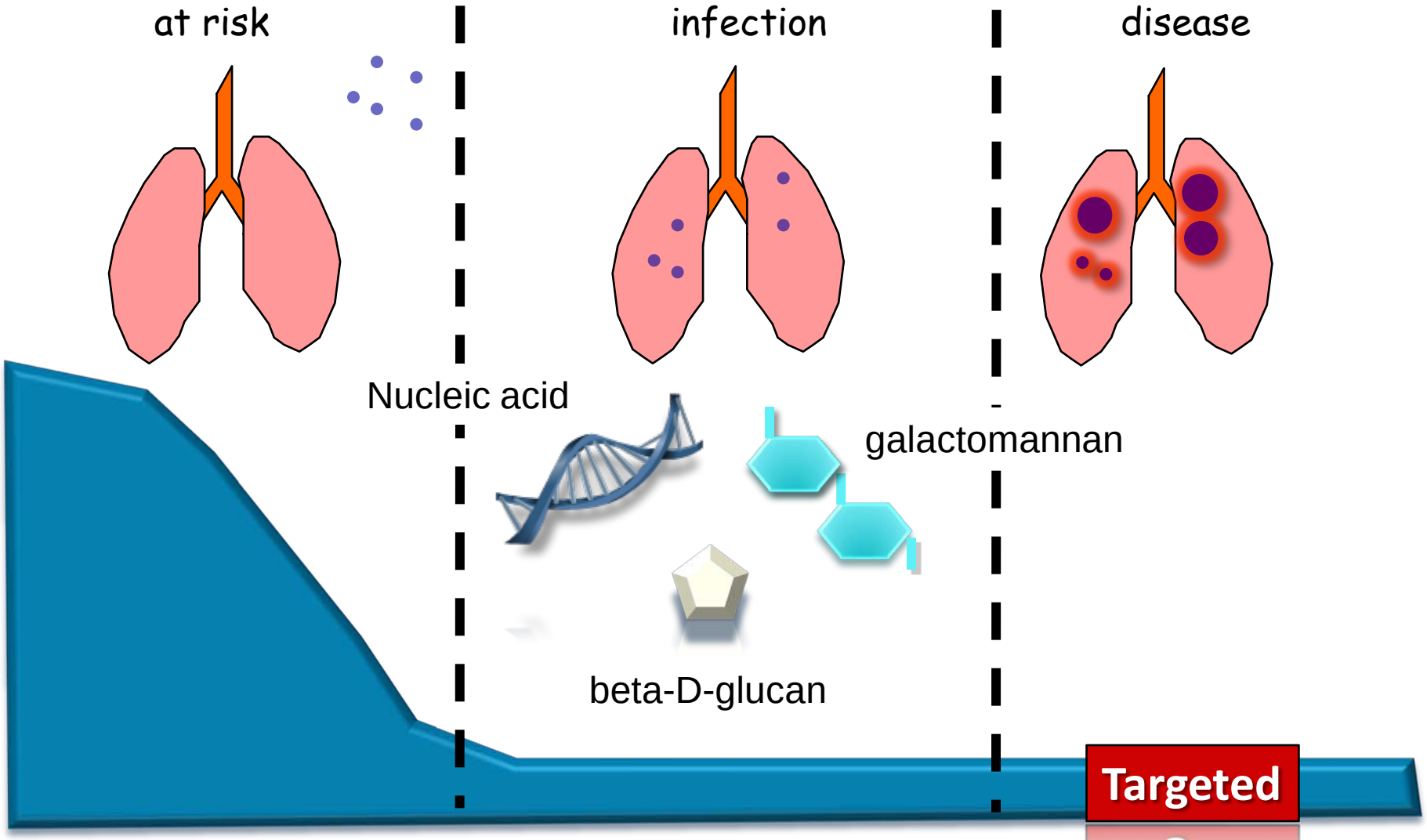
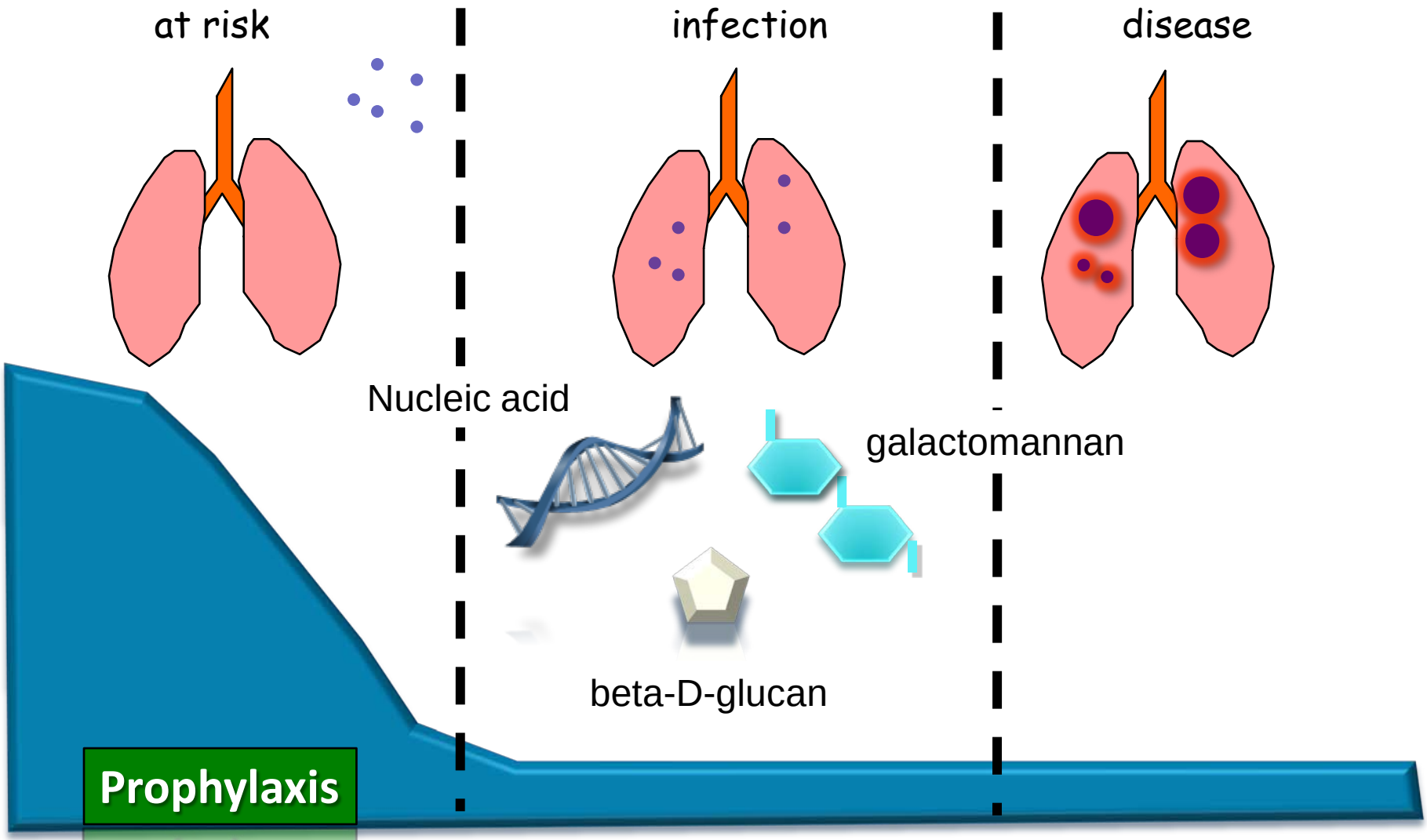
... and finally to disease.



