



Is pre-emptive therapy a realistic approach?

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Is pre-emptive therapy a realistic approach?

YES

NO

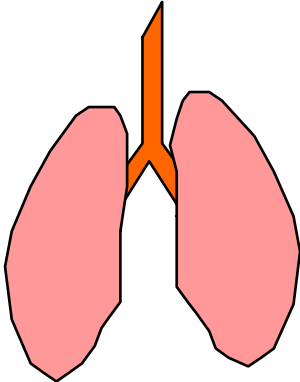
Contents

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

Evolution of invasive mould disease

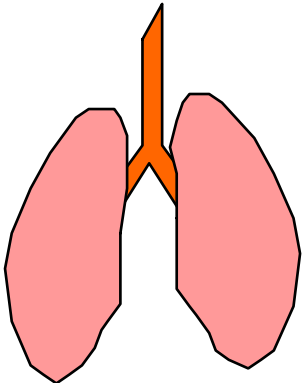
What if invasive mould disease...

at risk

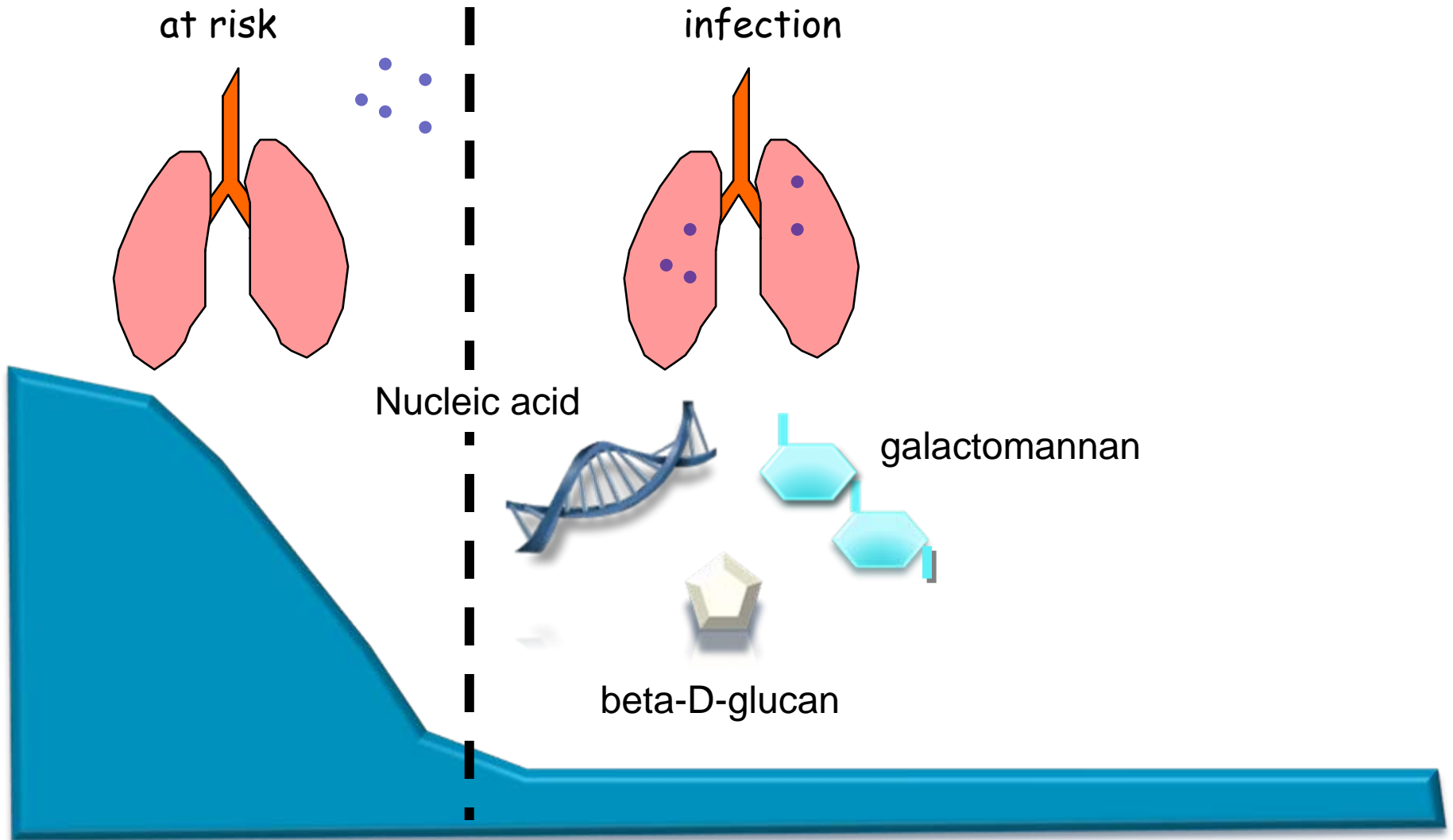


... begins with colonisation ...

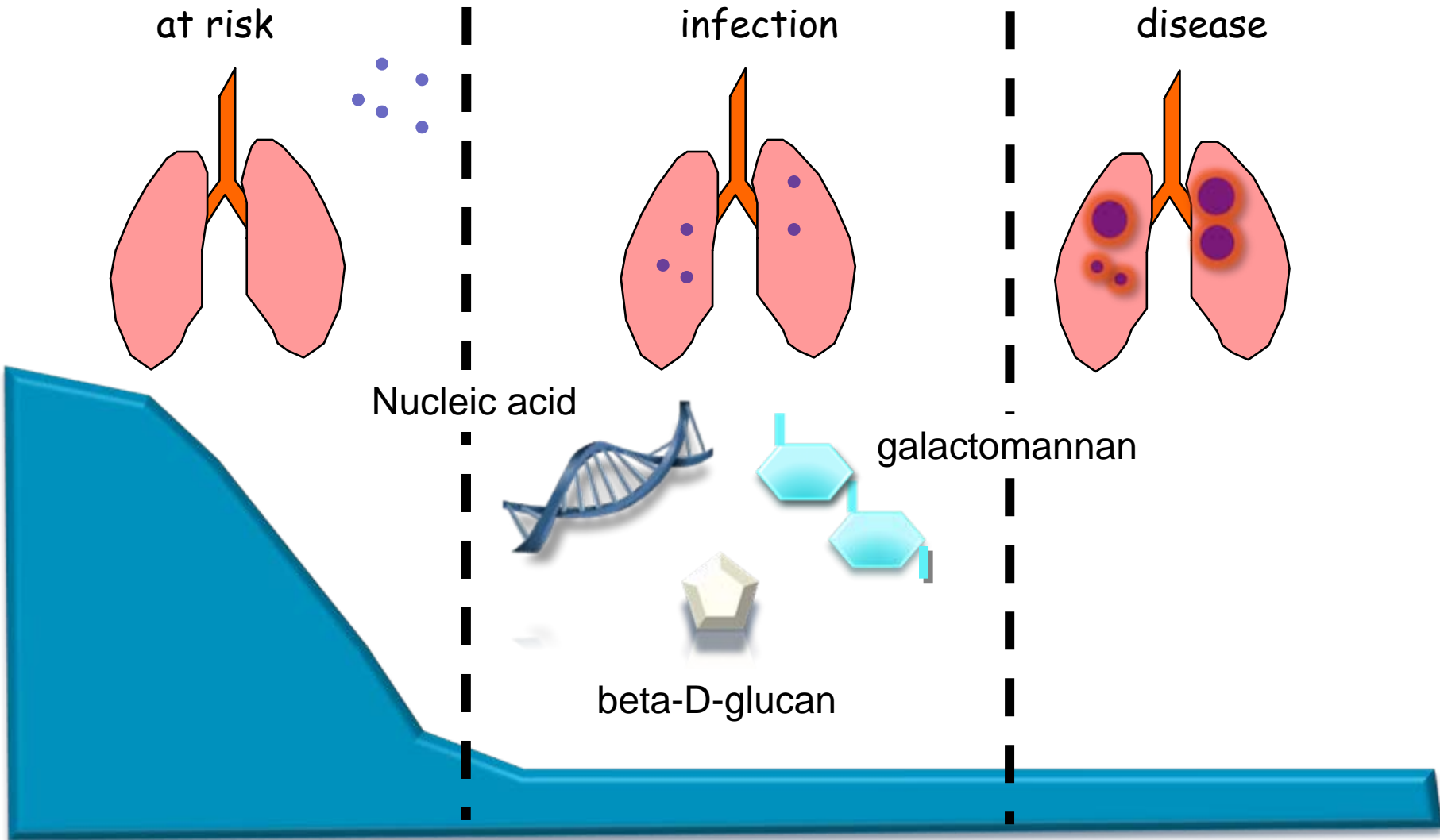
at risk



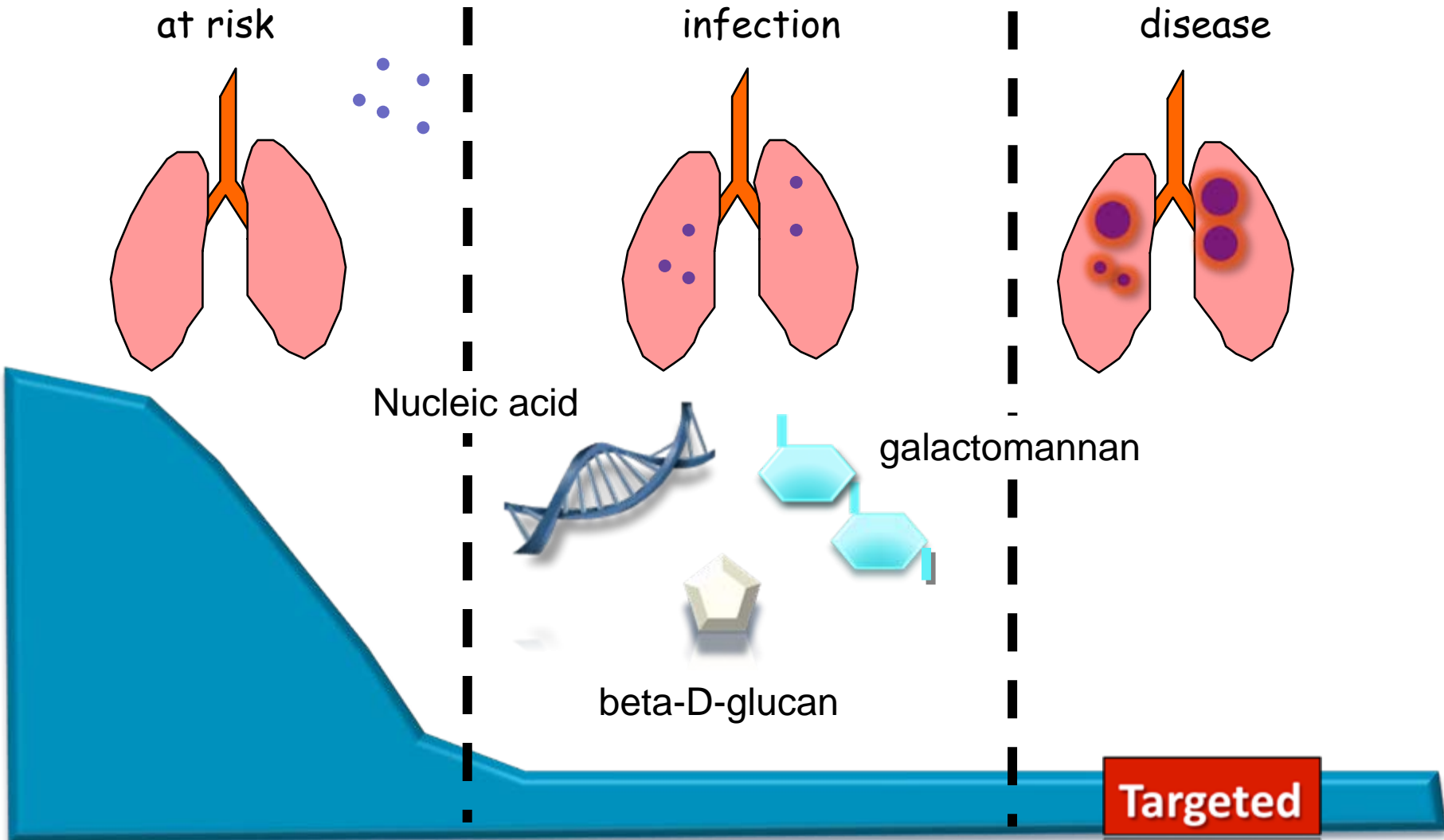
... then progresses to infection ...



