Torino
28 Febbraio 2014

La Terapia Antifungina

Francesco G. De Rosa

68-yr-old male with CLL at diagnosis

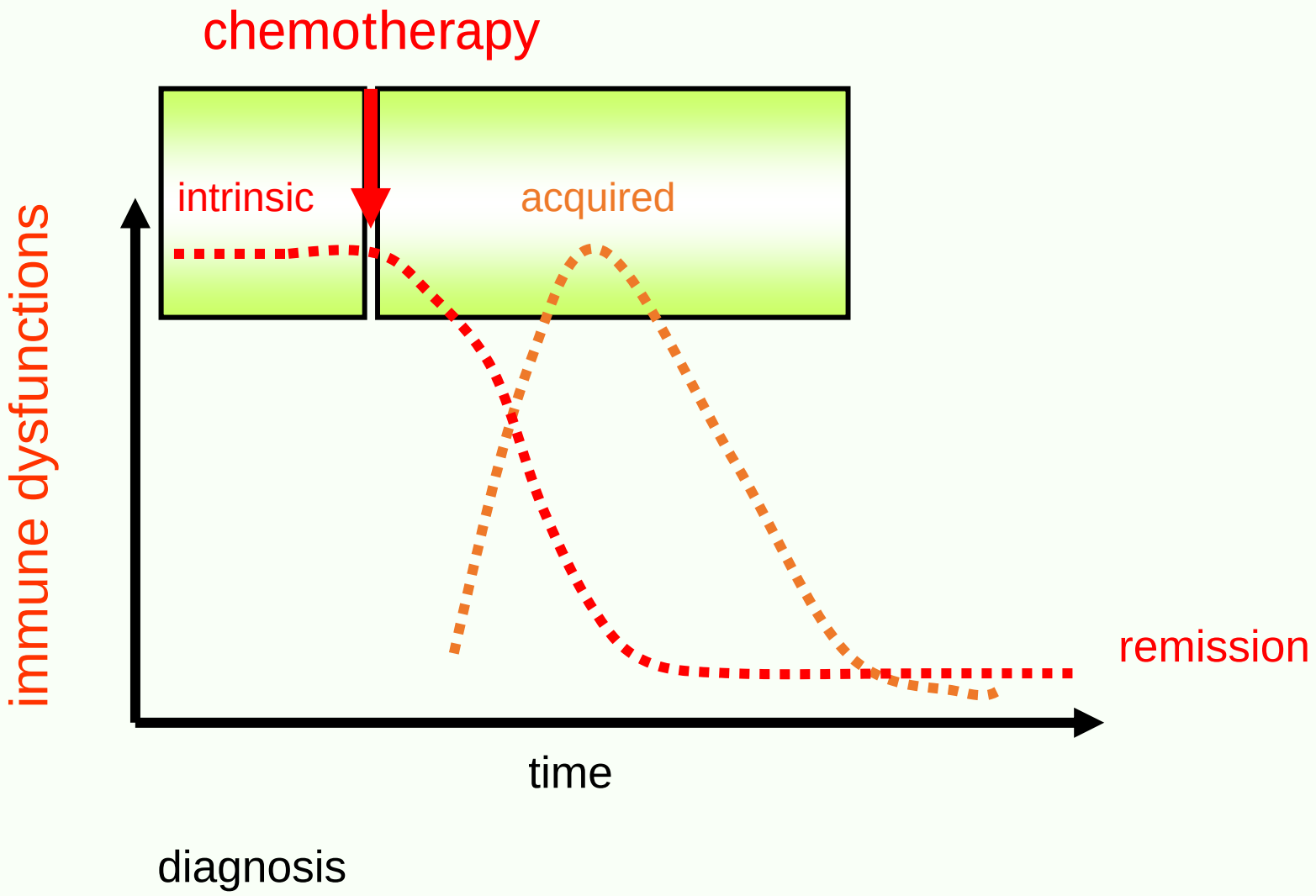
Sg-Emocromocitometrico		
WBC (Leucociti)	85.58	10^9/L
RBC (Eritrociti)	4.38	10^12/L
HGB (Emoglobina)	13.8	g/dL
PLTS (Trombociti)	139	10^9/L