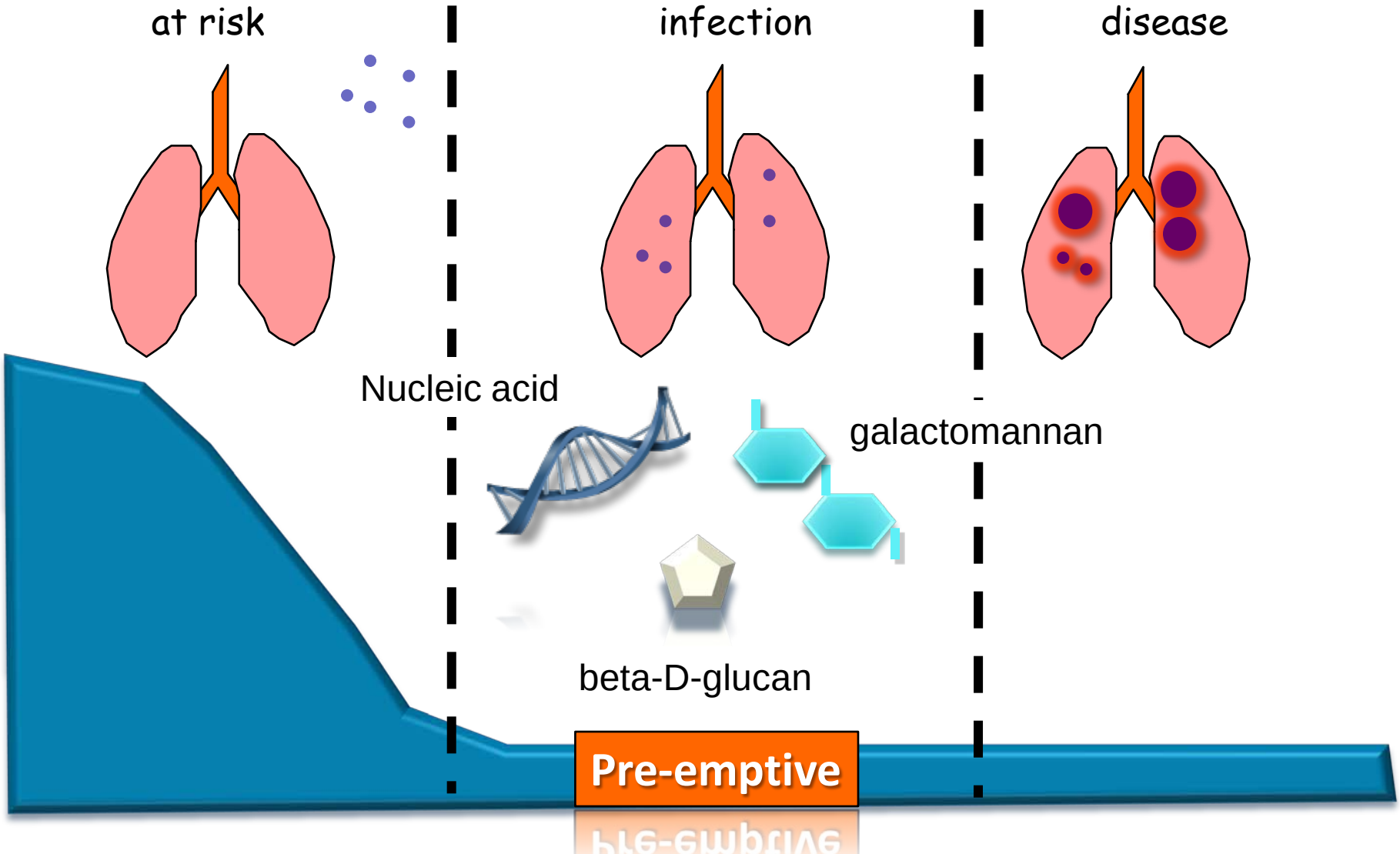
Deciding when to intervene



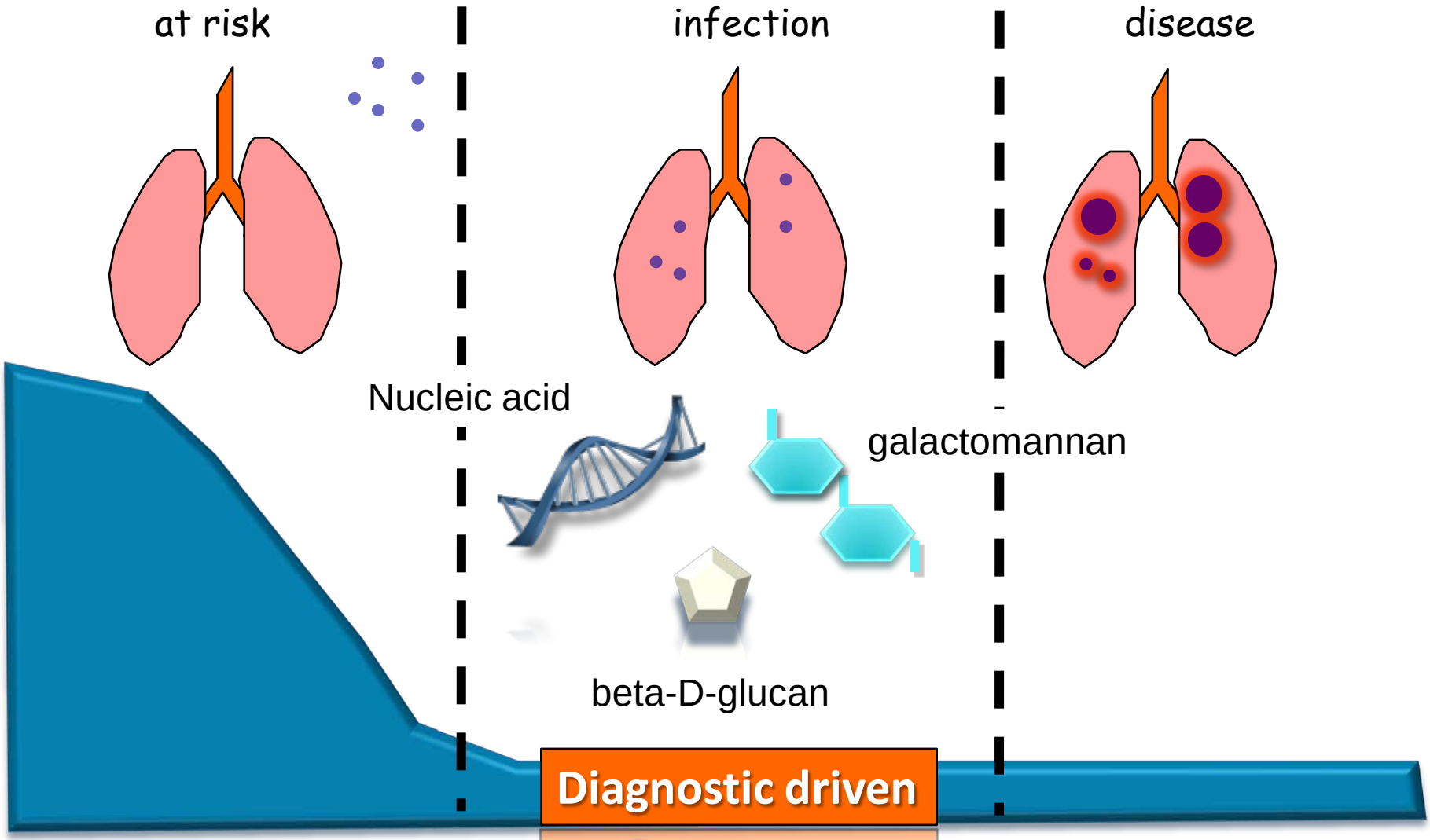
Deciding when to intervene



Deciding when to intervene



Deciding when to intervene



Are you happy with this model?

YES

NO

Treatment strategies

Defining invasive mould disease

	A	B	C				D	E
Radiological signs & clinical symptoms								
Mycology results								
Clinical evidence of IFD								
Mycological evidence of IFI								
Final diagnosis								

Defining invasive mould disease

	A	B	C				D	E
	-							
Radiological signs & clinical symptoms	No							
Mycology results	Negative							
Clinical evidence of IFD	No							
Mycological evidence of IFI	No							
Final diagnosis								

Defining invasive mould disease

	A	B	C				D	E
	-	-						
Radiological signs & clinical symptoms	No	Persistent Febrile neutropenia						
Mycology results	Negative	Negative						
Clinical evidence of IFD	No	No						
Mycological evidence of IFI	No	No						
Final diagnosis								

Defining invasive mould disease

	A	B	C				D	E
	-	-	I					
Radiological signs & clinical symptoms	No	Persistent Febrile neutropenia	No					
Mycology results	Negative	Negative	Positive biomarker or microscopy or culture					
Clinical evidence of IFD	No	No	No					
Mycological evidence of IFI	No	No	**Yes**					
Final diagnosis								

Defining invasive mould disease

	A	B	C				D	E
	-	-	I	II				
Radiological signs & clinical symptoms	No	Persistent Febrile neutropenia	No	Clinical (any new infiltrate not fulfilling the EORTC/MSG criteria)				
Mycology results	Negative	Negative	Positive biomarker or microscopy or culture	Negative				
Clinical evidence of IFD	No	No	No	No				
Mycological evidence of IFI	No	No	**Yes**	No				
Final diagnosis								

Defining invasive mould disease

	A	B	C				D	E
	-	-	I	II	III			
Radiological signs & clinical symptoms	No	Persistent Febrile neutropenia	No	Clinical (any new infiltrate not fulfilling the EORTC/MSG criteria)				
Mycology results	Negative	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture			
Clinical evidence of IFD	No	No	No	No	No			
Mycological evidence of IFI	No	No	**Yes**	No	**Yes**			
Final diagnosis								

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Defining invasive mould disease

	A	B	C				D	E
	-	-	I	II	III	IV		
Radiological signs & clinical symptoms	No	Persistent Febrile neutropenia	No	Clinical (any new infiltrate not fulfilling the EORTC/MSG criteria)		Radiological signs on CT (Dense, well-circumscribed lesions(s) with or without a halo sign, air-crescent sign, or cavity)		
Mycology results	Negative	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Negative		
Clinical evidence of IFD	No	No	No	No	No	**Yes**		
Mycological evidence of IFI	No	No	**Yes**	No	**Yes**	No		
Final diagnosis						**Possible IMD**		

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Defining invasive mould disease

	A	B	C				D	E
	-	-	I	II	III	IV	-	
Radiological signs & clinical symptoms	No	Persistent Febrile neutropenia	No	Clinical (any new infiltrate not fulfilling the EORTC/MSG criteria)		Radiological signs on CT (Dense, well-circumscribed lesions(s) with or without a halo sign, air-crescent sign, or cavity)		
Mycology results	Negative	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	
Clinical evidence of IFD	No	No	No	No	No	**Yes**	**Yes**	
Mycological evidence of IFI	No	No	**Yes**	No	**Yes**	No	**Yes**	
Final diagnosis						**Possible IMD**	**Probable IMD**	

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Defining invasive mould disease

	A	B	C				D	E
	-	-	I	II	III	IV	-	
Radiological signs & clinical symptoms	No	Persistent Febrile neutropenia	No	Clinical (any new infiltrate not fulfilling the EORTC/MSG criteria)		Radiological signs on CT (Dense, well-circumscribed lesions(s) with or without a halo sign, air-crescent sign, or cavity)		Not considered necessary
Mycology results	Negative	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Tissue positive
Clinical evidence of IFD	No	No	No	No	No	**Yes**	**Yes**	**Yes**
Mycological evidence of IFI	No	No	**Yes**	No	**Yes**	No	**Yes**	**Yes**
Final diagnosis						**Possible IMD**	**Probable IMD**	**Proven IMD**

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Are you happy with the EORTC/MSG definitions

YES

NO

Treating invasive mould disease

	A	B	C				Directed	
	-	-	I	II	III	IV		
Radiological signs & clinical symptoms	No	Persistent Febrile neutropenia	No	Clinical (any new infiltrate not fulfilling the EORTC/MSG criteria)		Radiolog cal signs on CT (D nse, well-circu scribed lesion s) with or without halo sign, air-cres nt sign, or c vity)		Not considered necessary
Mycology results	Negative	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Tissue positive
Clinical evidence of IFD	No	No	No	No	No	**Yes**	**Yes**	**Yes**
Mycological evidence of IFI	No	No	**Yes**	No	**Yes**	No	**Yes**	**Yes**
Final diagnosis						**Possible IMD**	**Probable IMD**	**Proven IMD**

Treating invasive mould disease

Prophylaxis

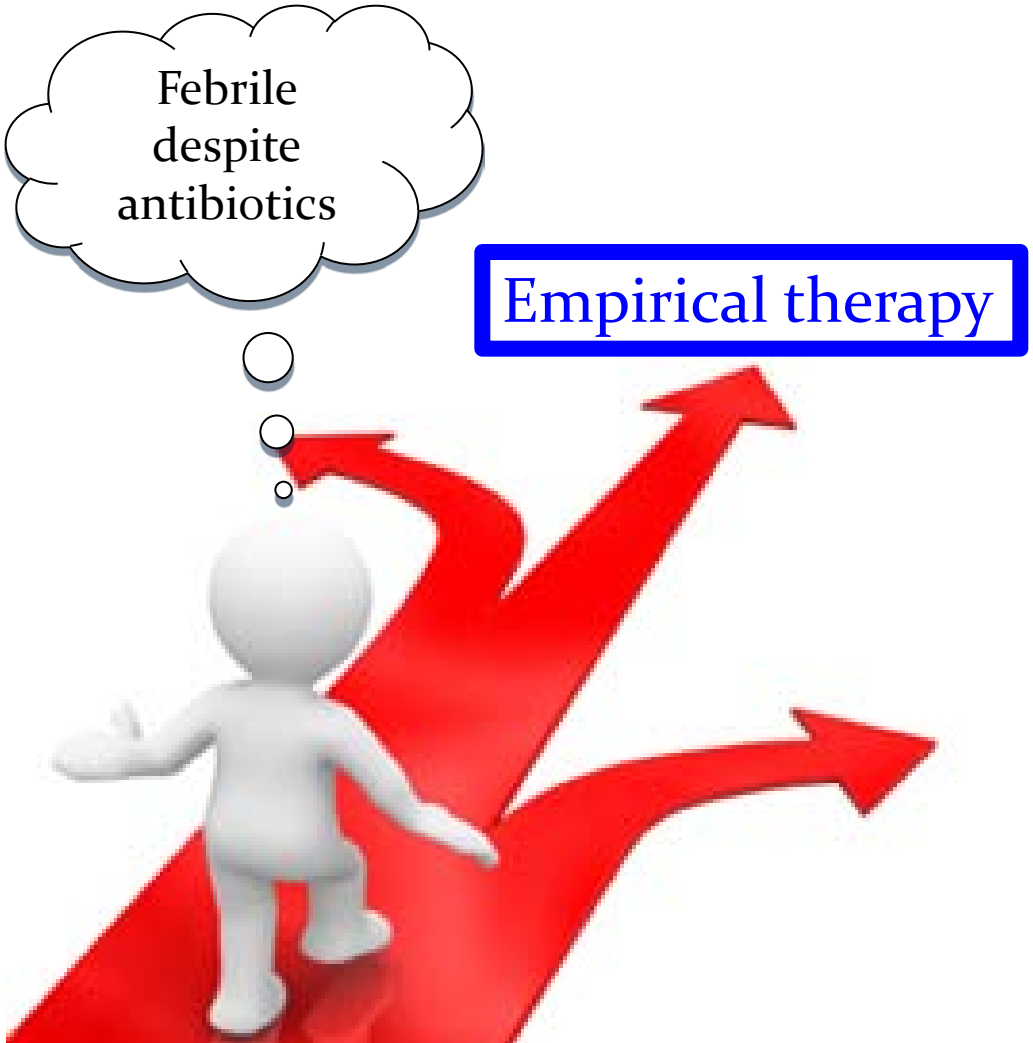
	A	B	C				D	E
		-	I	II	III	IV	-	
Radiological signs & clinical symptoms	No	Persistent Febrile neutropenia	No	Clinical (any new infiltrate not fulfilling the EORTC/MSG criteria)		Radiological signs on CT (Dense, well-circumscribed lesions(s) with or without a halo sign, air-crescent sign, or cavity)		Not considered necessary
Mycology results	Negative	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Tissue positive
Clinical evidence of IFD	No	No	No	No	No	**Yes**	**Yes**	**Yes**
Mycological evidence of IFI	No	No	**Yes**	No	**Yes**	No	**Yes**	**Yes**
Final diagnosis	**no IMD**					**Possible IMD**	**Probable IMD**	**Proven IMD**