... and finally to disease.



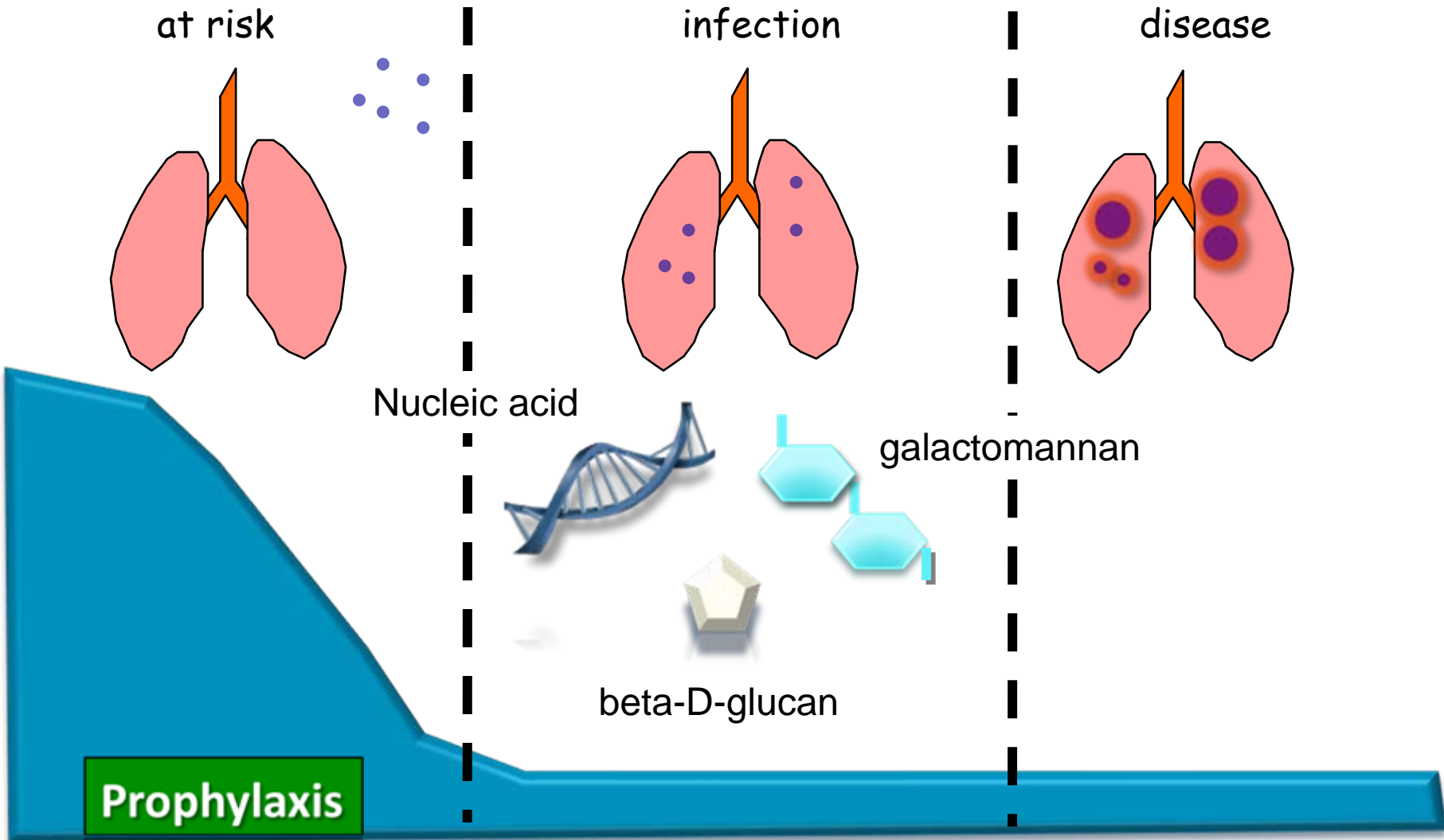
Deciding when to intervene



Targeted

19186169

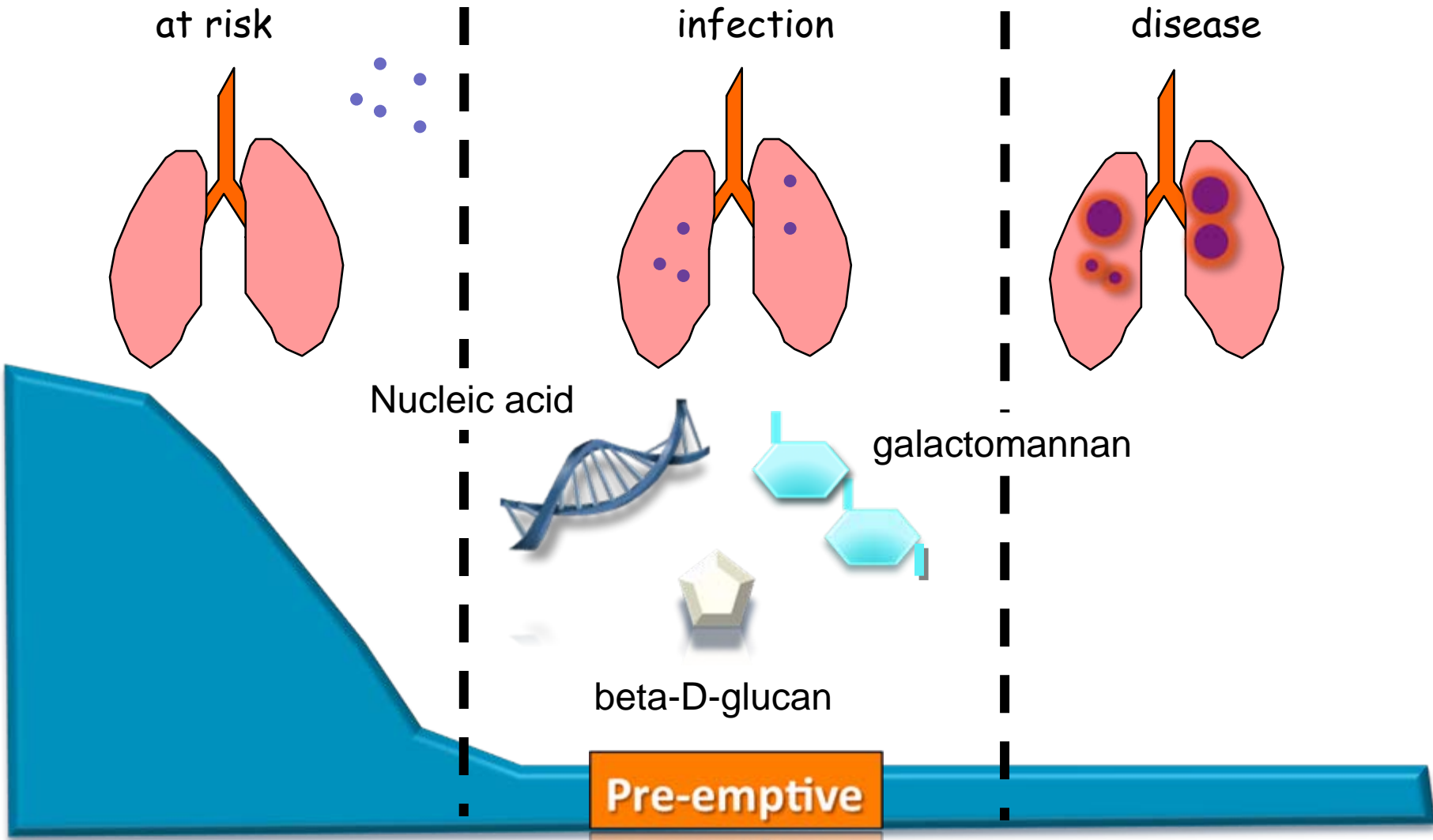
Deciding when to intervene



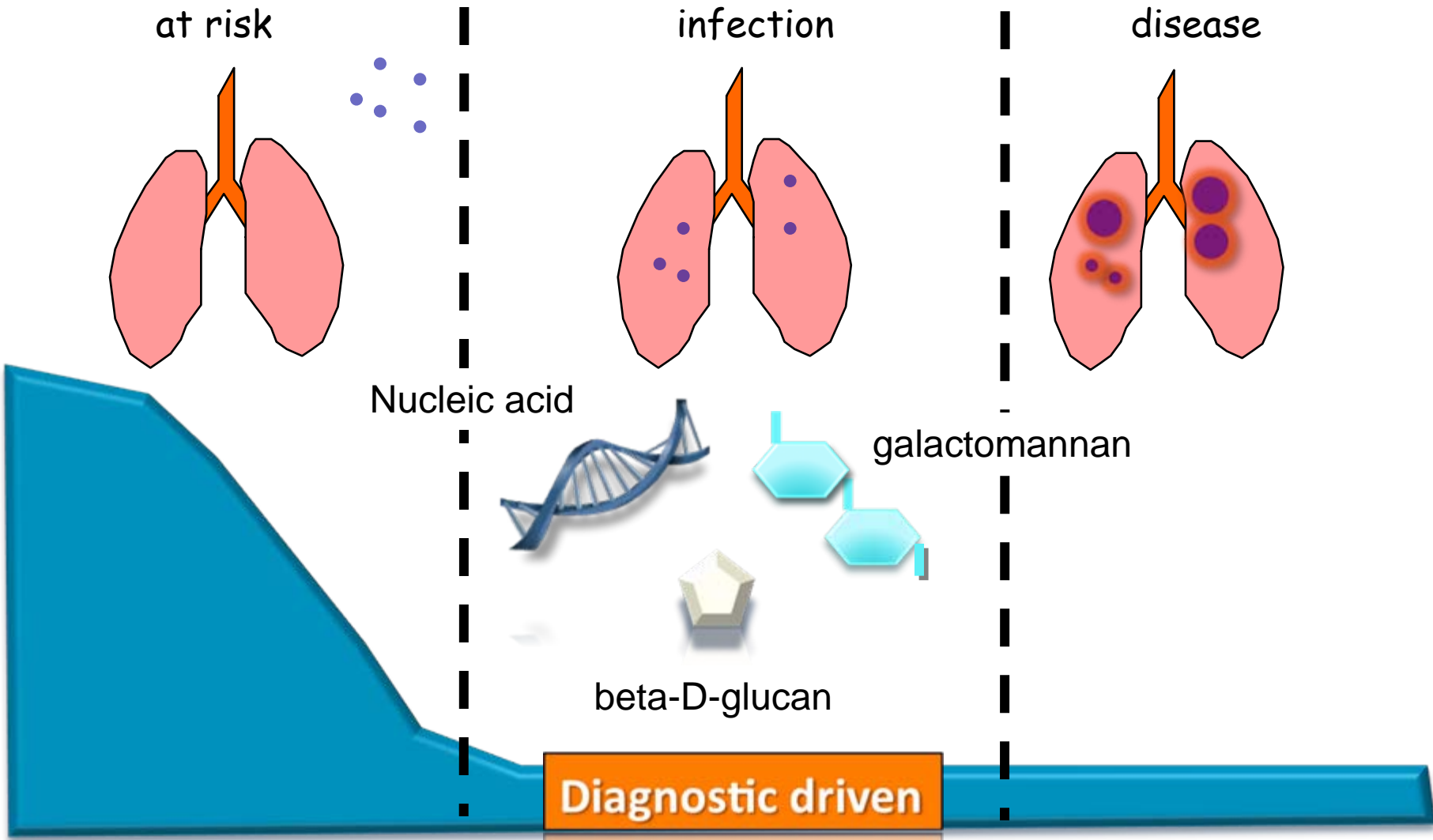
Prophylaxis

προβουλιξίς

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							

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		
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		

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		
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	

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		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

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)		Radiological signs on CT (Dense, well-circumscribed lesions) with or without a halo sign, air-crescent sign, or		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