Neutrofili #	9.02
Linfociti #	76.35
Monociti #	0.09
Eosinofili #	0.00
Basofili #	0.12

s-Immunoglobuline G	360	mg/dL
s-Immunoglobuline A	60	mg/dL
s-Immunoglobuline M	16	mg/dL

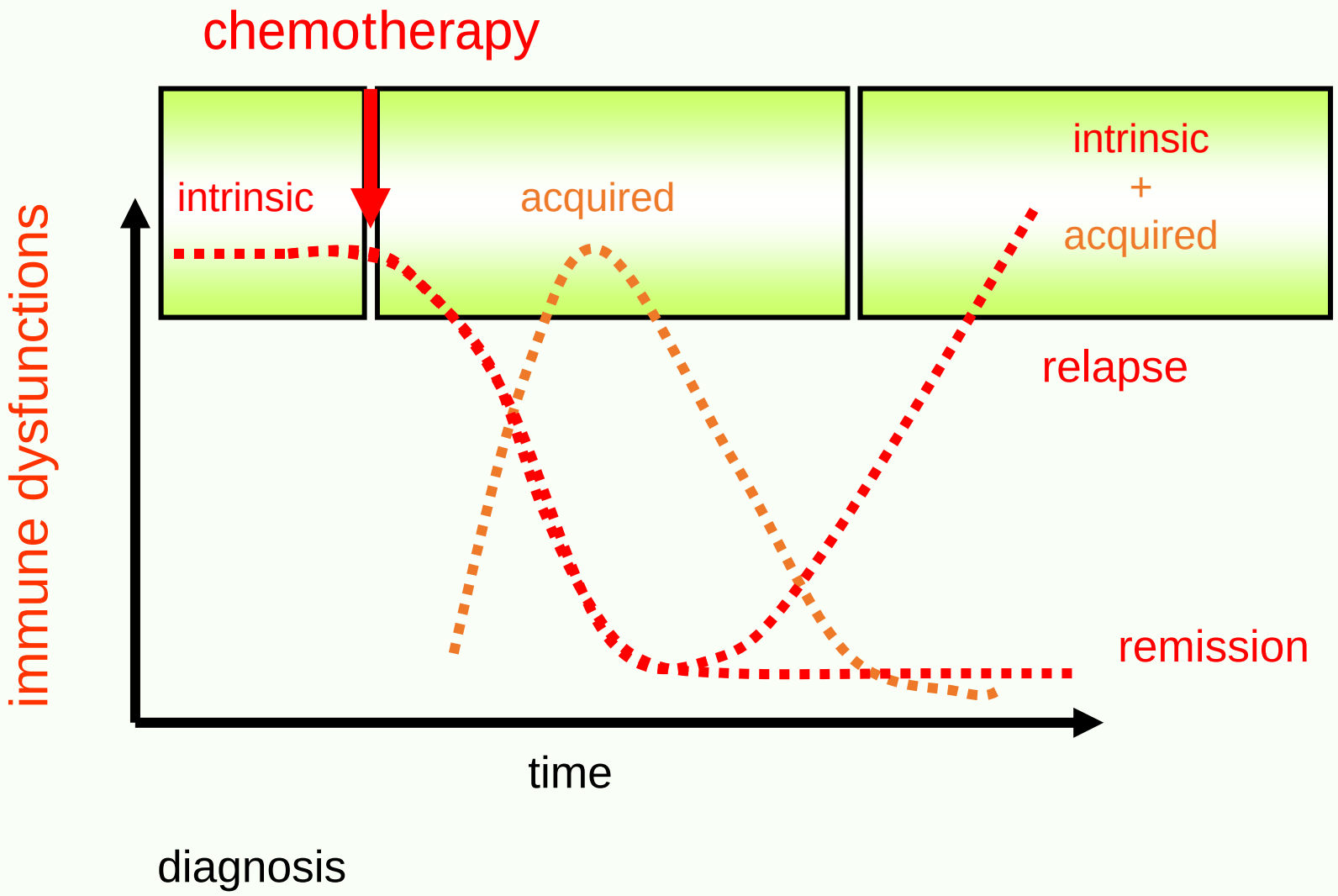
40-yr-old female with AML at diagnosis

Sg-Emocromocitometrico		
WBC (Leucociti)	**211.95**	10^9/L
RBC (Eritrociti)	**2.81**	10^12/L
HGB (Emoglobina)	**8.7**	g/dL
HCT (Ematocrito)	**26.5**	%
MCV (Volume Globulare Medio)	**94**	fL
MCH (Contenenuto Medio HGB)	**31.0**	pg
MCHC (Concentrazione Media HGB)	**32.8**	g/dL
RDW-SD (Distribuzione Vol. RBC)	**59.0**	fL
RDW-CV (Distribuzione Vol. RBC)	**17.2**	%
PLTS (Trombociti)	**28**	10^9/L
PDW (Distribuzione Vol. PLTS)		


chemotherapy
intrinsic
acquired
immune dysfunctions
remission
time
diagnosis

38-yr-old male with AML during induction CT

Sg-Emocromocitometrico		
WBC (Leucociti)	**0.10**	10^9/L
RBC (Eritrociti)	**2.47**	10^12/L
HGB (Emoglobina)	**7.6**	g/dL
HCT (Ematocrito)	**20.4**	%
MCV (Volume Globulare Medio)	**83**	fL
MCH (Contenenuto Medio HGB)	**30.8**	pg
MCHC (Concentrazione Media HGB)	**37.3**	g/dL
RDW-SD (Distribuzione Vol. RBC)	**39.7**	fL
RDW-CV (Distribuzione Vol. RBC)	**13.2**	%
PLTS (Trombociti)	**6**	10^9/L


chemotherapy
intrinsic
acquired
intrinsic
+
acquired
relapse
remission
immune dysfunctions
time
diagnosis