Treating invasive mould disease

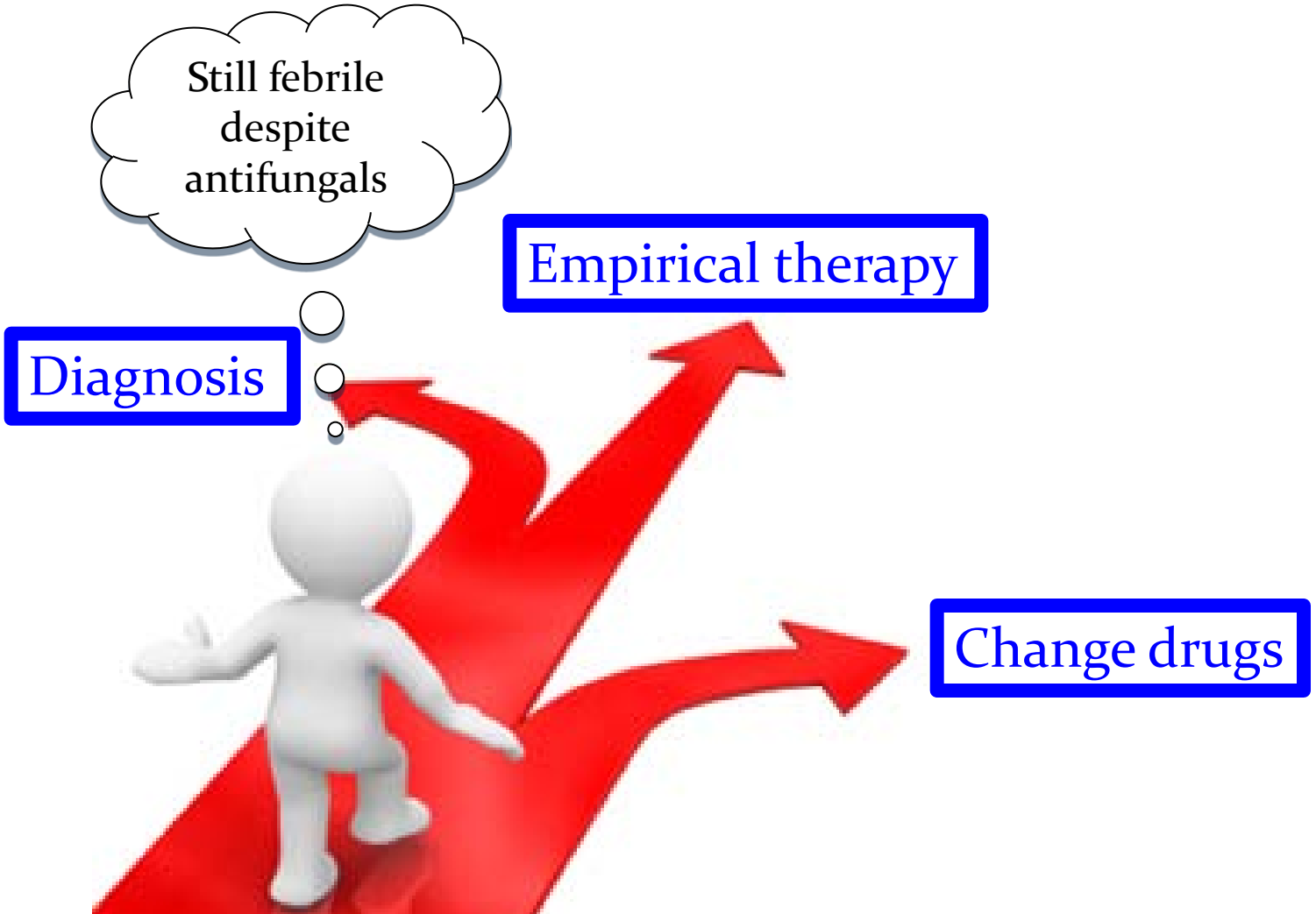
	A	Empirical	C				D	E
	-		I	II	III	IV	-	
Radiological signs & clinical symptoms	No	Persistent Febrile neutropenia	No	Clinical (any new infiltrate not fulfilling the EORTC/MSG criteria)		Radiological signs on CT (Dense, well-circumscribed lesions(s) with or without a halo sign, air-crescent sign, or cavity)		Not considered necessary
Mycology results	Negative	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Tissue positive
Clinical evidence of IFD	No	No	No	No	No	**Yes**	**Yes**	**Yes**
Mycological evidence of IFI	No	No	**Yes**	No	**Yes**	No	**Yes**	**Yes**
Final diagnosis		**no IMD**				**Possible IMD**	**Probable IMD**	**Proven IMD**

Adapted by Maertens & Donnelly from Herbrecht & Berceanu Clin Infect Dis. 2008;46:886-889