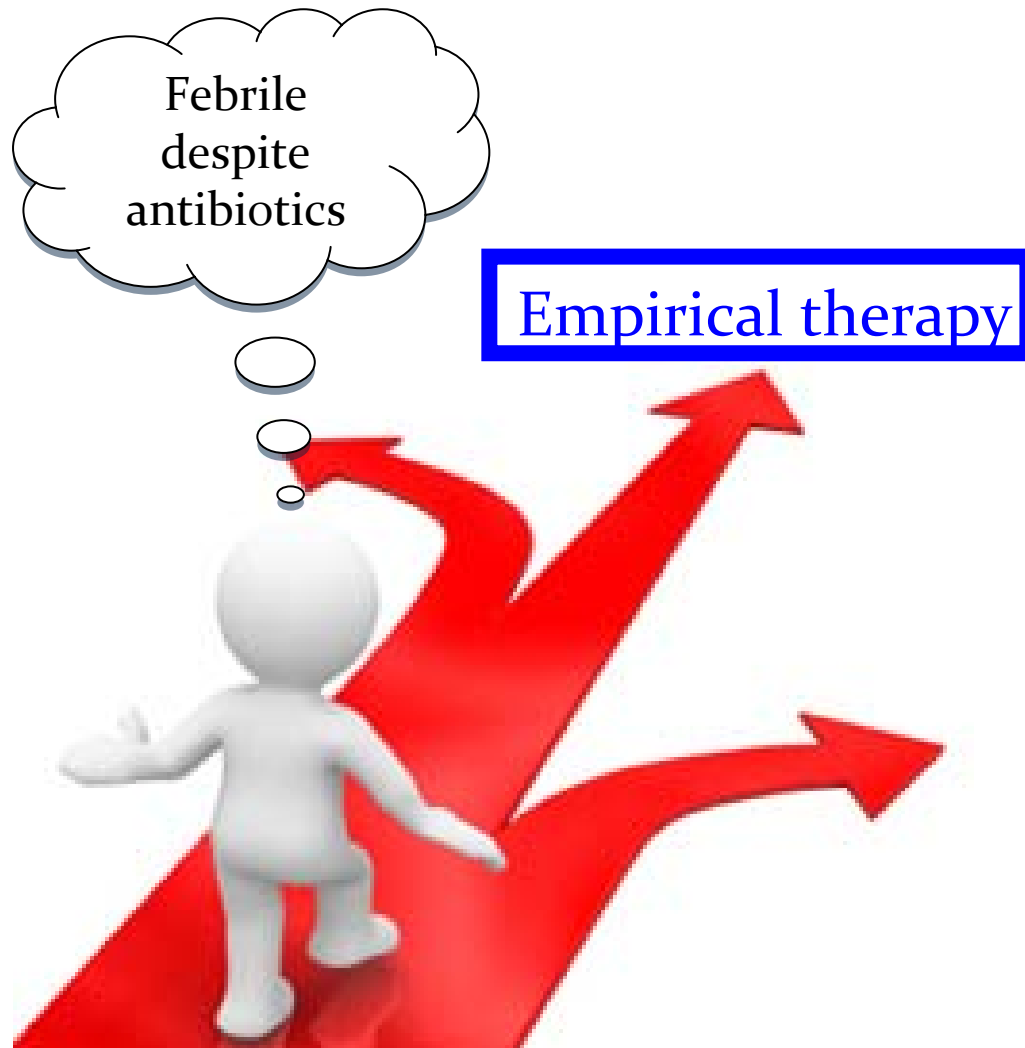
		B	C				D	E
Prophylaxis		-	I	II	III	IV	-	
Radiological signs & clinical symptoms	No	Persistent Febrile neutropenia	No	Clinical (any new infiltrate not fulfilling the EORTC/MSG criteria)		Radiological signs on CT (Dense, well-circumscribed lesions(s) with or without a halo sign, air-crescent sign, or		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

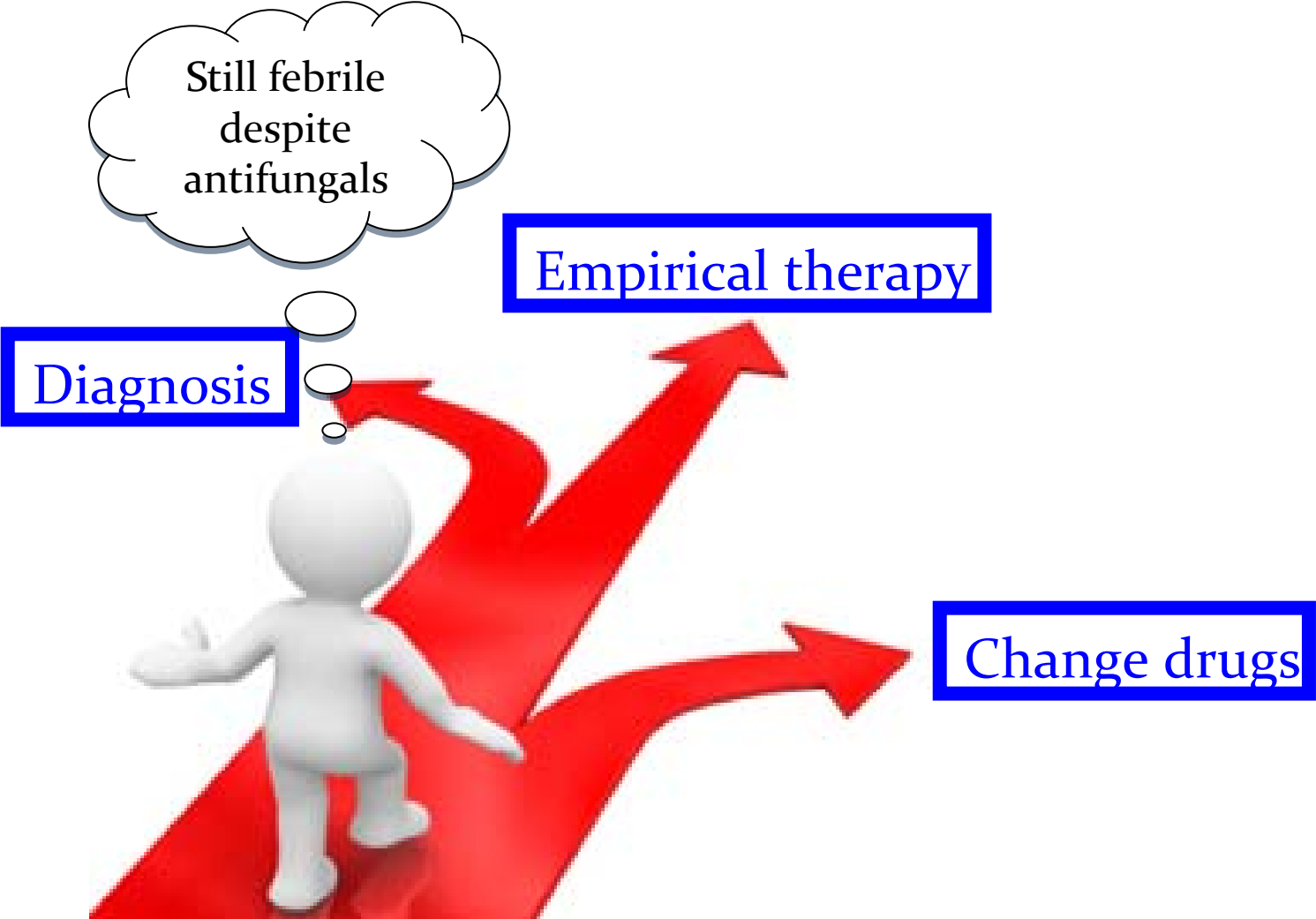
	A	Empirical	C				D	E
	-		I	II	III	IV	-	
Radiological signs & clinical symptoms	No	Persistent Febrile neutropenia	No	Clinical (any new infiltrate not fulfilling the EORTC/MSG criteria)		Radiological signs on CT (Dense, well-circumscribed lesions(s) with or without a halo sign, air-crescent sign, or		Not 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