AUTOPSY SURVEY ASPERGILLUS INFECTIONS

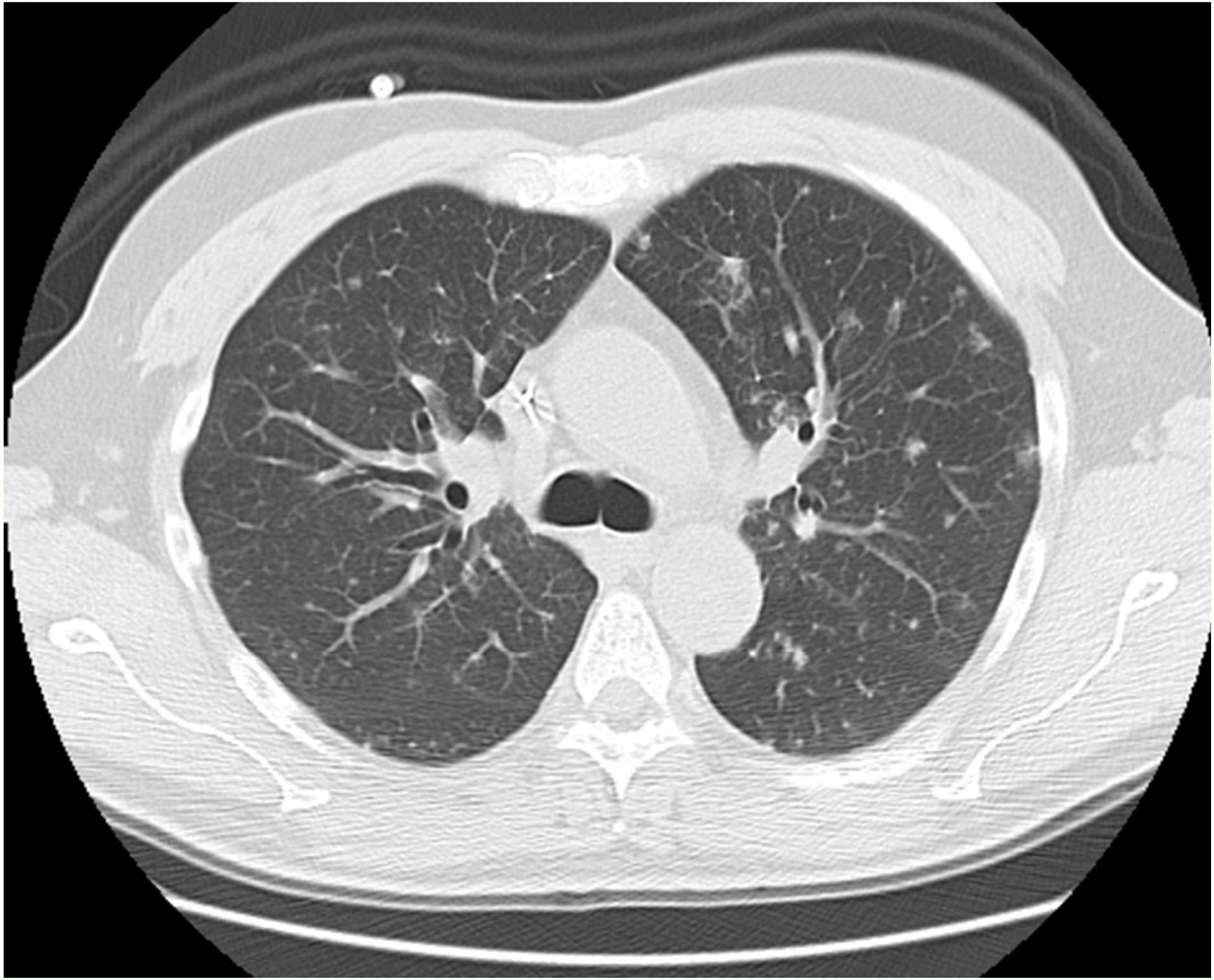
Bodey et al. Eur J Clin Microbiol Infect Dis 1992