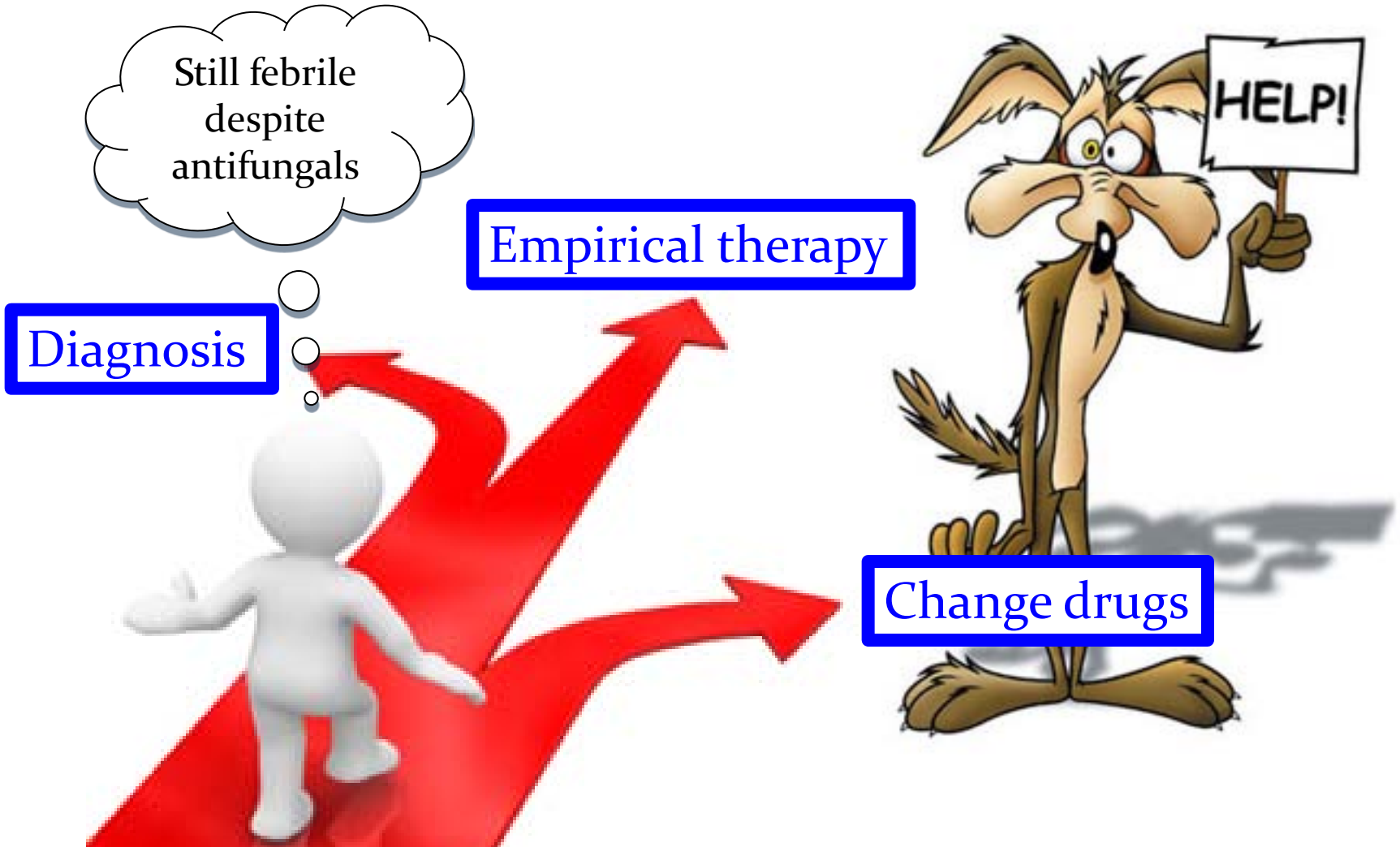
Choices choices choices



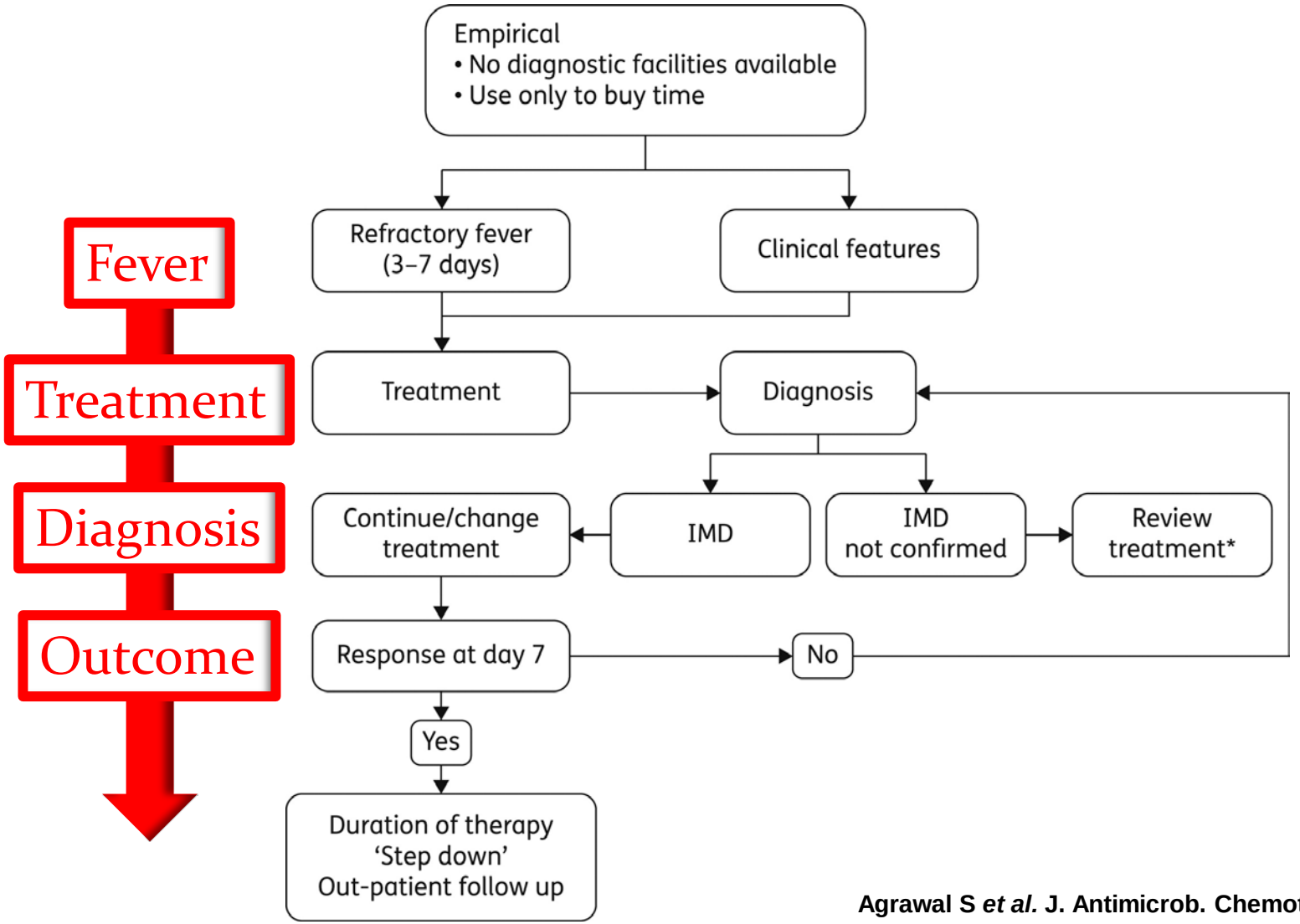
Choices choices choices



Choices choices choices

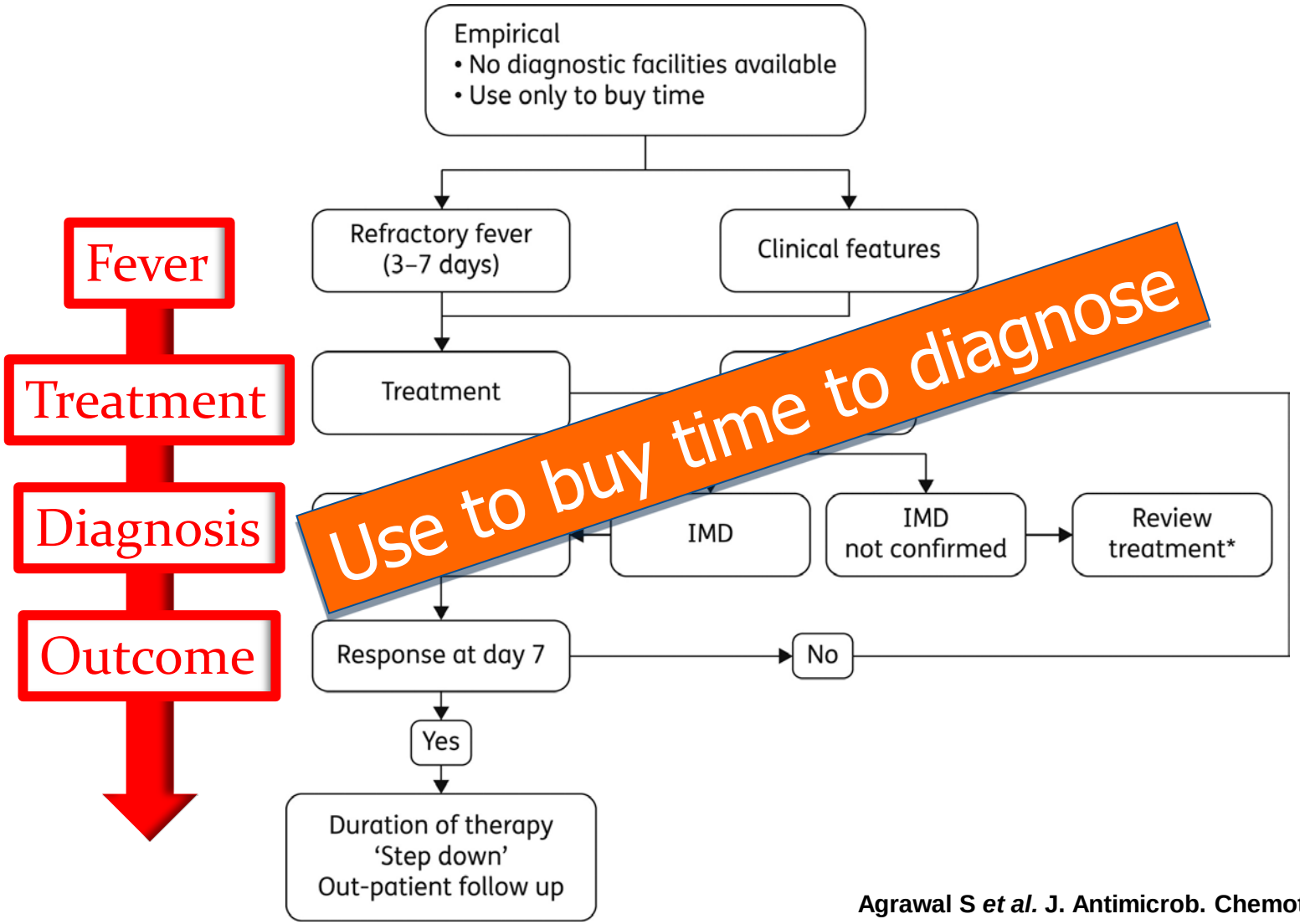


Empirical integrated care pathway



Agrawal S *et al.* J. Antimicrob. Chemother. 2011;66:i45-i53

Empirical integrated care pathway



Agrawal S *et al.* J. Antimicrob. Chemother. 2011;66:i45-i53

Do you use empirical therapy?

YES

NO

Pre-emptive therapy

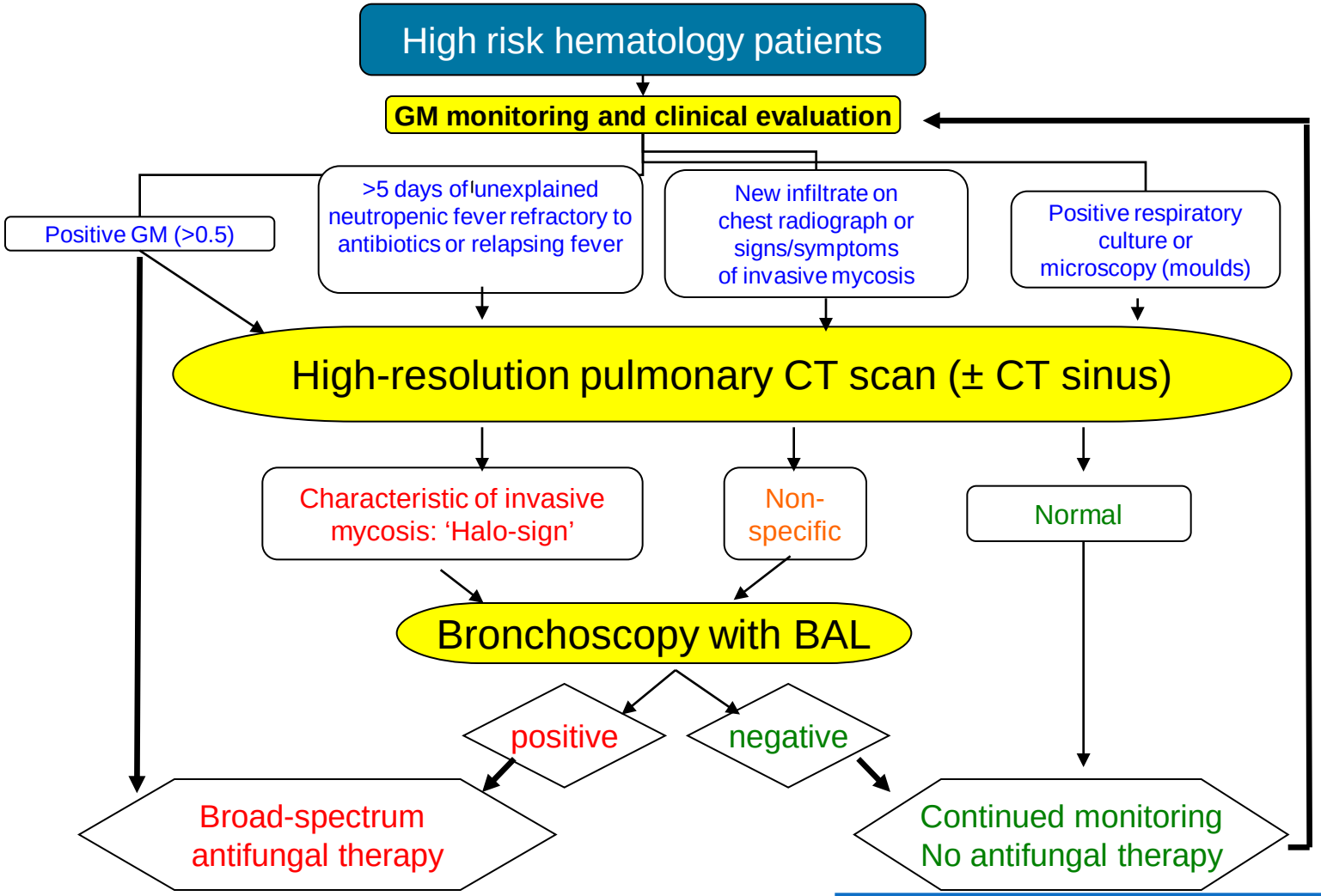
Diagnostic-driven strategy (Pre-emptive therapy)