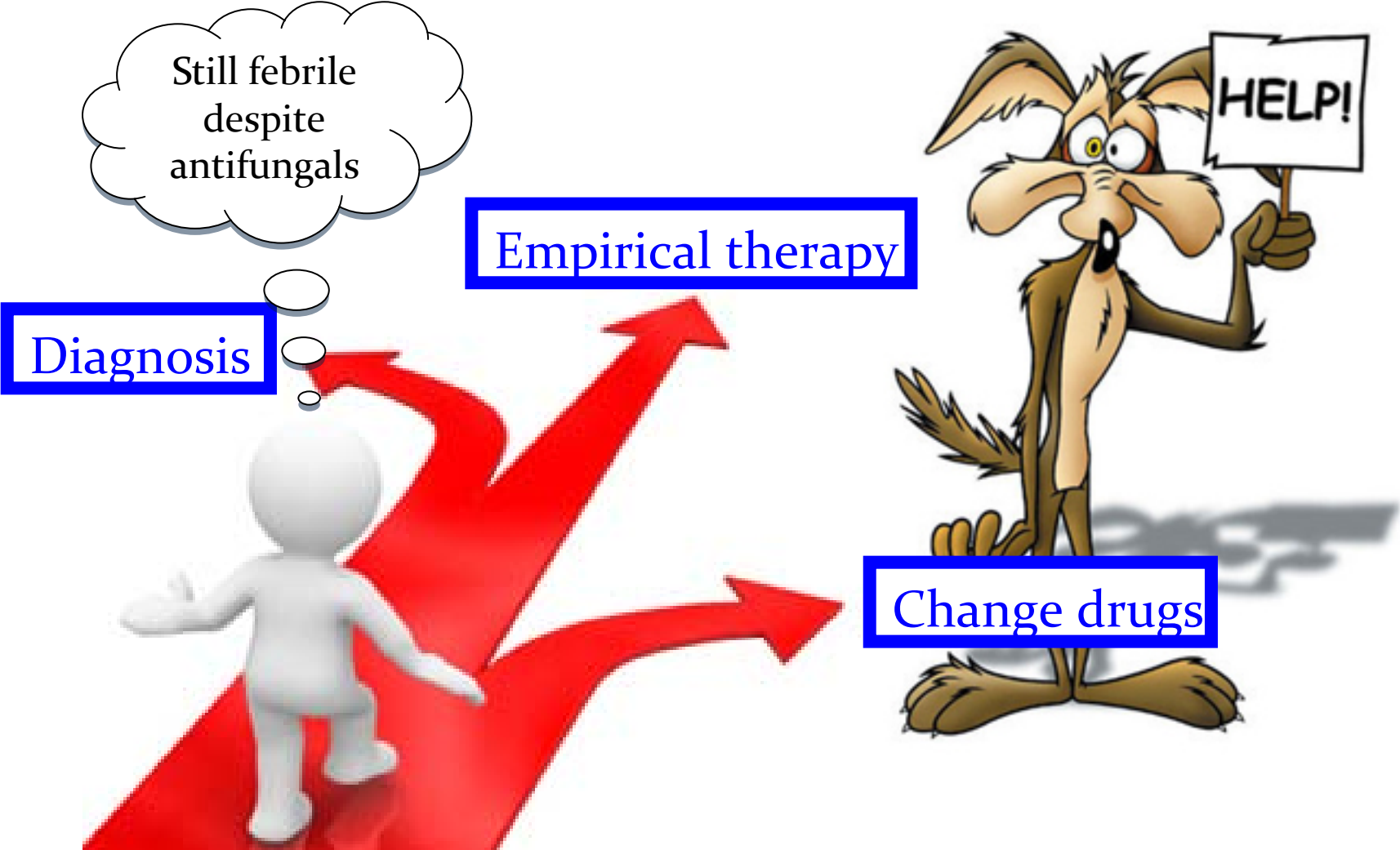
Choices choices choices



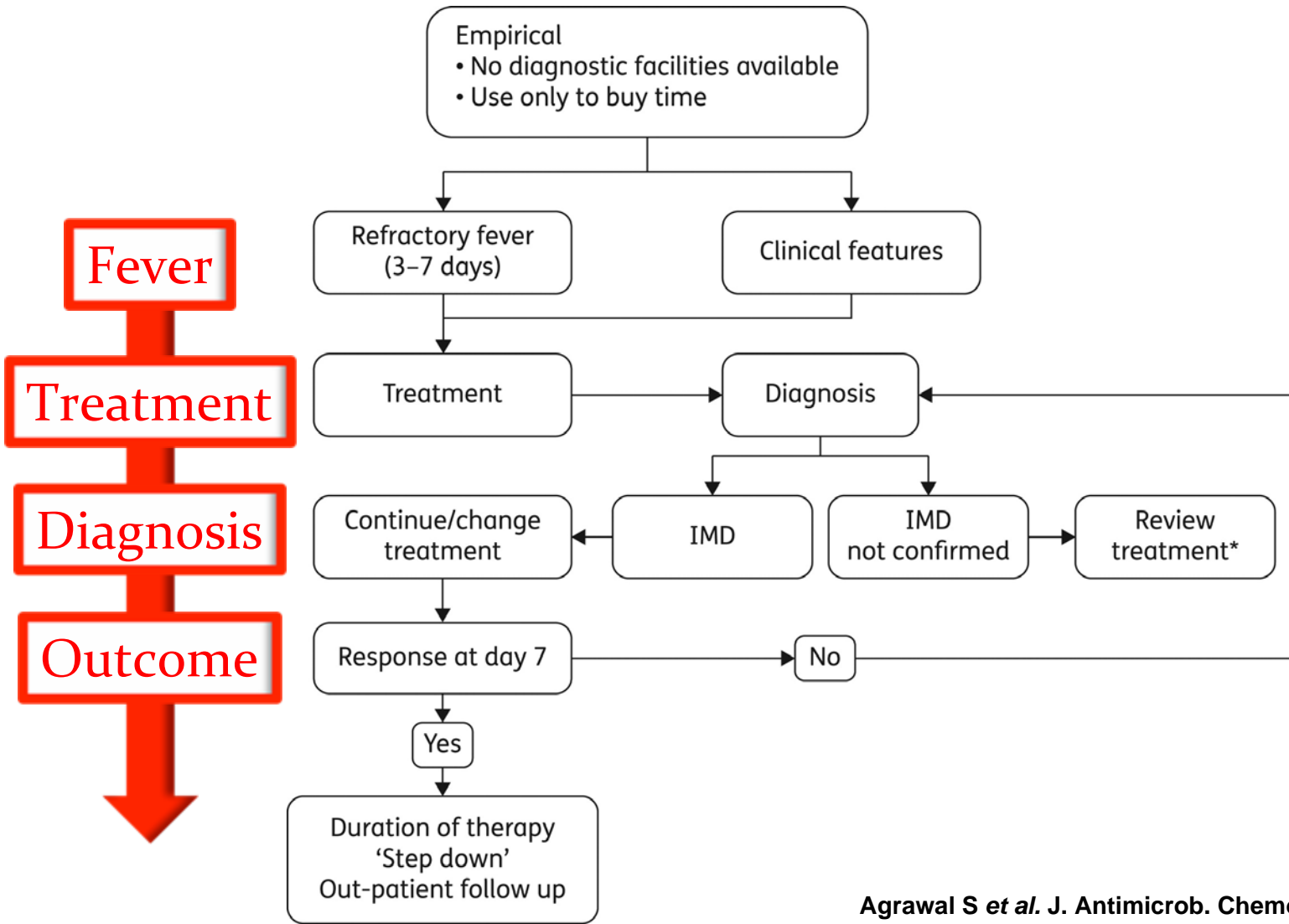
Choices choices choices



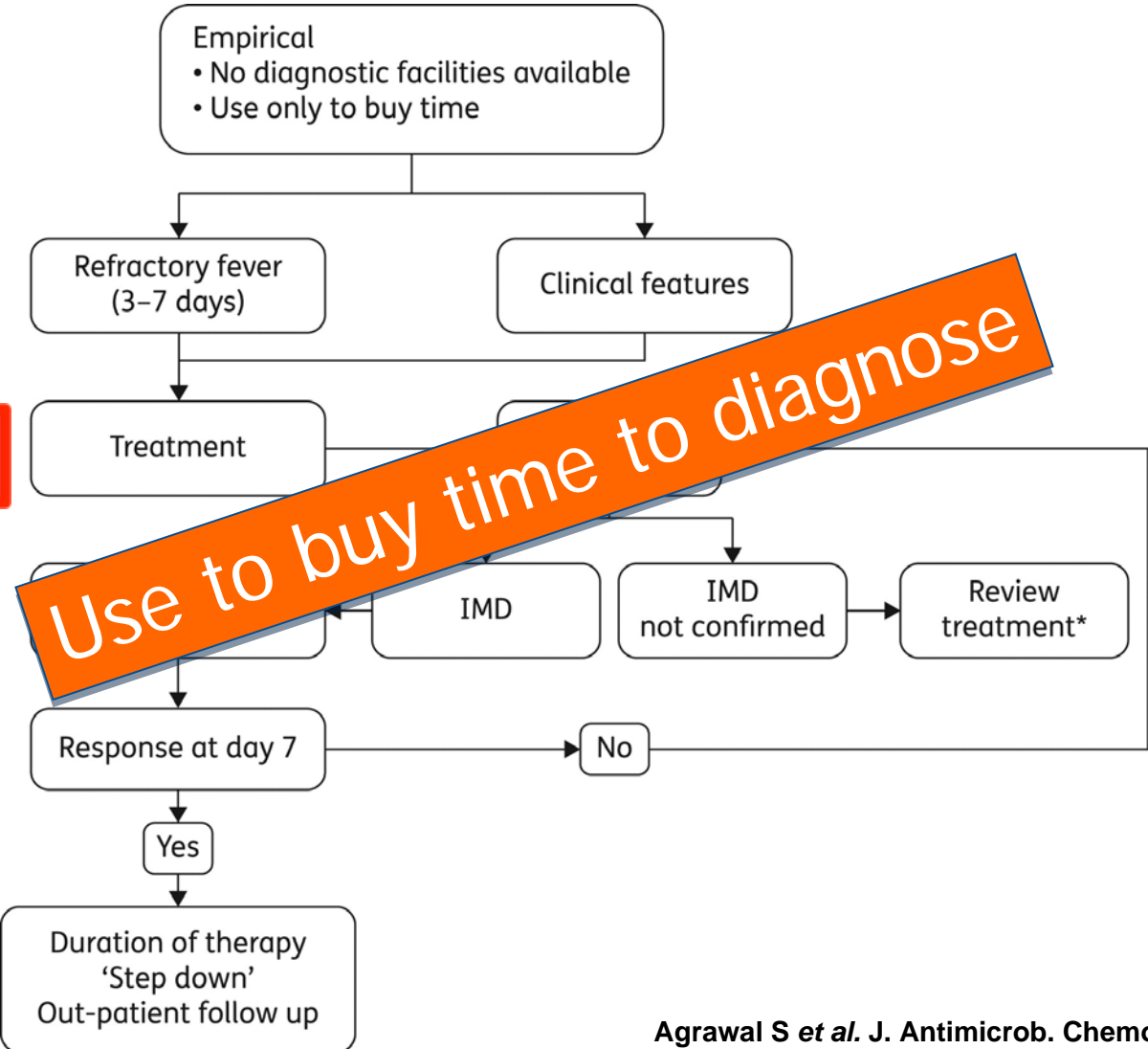
Choices choices choices



Empirical integrated care pathway



Empirical integrated care pathway



Do you use empirical therapy?