15-30% OF PATIENTS WITH

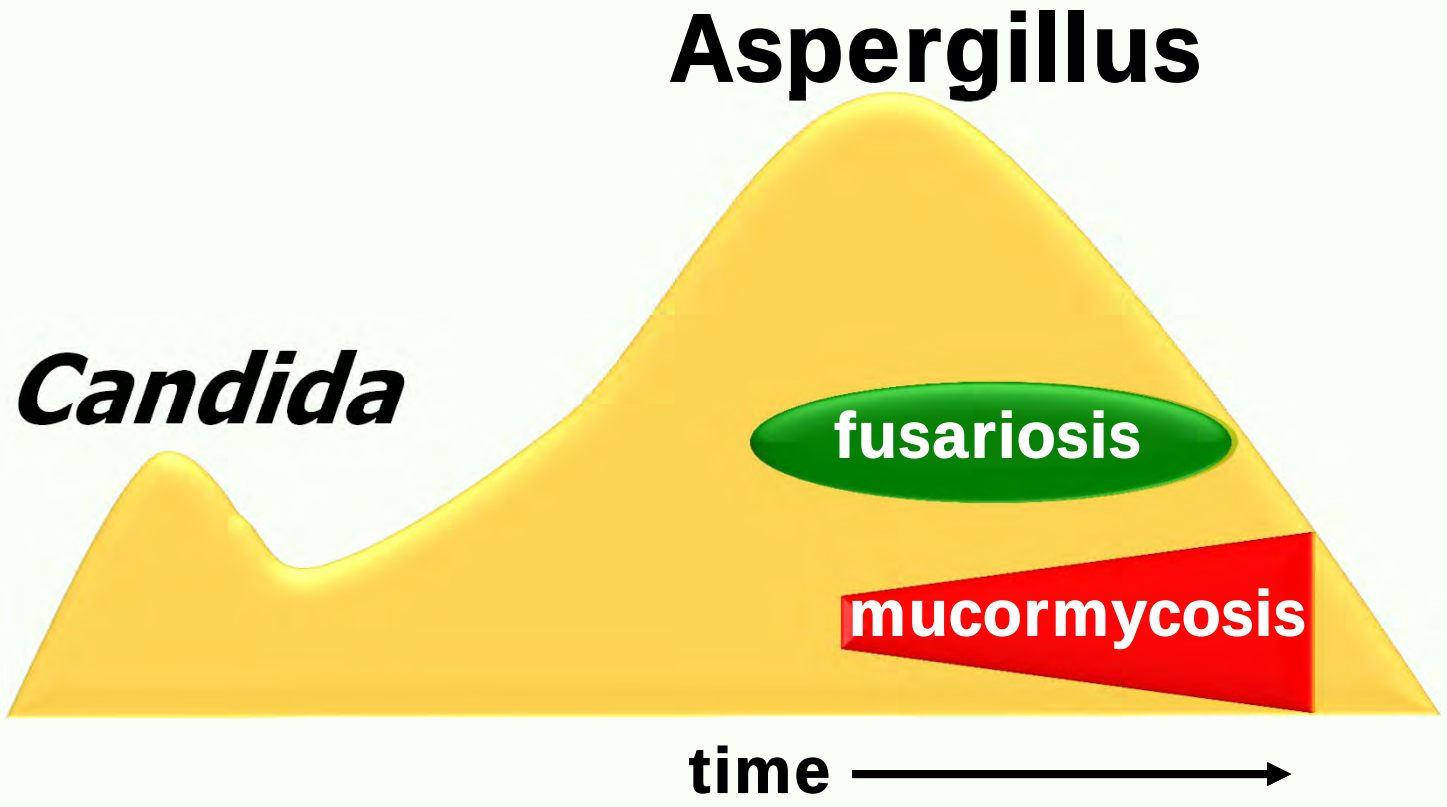
INVASIVE FUNGUS AT AUTOPSY

NEVER RECEIVED

ANY SYSTEMIC ANTIFUNGAL THERAPY



FUNGI IN RELATION TO DEFECTS IN THE DEFENSE SYSTEMS



RISK FACTORS AND INCIDENCE OF INVASIVE *CANDIDA* INFECTIONS

Marchetti et al. Clin Infect Dis 2004; 38:311-320

Candida

Postsurgical ICU

Neutropenia

Parenteral nutrition

Burns

Neonates

Antibacterials

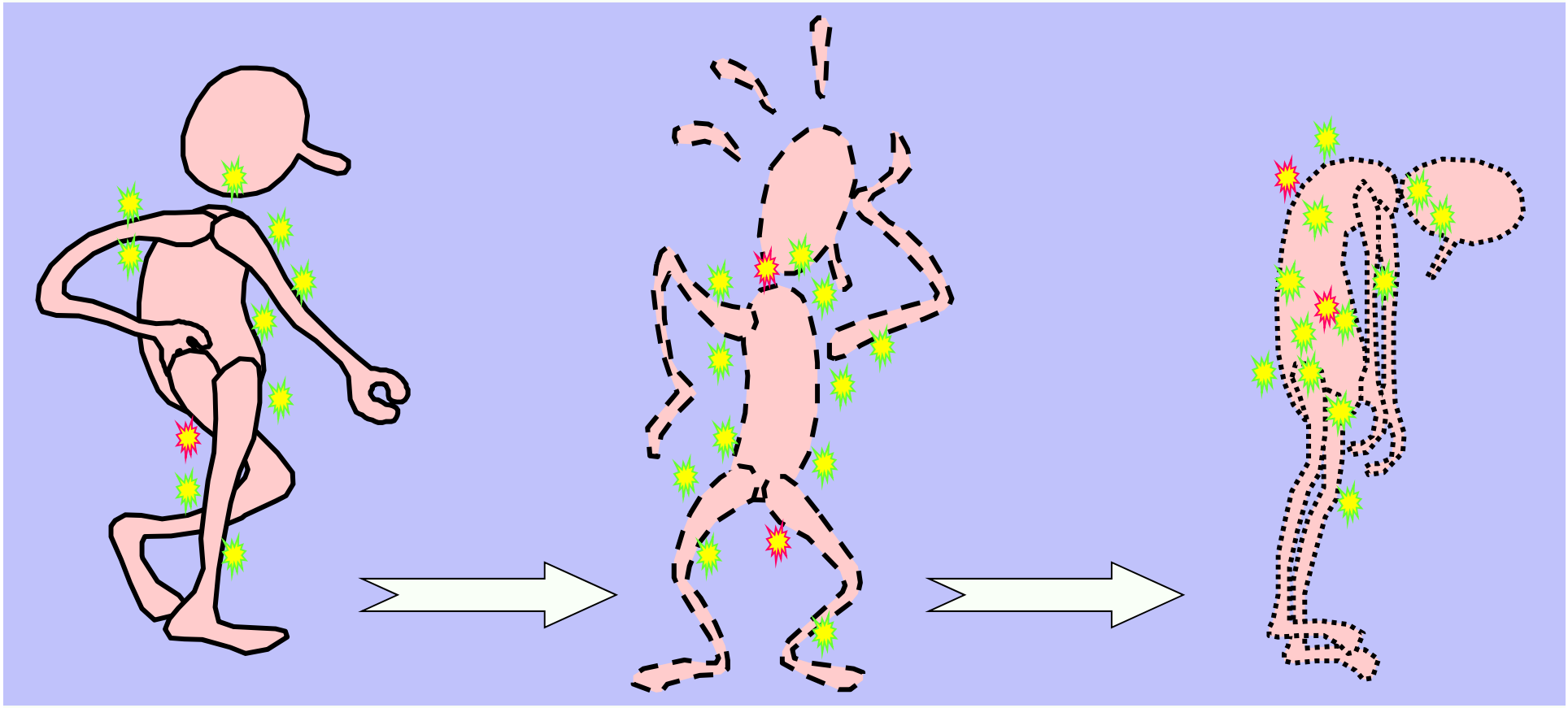
IV drug abuse

Endogenous

Contact / Catheters

n = 1137 ICU patients	Incidence %
Coag-neg staphylococci	20
Escherichia coli	19
Staphylococcus aureus	13
Streptococcus pneumoniae	7
Viridans streptococci	5
Klebsiella species	4
***Candida* species**	**3**
Enterococci	3
Pseudomonas species	3
Anaerobes	1

FROM COLONIZATION TO INVASION



Colonization **(superficial) infection** **disease**

CHARACTERISTICS OF ASPERGILLOSIS (IN THE ICU)

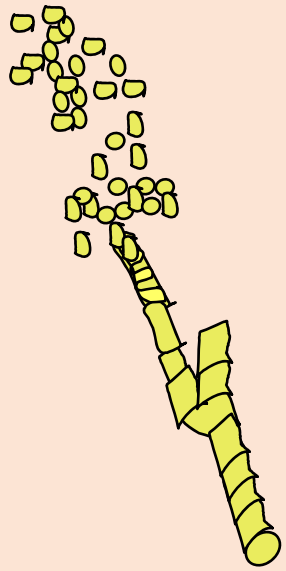
Meersseman et al. Clin Infect Dis 2007; 45: 205-216

High risk:

treated hematological malignancies

Medium:

prolonged (>7 days) corticosteroids
treated malignancies
COPD
livercirrhosis
(prolonged) use of immunosuppressants
HIV
lung transplants