Treating invasive mould disease

Diagnostic driven

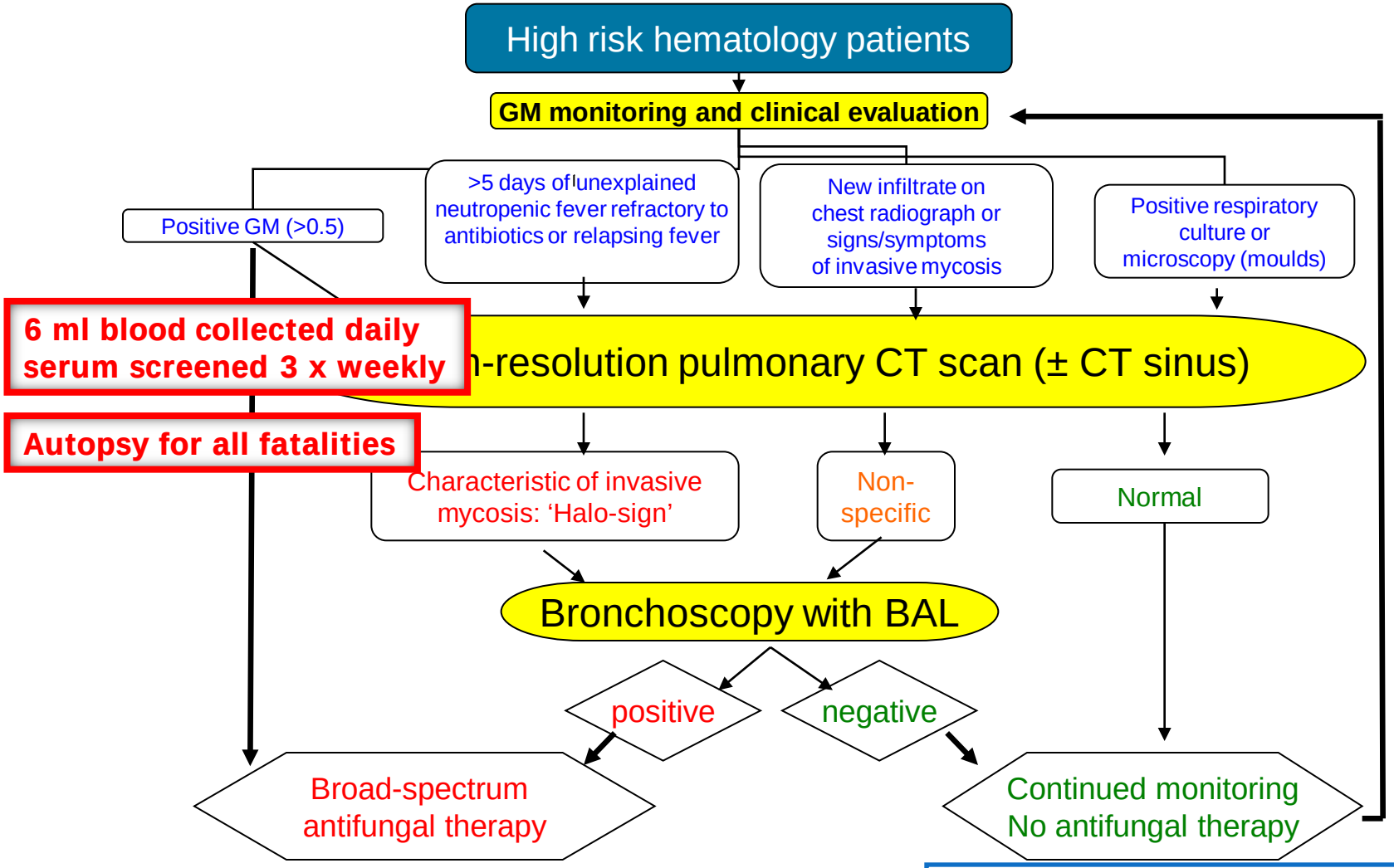
	A	B					D	E
	-	-					-	
Radiological signs & clinical symptoms	No	Persistent Febrile neutropenia	No	Clinical (any new infiltrate not fulfilling the EORTC/MSG criteria)		Radiological signs on CT (Dense, well-circumscribed lesion(s) with or without halo sign, air-crescent sign, or cavity)		Not considered necessary
Mycology results	Negative	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Negative	Positive biomarker or microscopy or culture	Tissue positive
Clinical evidence of IFD	No	No	No	No	No	**Yes**	**Yes**	**Yes**
Mycological evidence of IFI	No	No	**Yes**	No	**Yes**	No	**Yes**	**Yes**
Final diagnosis			**IMD or IFI**			**Possible IMD**	**Probable IMD**	**Proven IMD**

A diagnostic versus and empirical approach



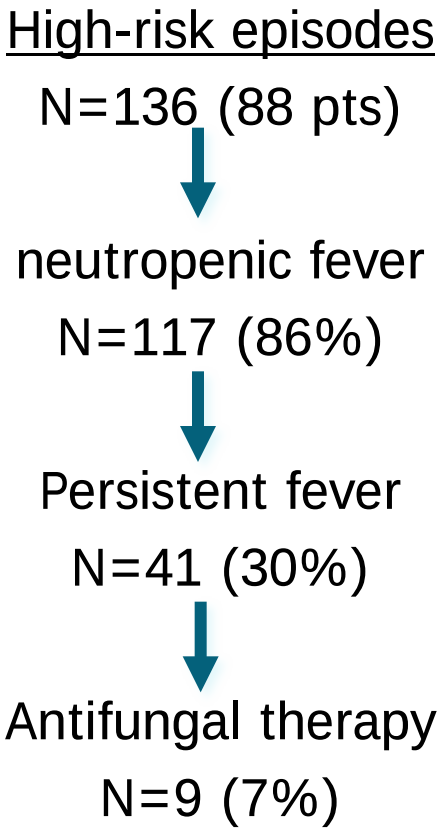
Maertens et al. Clin Infect Dis 2005; 41: 1242

A diagnostic versus and empirical approach



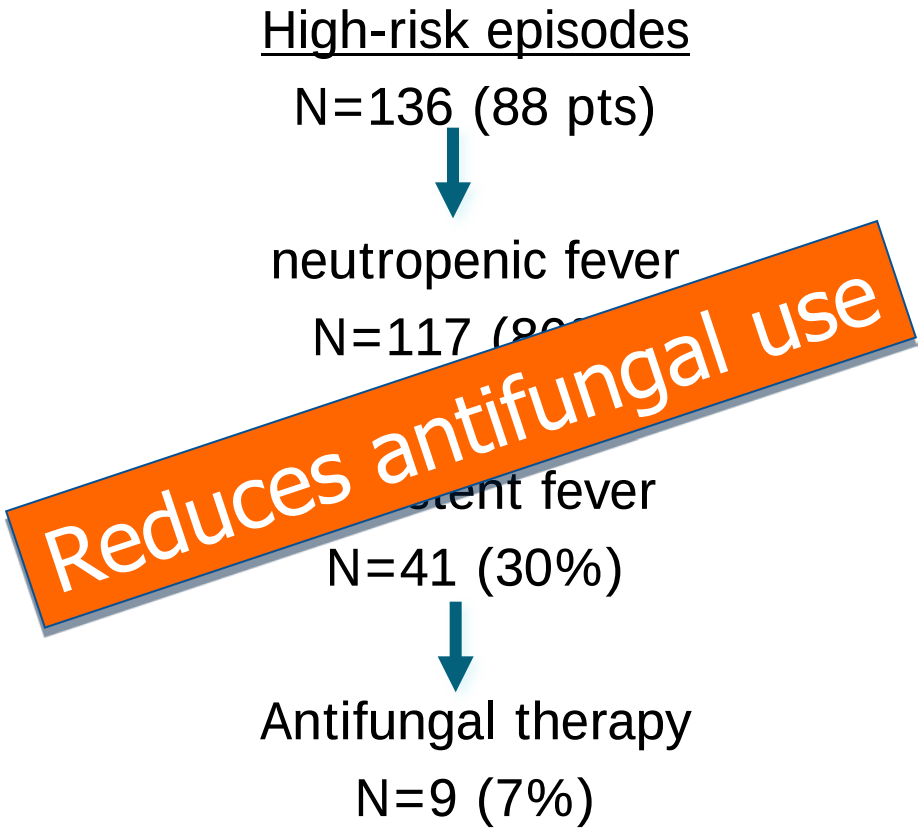
Maertens et al. Clin Infect Dis 2005; 41: 1242

Leuven's approach



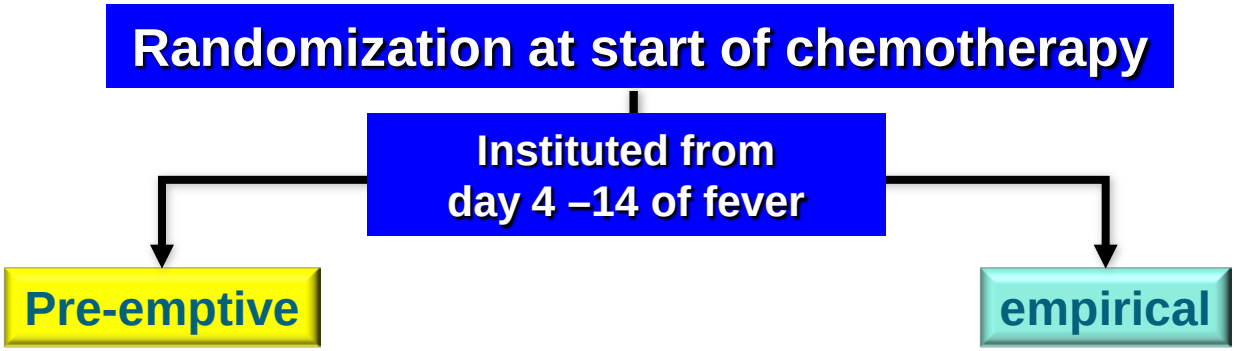
Maertens et al. Clin Infect Dis 2005; 41: 1242

Leuven's approach



Maertens et al. Clin Infect Dis 2005; 41: 1242

The PREVERT study

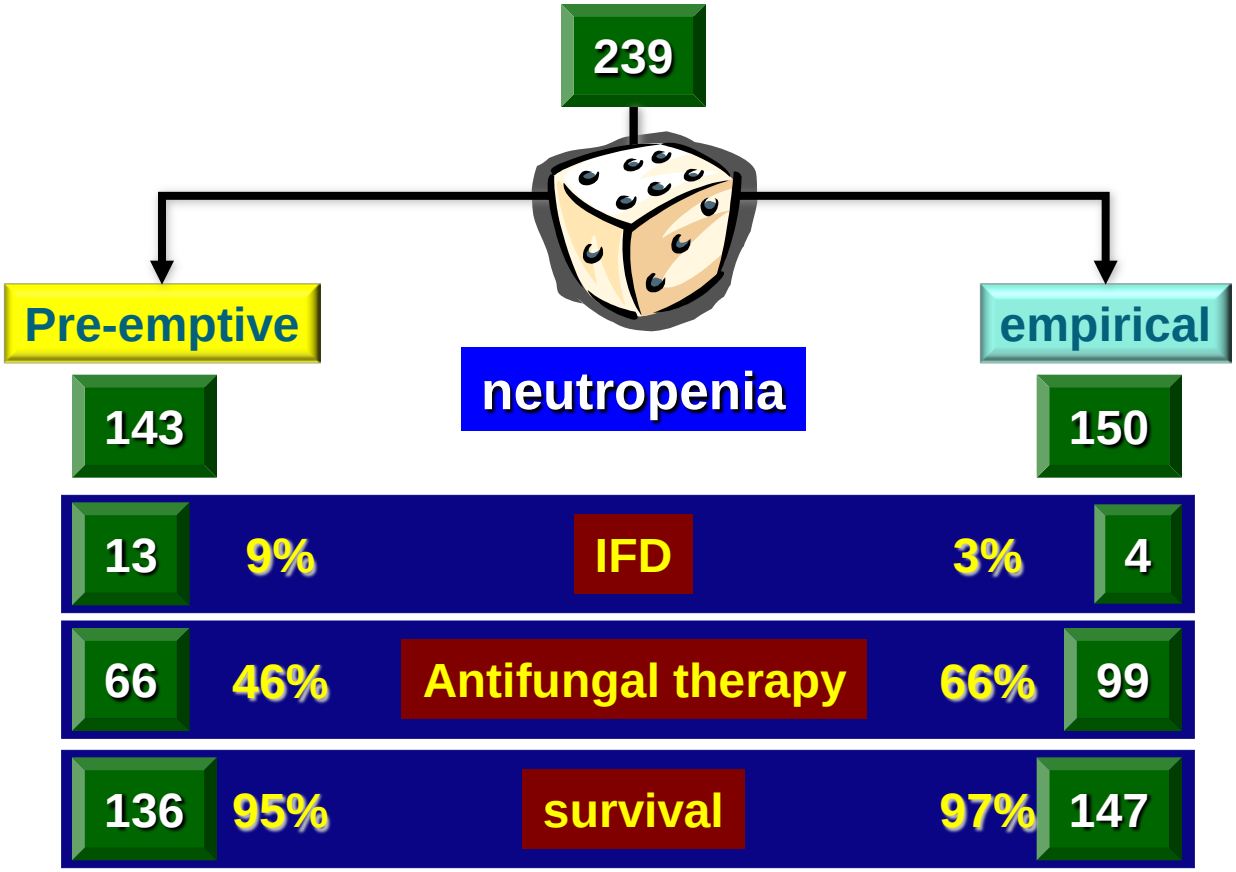


Pneumonia, severe mucositis, ,septic shock, positive galactomannan antigen test, skin lesion, sinusitis or periorbital inflammation, neurological symptoms, diarrhea