YES

NO

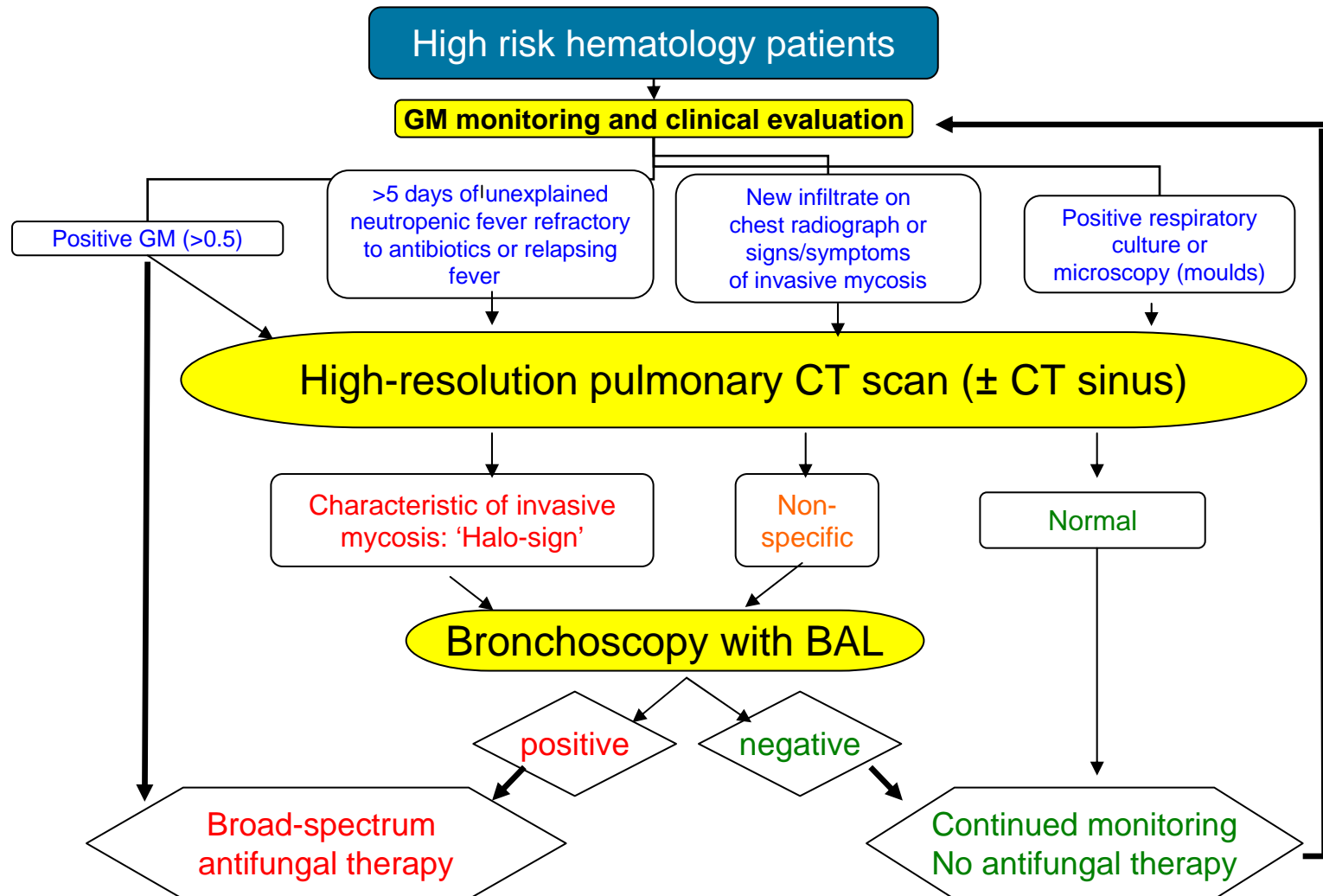
Pre-emptive therapy

Diagnostic-driven strategy
(Pre-emptive therapy)

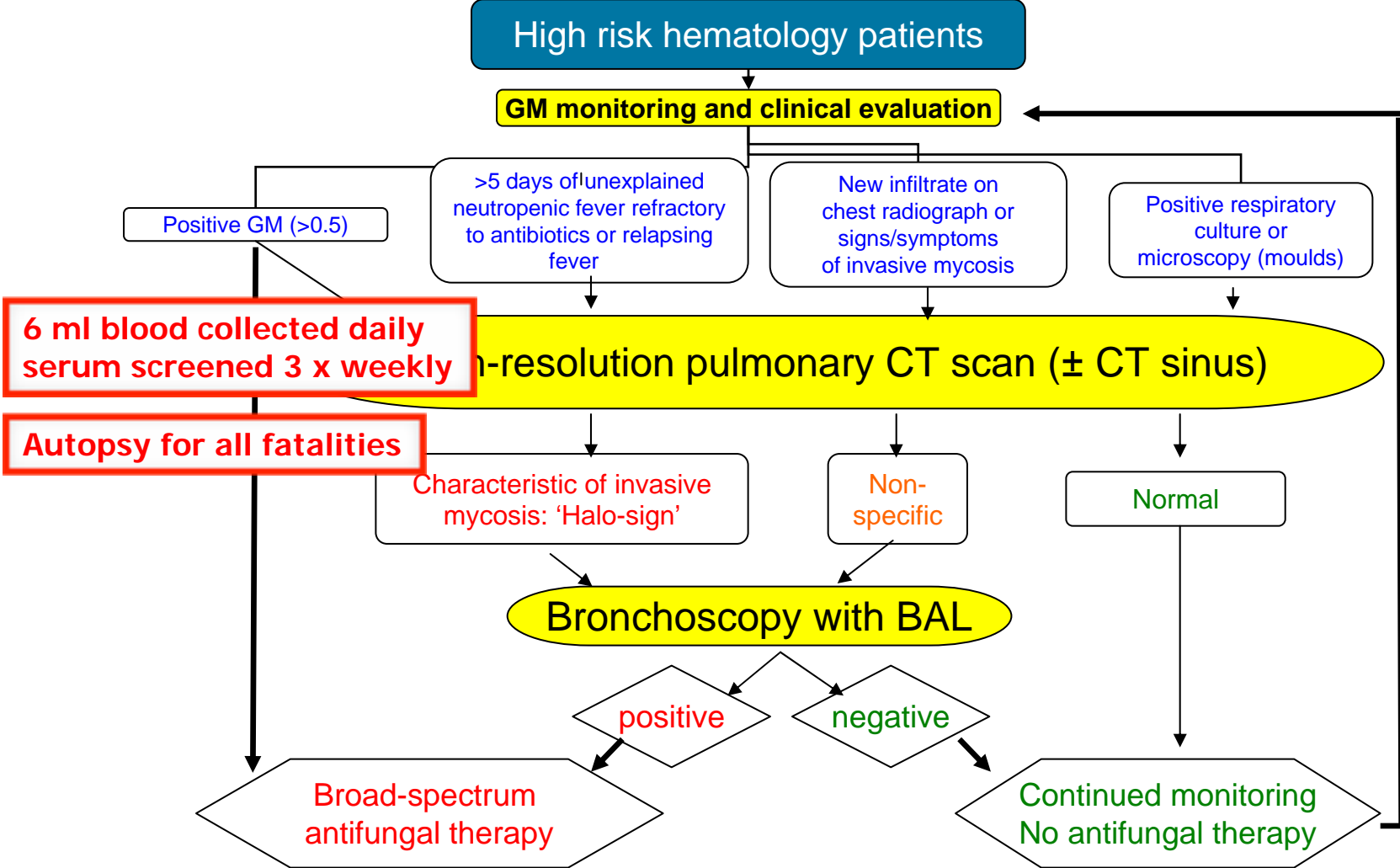
Treating invasive mould disease

	A	B	Diagnostic driven				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 (Described lesions) with or without halo sign, air-crescent sign, or	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

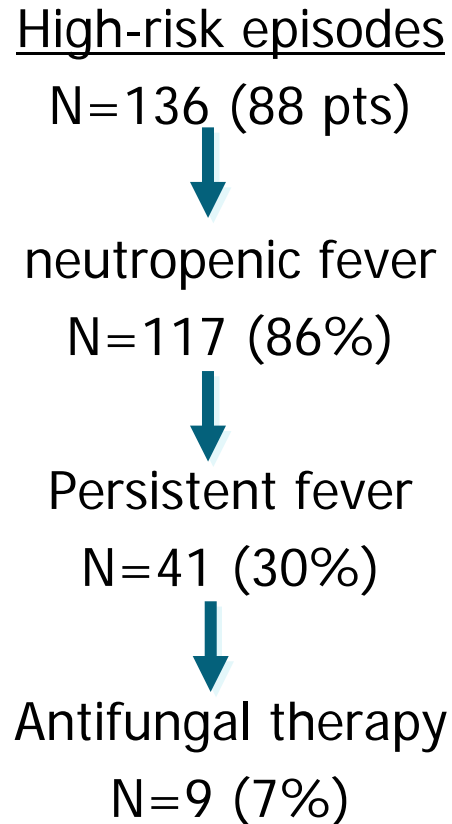
A diagnostic versus and empirical approach



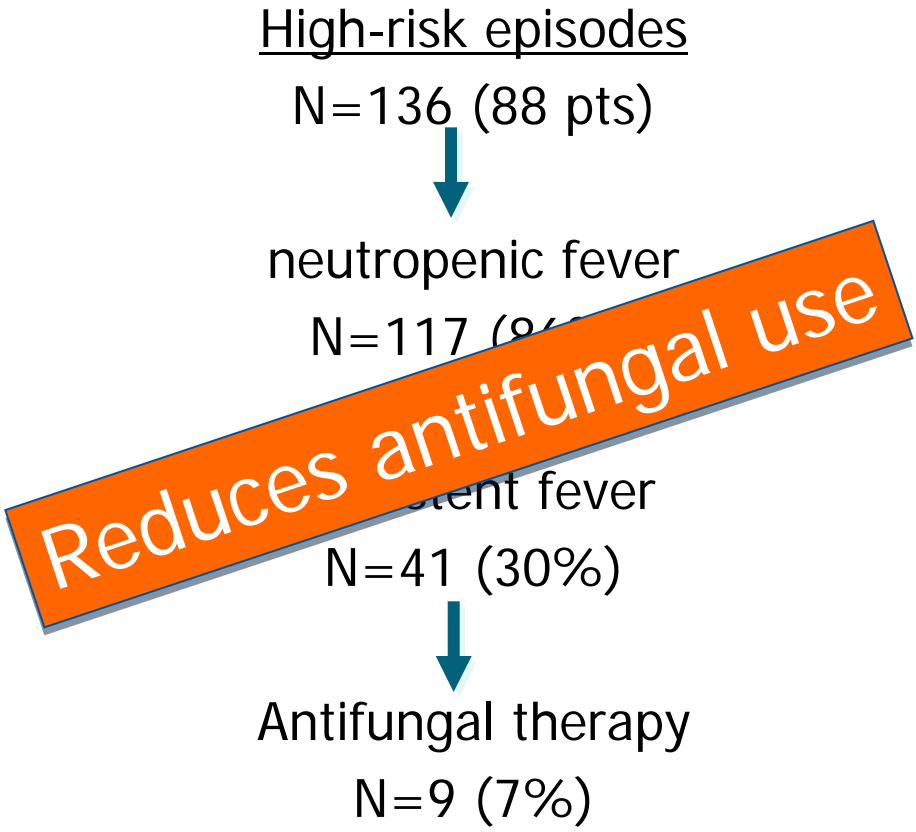
A diagnostic versus and empirical approach