Fever driven

Cordonnier et al. 2009 Clin Infect Dis 48:1042–51

The PREVERT study - GM & CT



Cordonnier et al. 2009 Clin Infect Dis 48:1042–51

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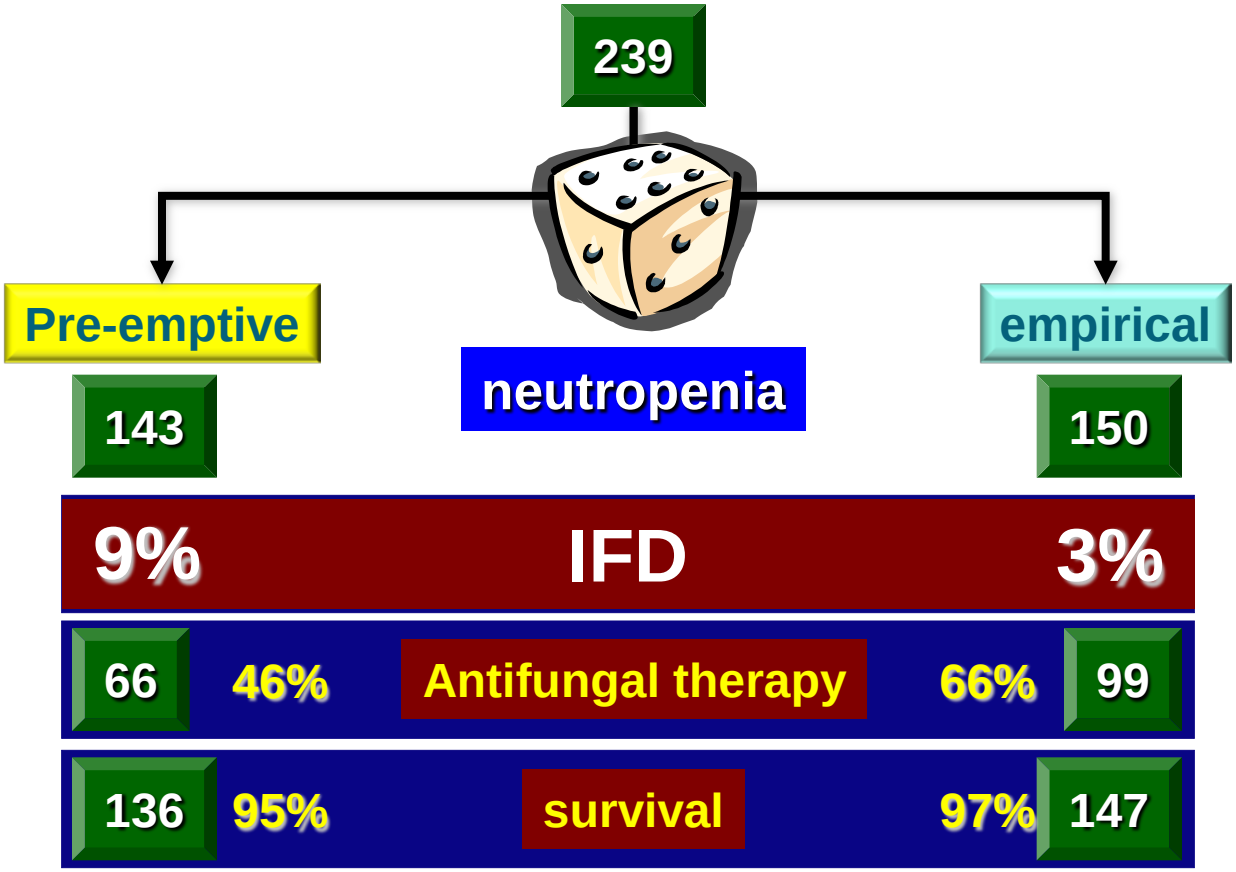

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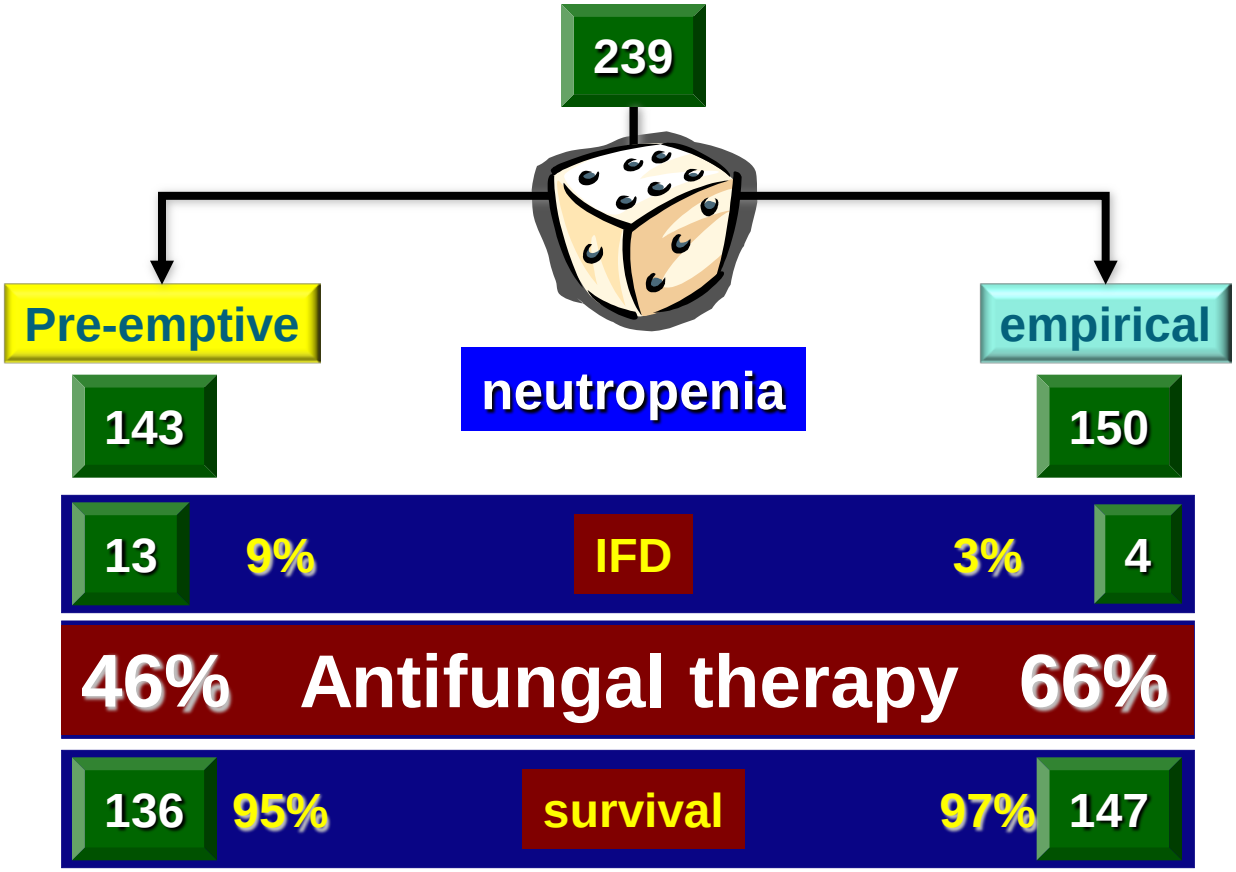
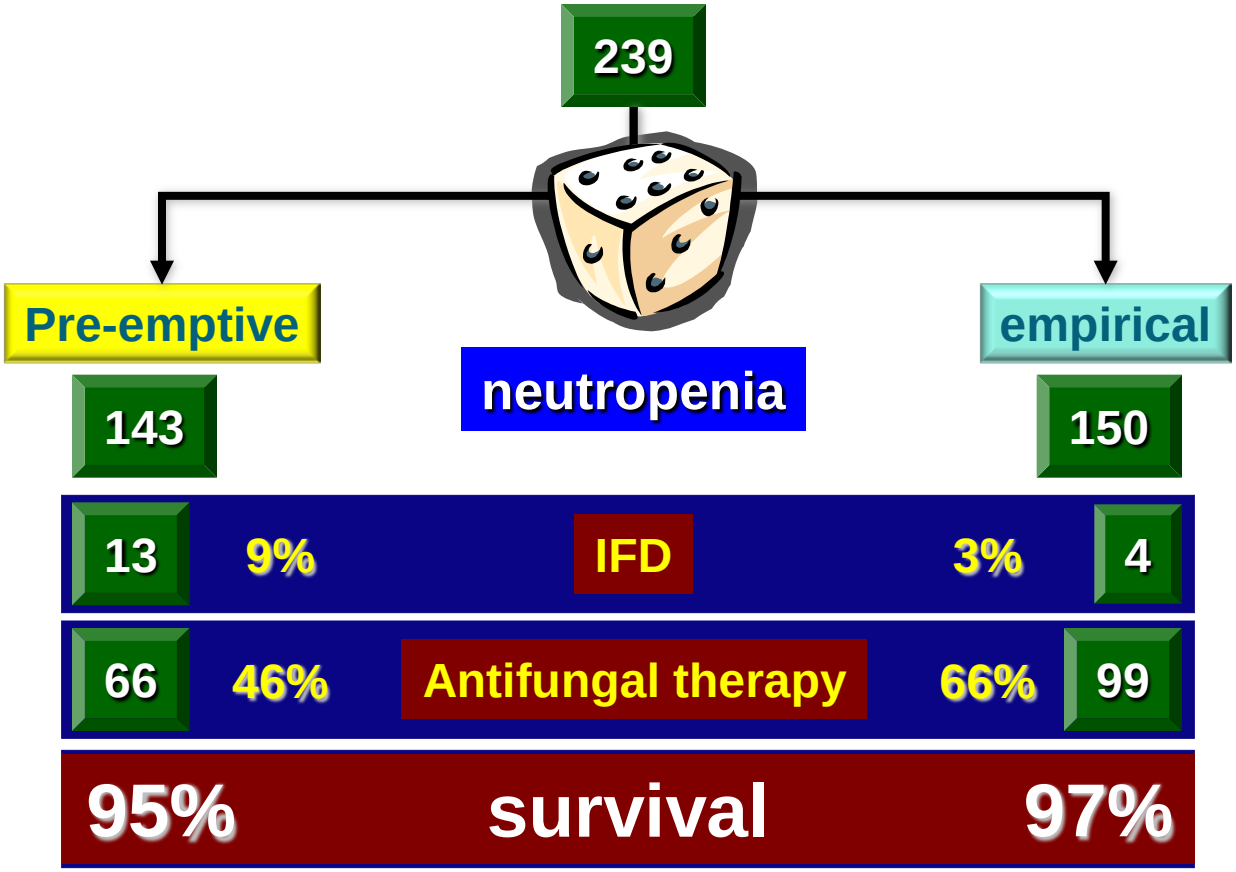


Cordonnier et al. 2009 Clin Infect Dis 48:1042–51

The PREVERT study



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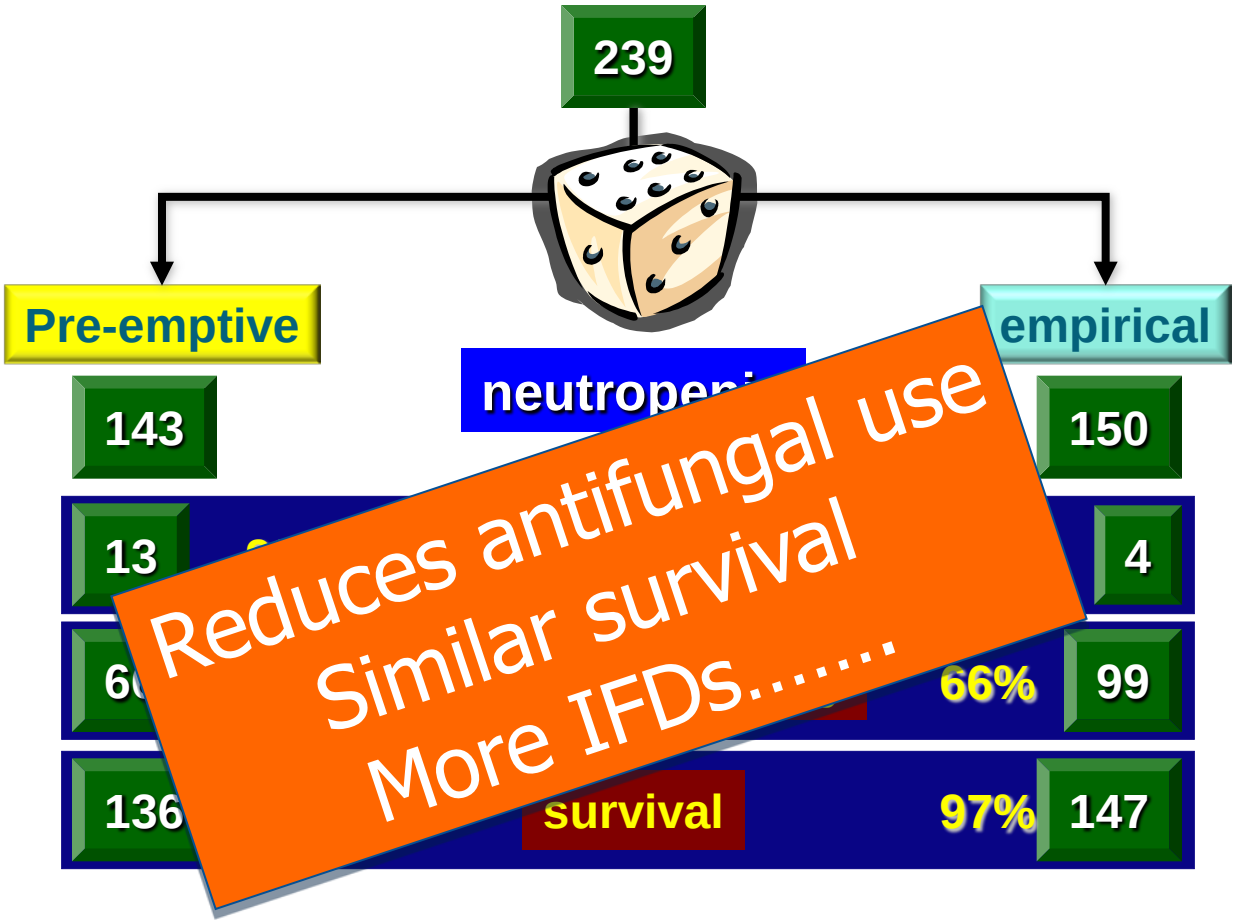


Cordonnier et al. 2009 Clin Infect Dis 48:1042–51

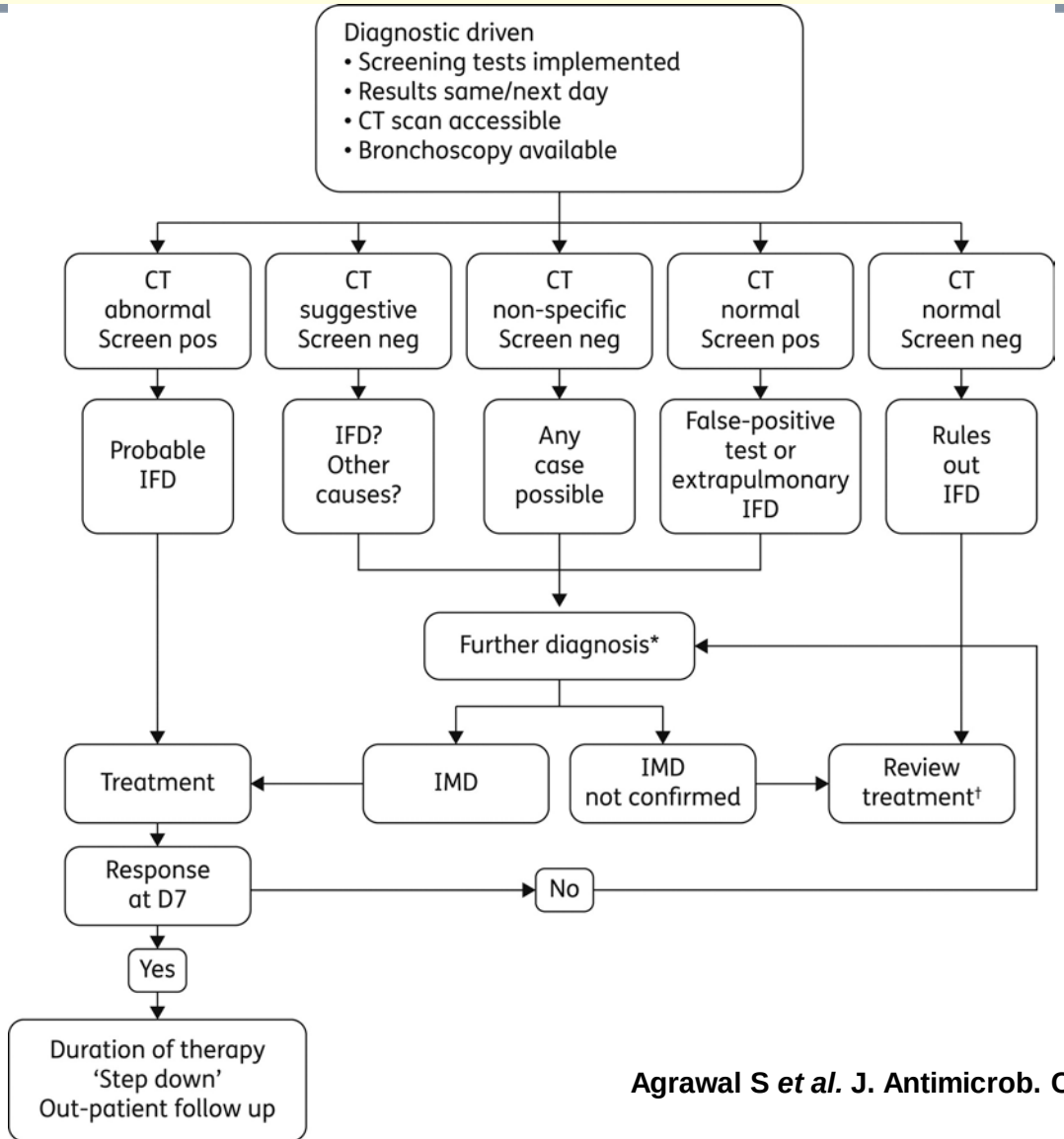
Diagnostic-driven integrated care pathway.

Triggers

Diagnosis

Treatment

Outcome



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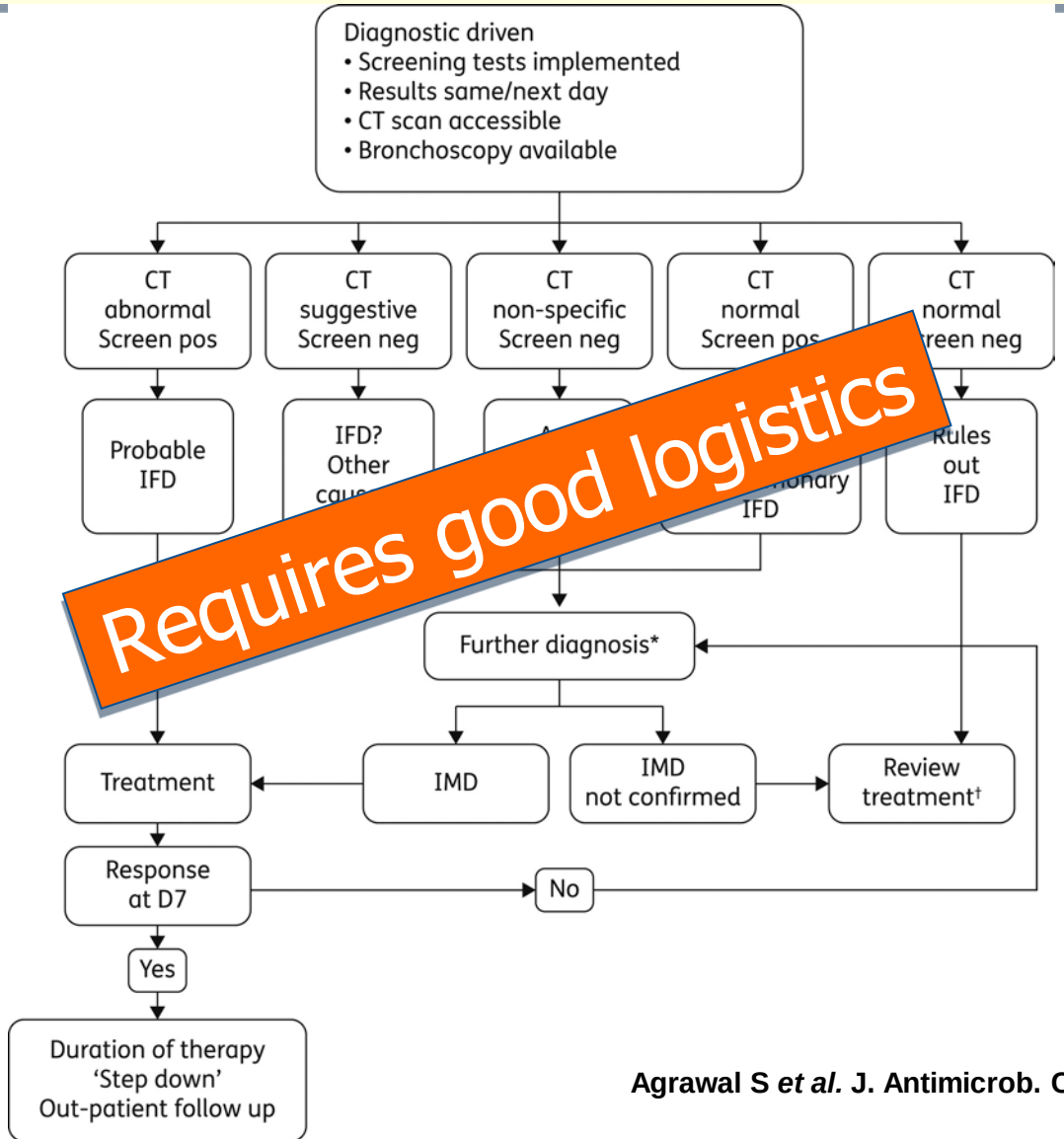
Diagnostic-driven integrated care pathway.