Leuven's approach



Leuven's approach



The PREVERT study

Randomization at start of chemotherapy

**Instituted from
day 4 –14 of fever**

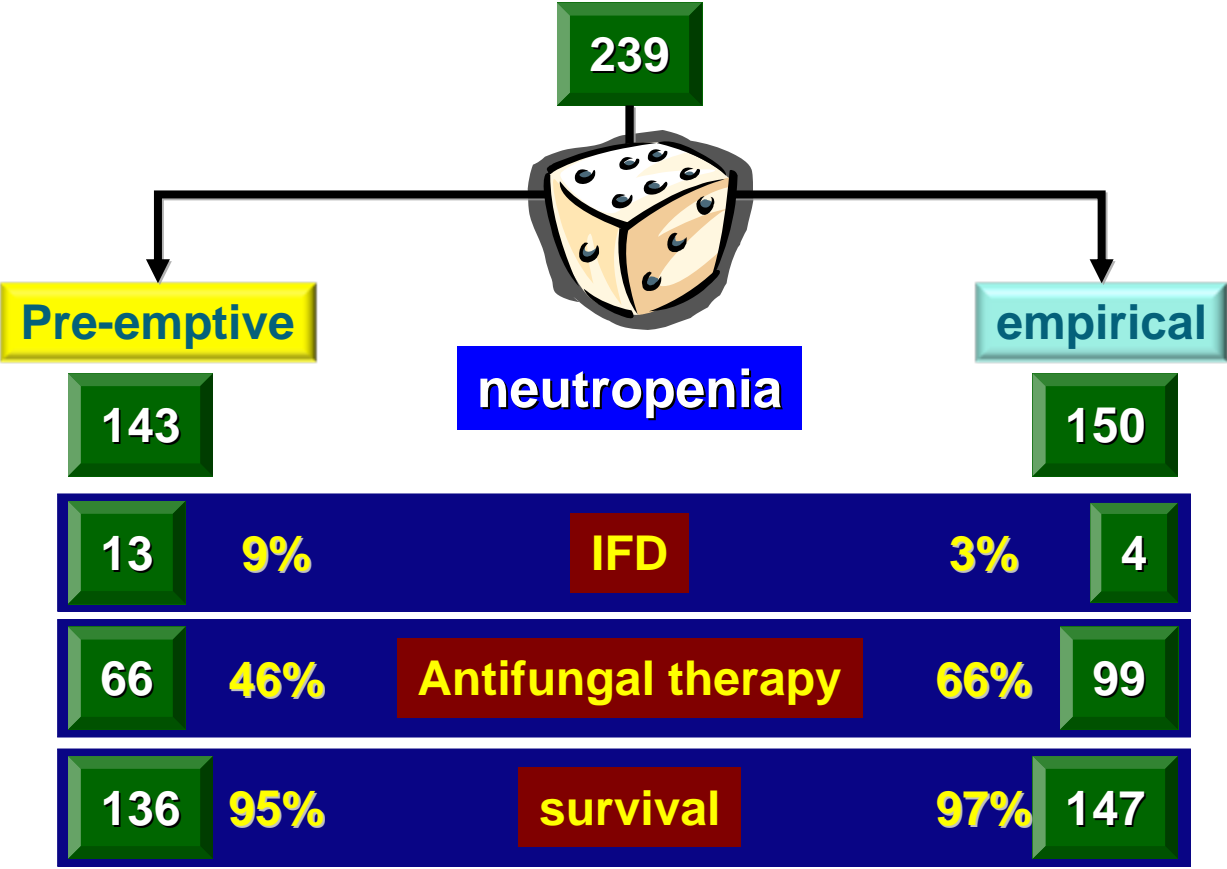
Pre-emptive

empirical

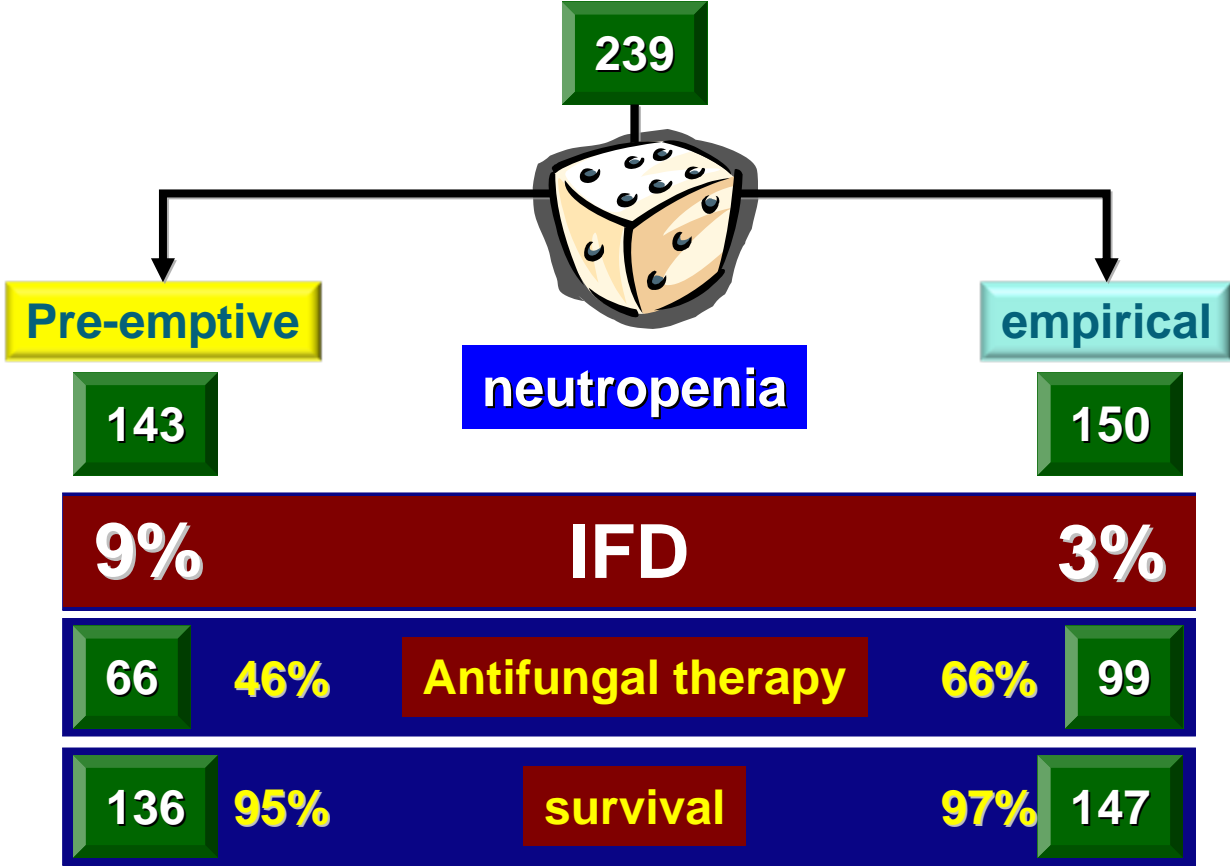
**Pneumonia, severe
mucositis, ,septic shock,
positive galactomannan
antigen test, skin lesion,
sinusitis or periorbital
inflammation, neurological
symptoms, diarrhea**