Triggers

Diagnosis

Treatment

Outcome



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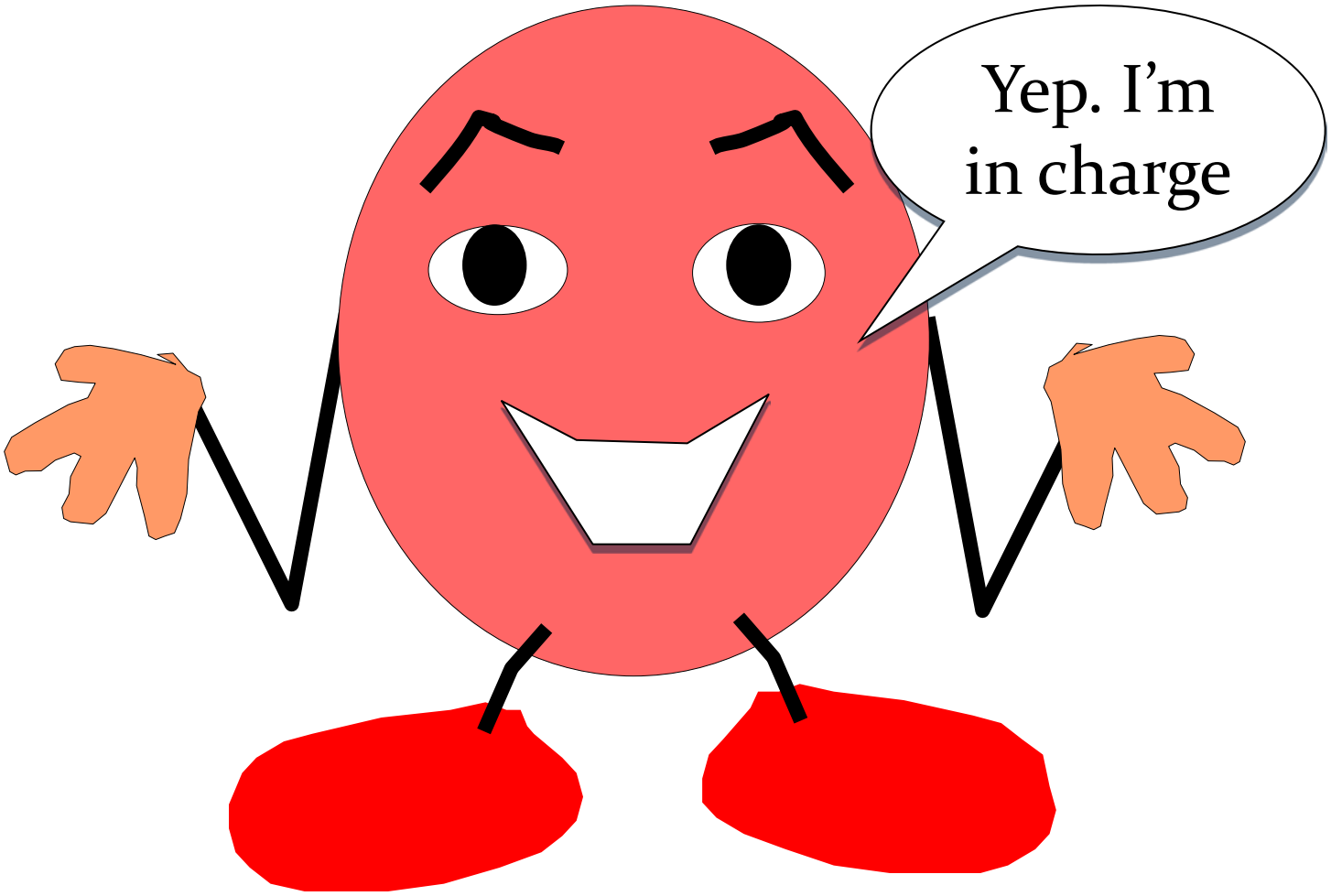
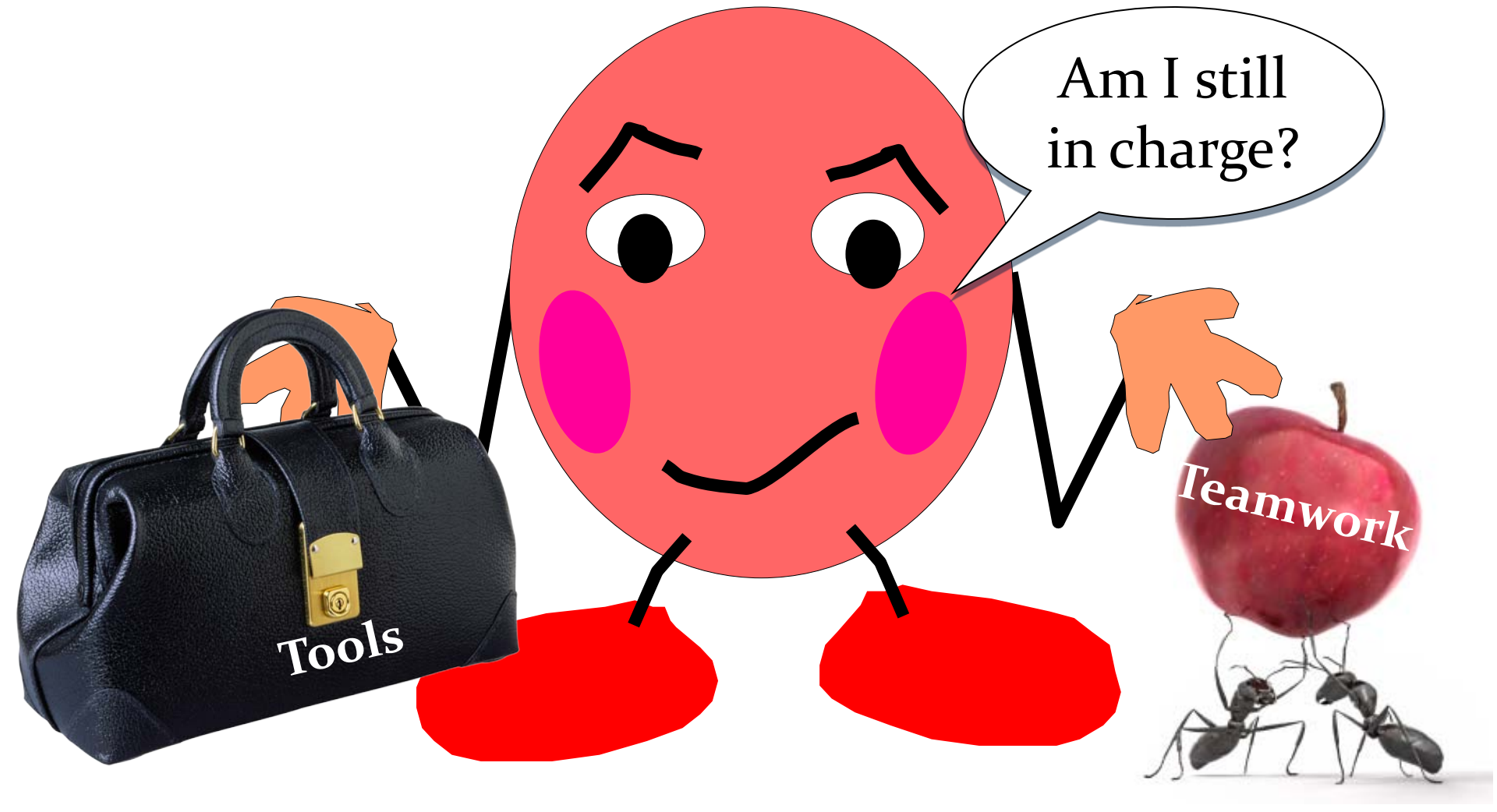
Empirical versus diagnostic-driven approach

	Empirical	Diagnostic driven
History	Strategy developed to reduce risk of fatal IFD in an era of few diagnostic tests and limited drugs	Strategy developed to direct therapy more effectively once CT scan and tests such as GM became widely available.
Standard of care	Most centres	Few centres
Principle	Neutropenia and persistent or relapsing fever despite broad-spectrum antibiotics for 3-7 days: no alternative microbiological etiology found AND IFD cannot be ruled out	include all patients likely to have IFD and treat them with the safest and most effective drug: exclude all patients unikely to have IFD and adopt a Wait-and-see approach
ECIL	BII	-
Feasible	Yes	Unknown

Pre-requisites for a empirical approach?



Pre-requisites for a diagnosis driven approach?



Pre-requisites for a diagnosis driven approach?

Is pre-emptive therapy a realistic approach?

YES

NO

Future initiatives

EORTC
Infectious Diseases Group

EORTC 65091-06093

Empirical versus “pre-emptive” antifungal therapy of patients with haematological malignancies and recipients of an allogeneic HSCT following myeloablative therapy. A therapeutic phase III strategy study

EORTC
Infectious Diseases Group

EORTC 65091-06093

Empirical versus “pre-emptive” antifungal therapy of patients with haematological malignancies and recipients of an allogeneic HSCT following myeloablative therapy. A therapeutic phase III strategy study

Joint IDG- AL study

Randomized phase III (new standard of care)

Translational - utility of *Aspergillus* PCR and BDG and evaluation of potential genetic SNPs signatures

556 patients,10 countries, 22 centres

EORTC 65091-06093

remission induction chemotherapy for acute myeloid leukaemia or myelodysplastic syndrome that is newly diagnosed or in first relapse

OR a myeloablative conditioning regimen to prepare for an allogeneic HSCT

Randomise on admission

Oral or iv fluconazole for *Candida* prophylaxis; no other antifungal prophylaxis allowed

Primary endpoint: survival at 42 days after radmonization

EORTC
Infectious Diseases Group

EORTC 65091-06093

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Study 1 of 1 for search of: 65091
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Caspofungin Acetate in Treating Patients With Acute Myeloid Leukemia or Myelodysplastic Syndrome That is Newly Diagnosed or in First Relapse

This study is not yet open for participant recruitment.
Verified on January 2011 by National Cancer Institute (NCI)

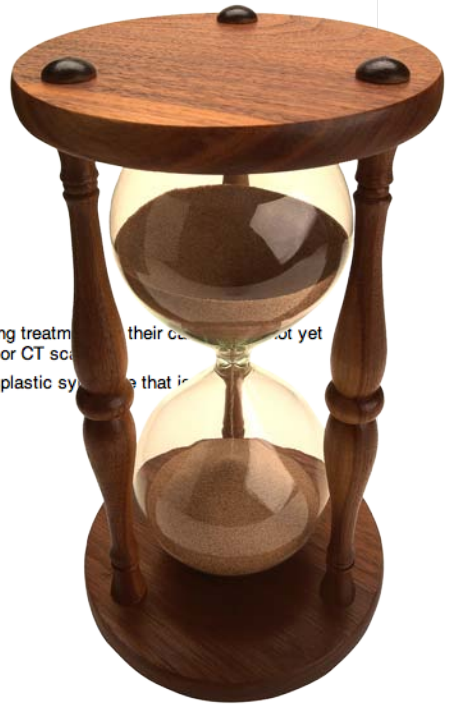
First Received on February 1, 2011. No Changes Posted

Sponsor:	European Organization for Research and Treatment of Cancer
Information provided by:	National Cancer Institute (NCI)
ClinicalTrials.gov Identifier:	NCT01288378

ients with acute myeloid leukemia or myelodysplastic syndrome who are receiving treatm their c yet
elopment of a fever or after the infection is shown in laboratory test, chest x-ray, or CT sc
gin acetate therapy in treating patients with acute myeloid leukemia or myelodysplastic sy that i

MERCK

d to start Q3 2011



Thank you!