Fever driven

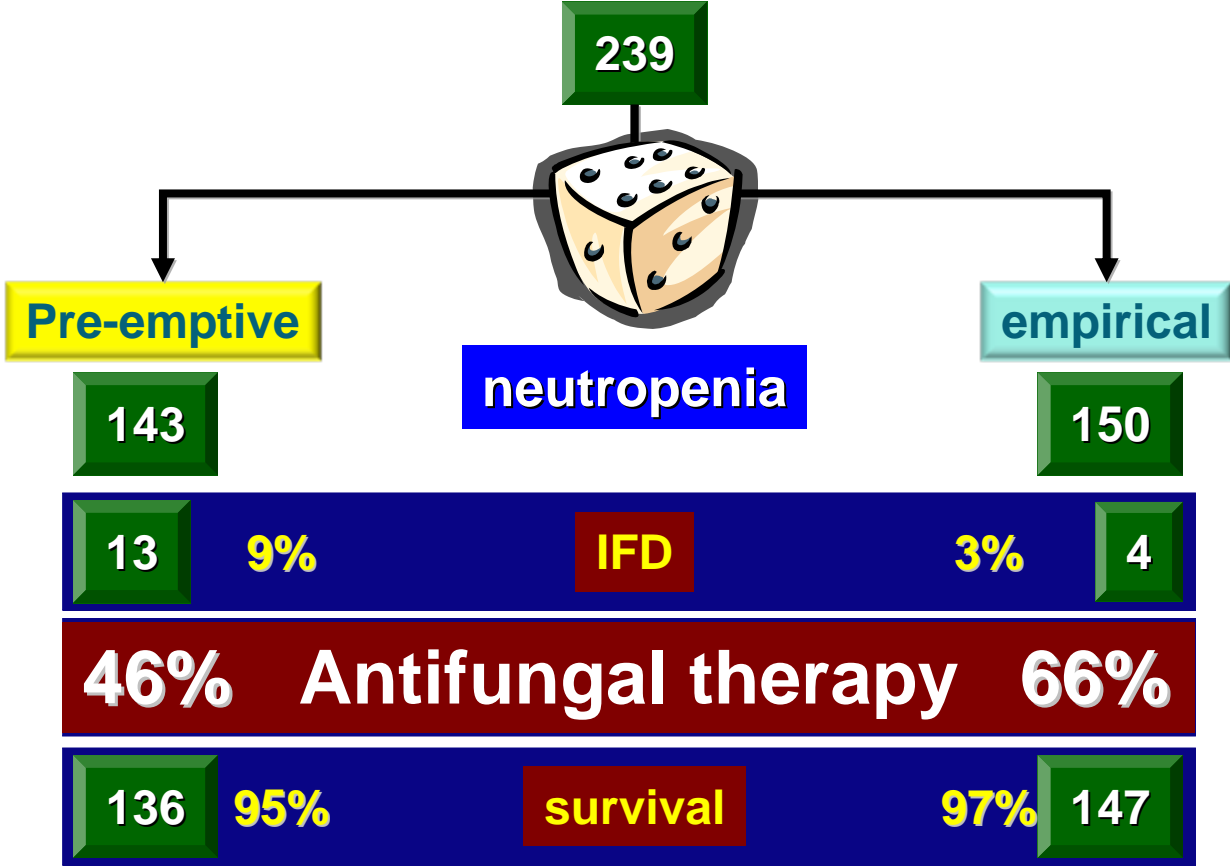
The PREVERT study - GM & CT



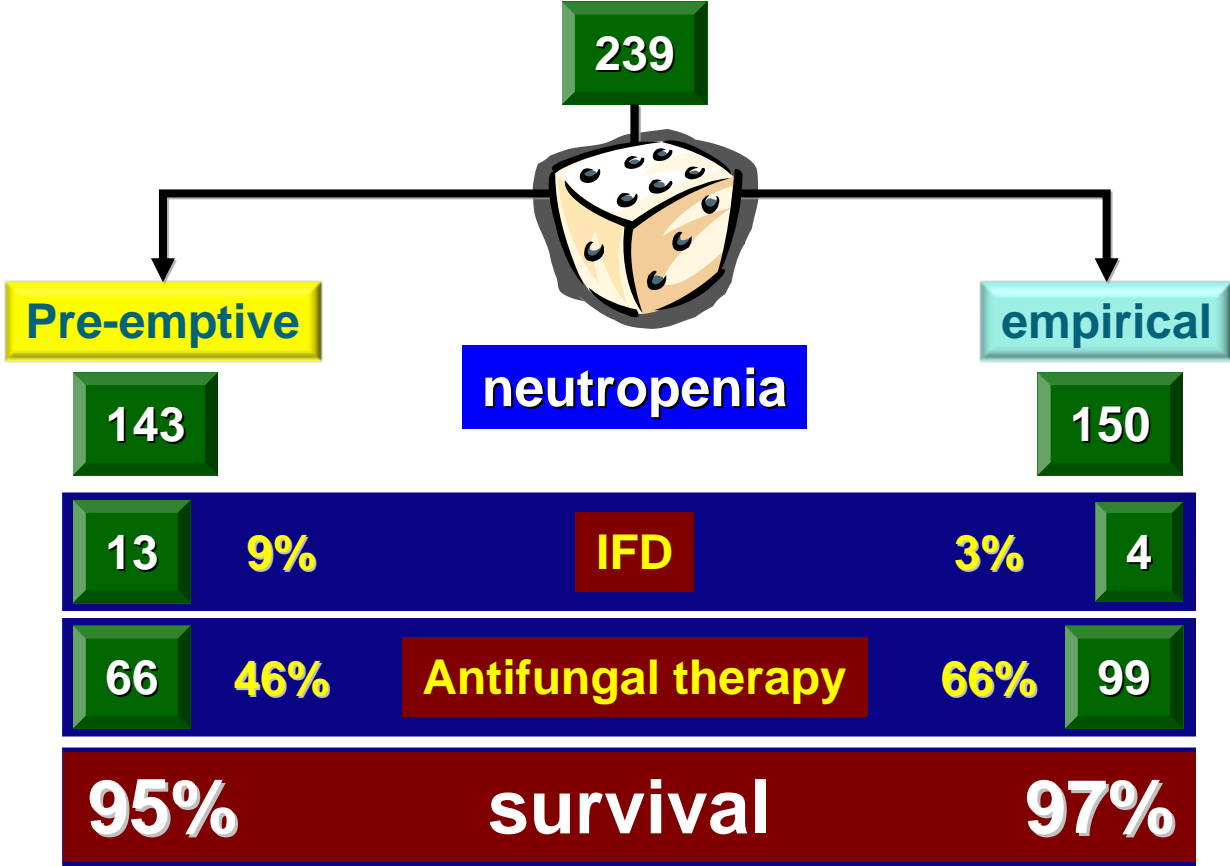
The PREVERT study



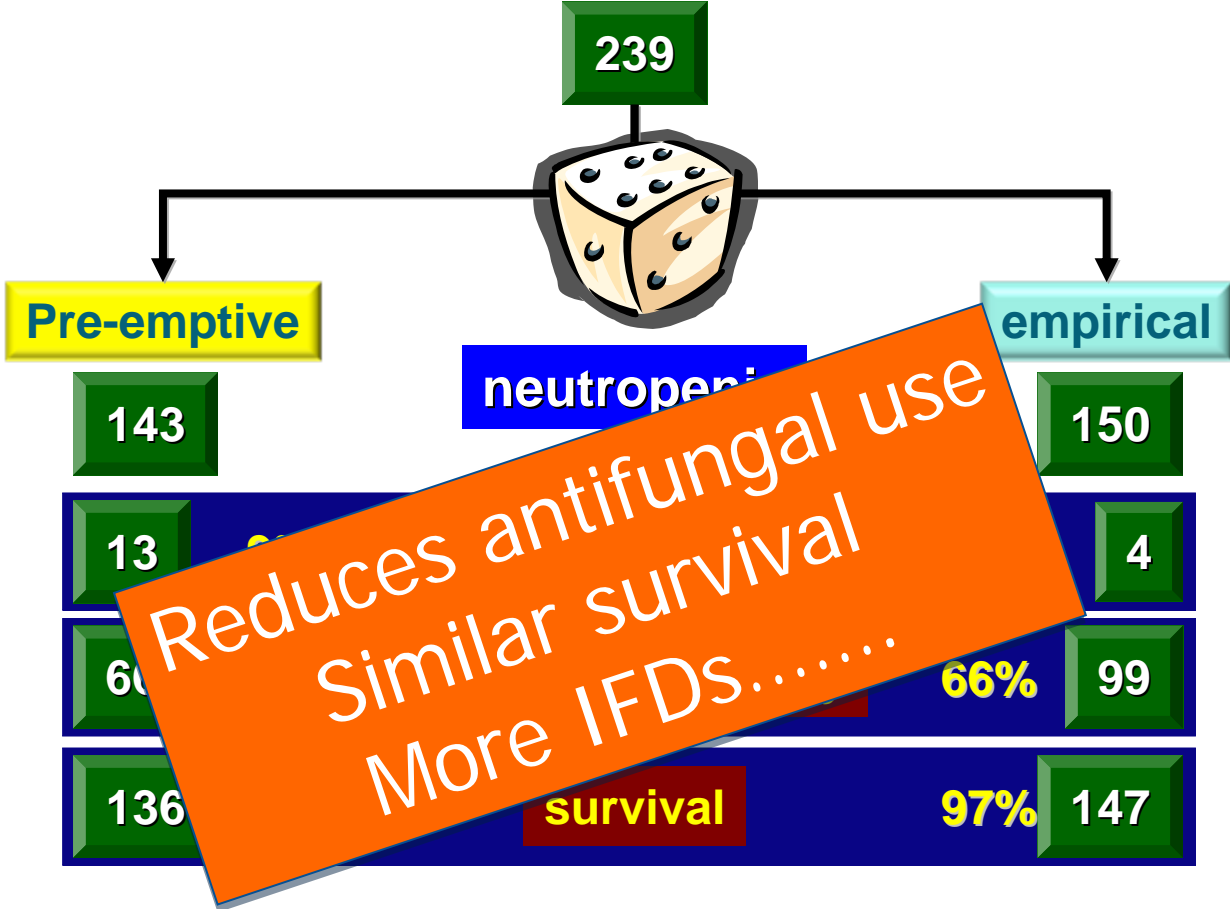
The PREVERT study



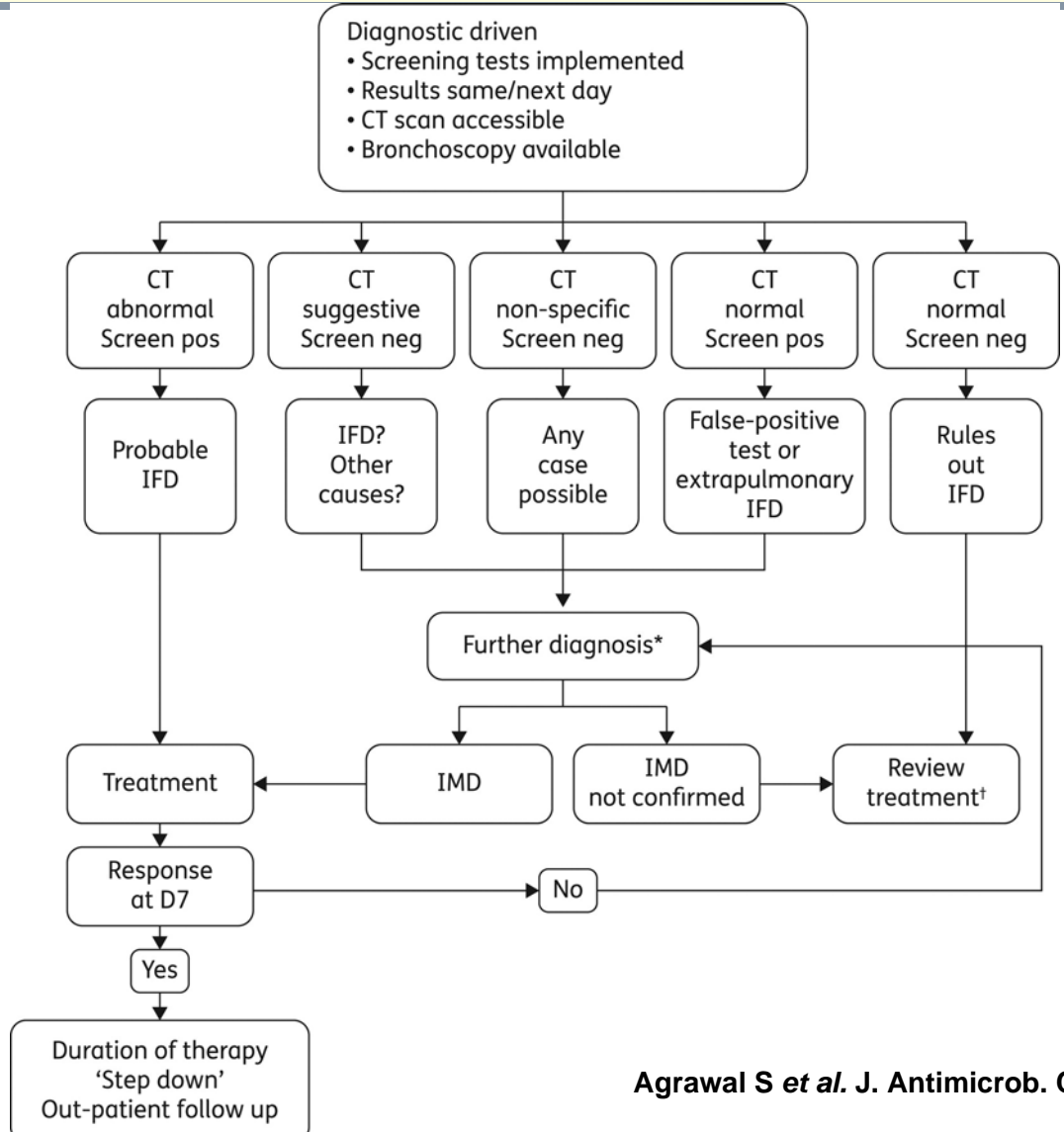
The PREVERT study



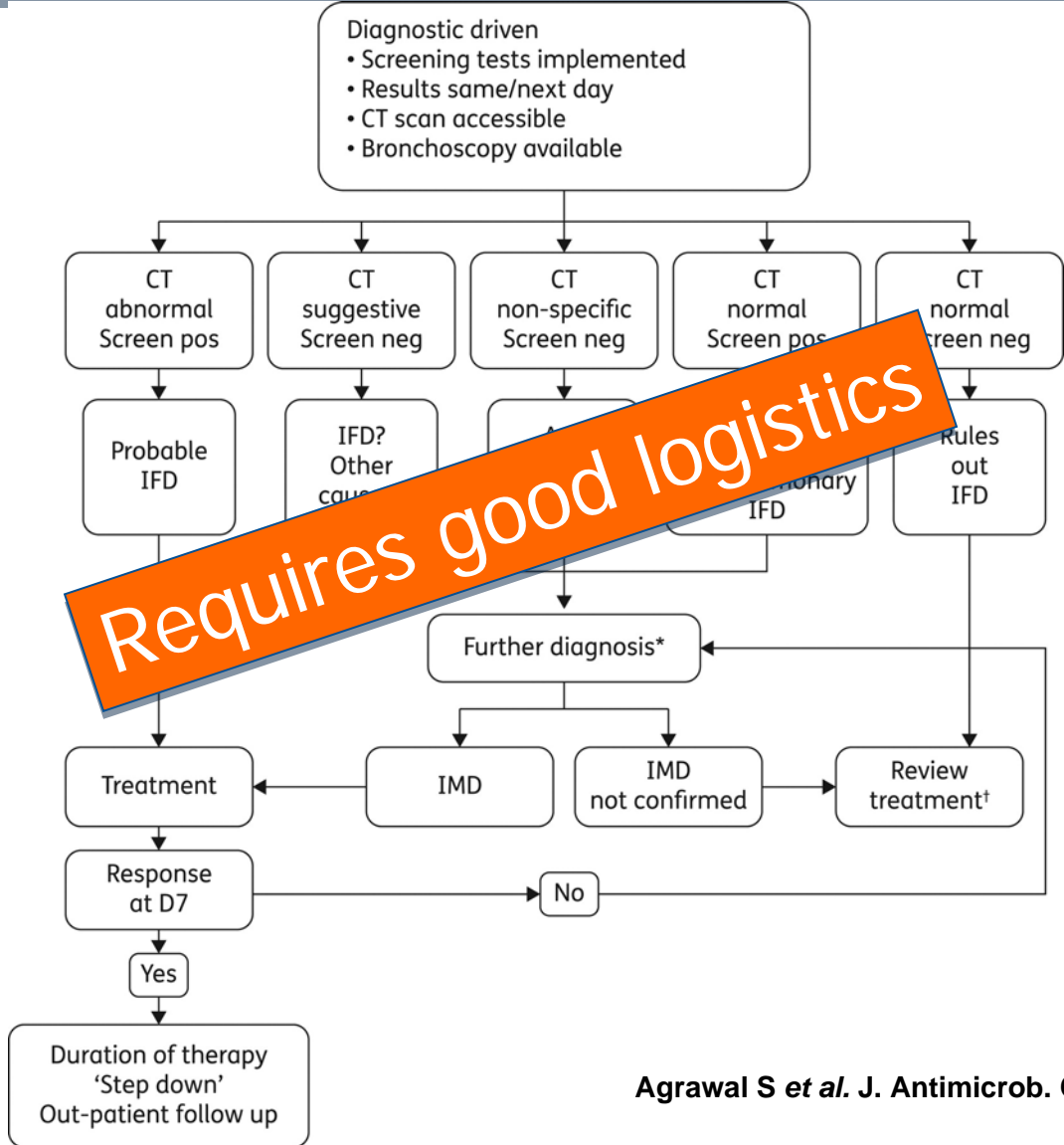
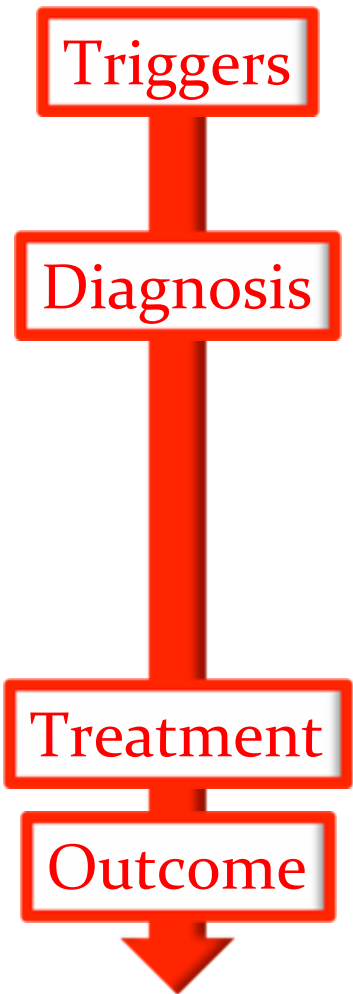
The PREVERT study



Diagnostic-driven integrated care pathway.



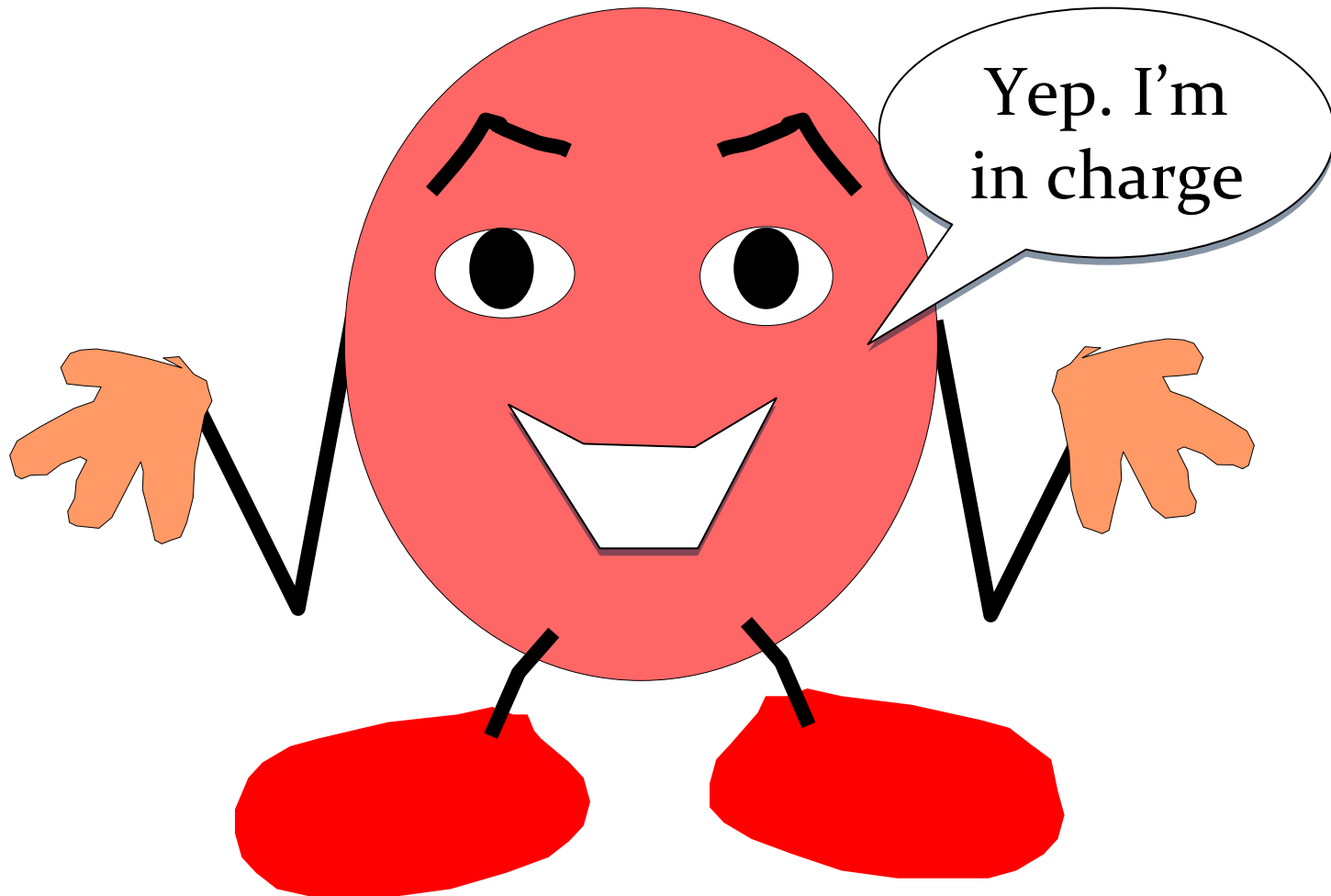
Diagnostic-driven integrated care pathway.



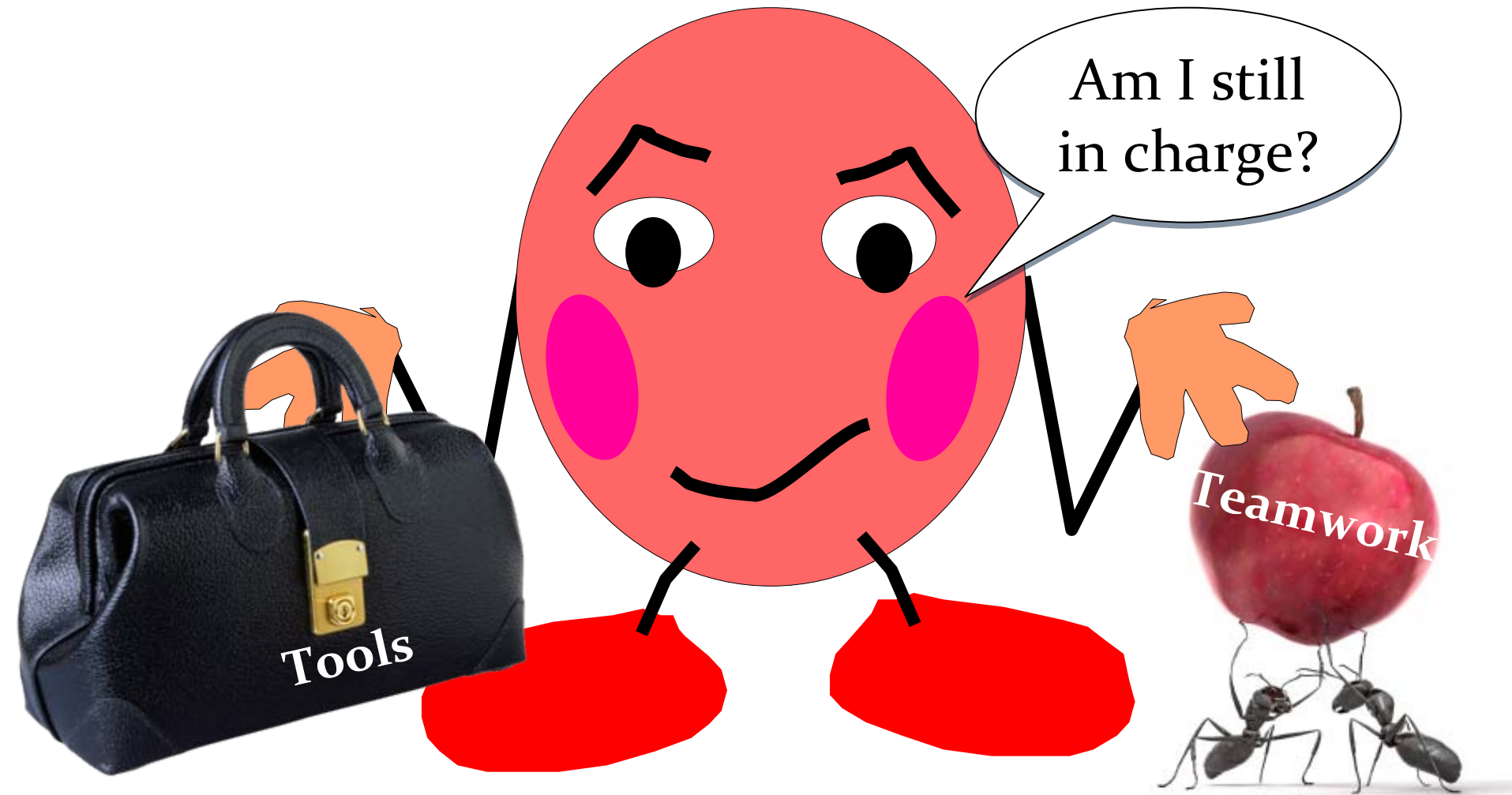
Empirical versus diagnostic-driven approach

	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 unlikely 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 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 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 randomization

EORTC 65091-06093

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 treatment for their cancer not yet
velopment of a fever or after the infection is shown in laboratory test, chest x-ray, or CT scan
gin acetate therapy in treating patients with acute myeloid leukemia or myelodysplastic syndrome that is



MERCK

to start Q3 2011

Thank you!