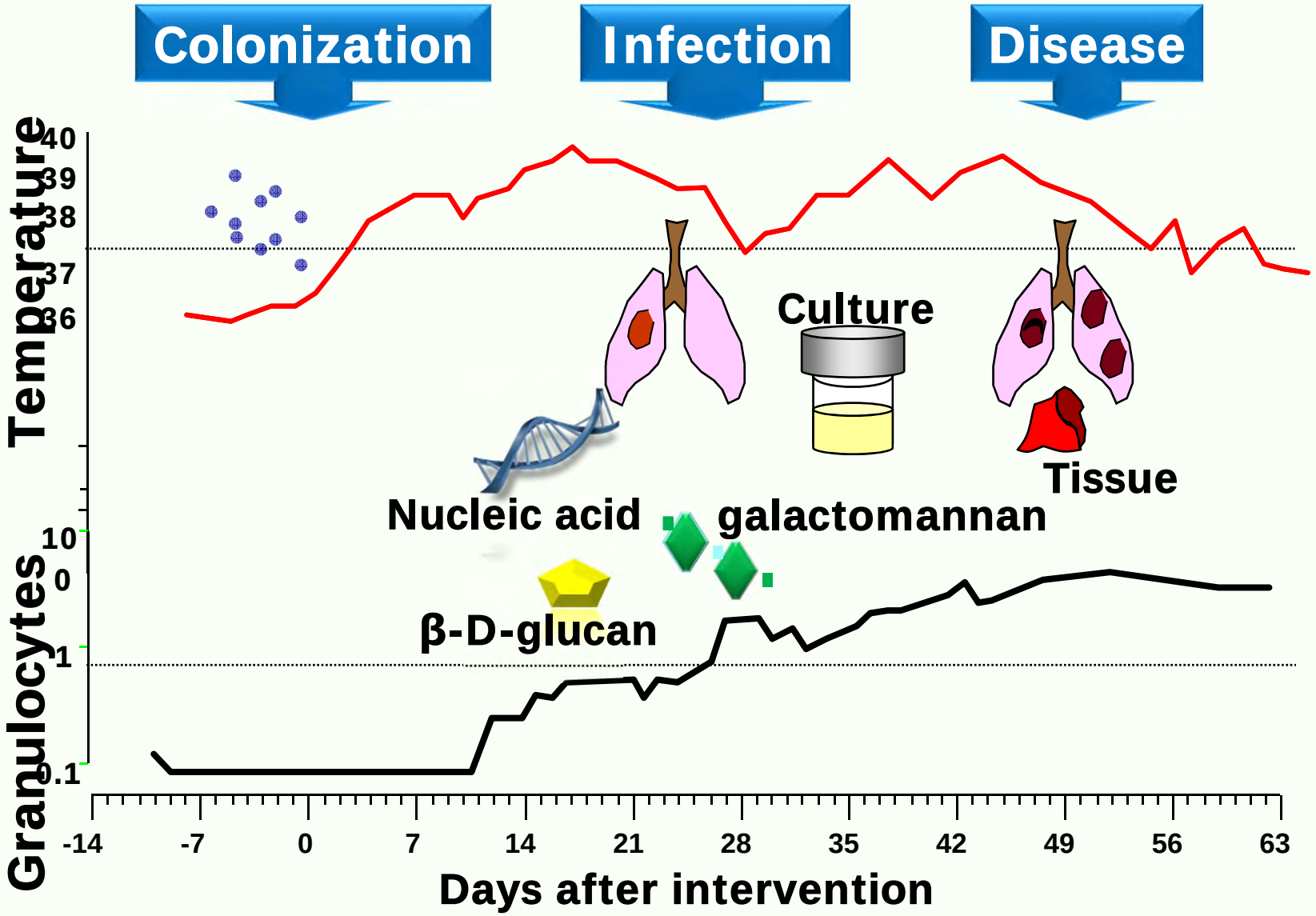


Aspergillus

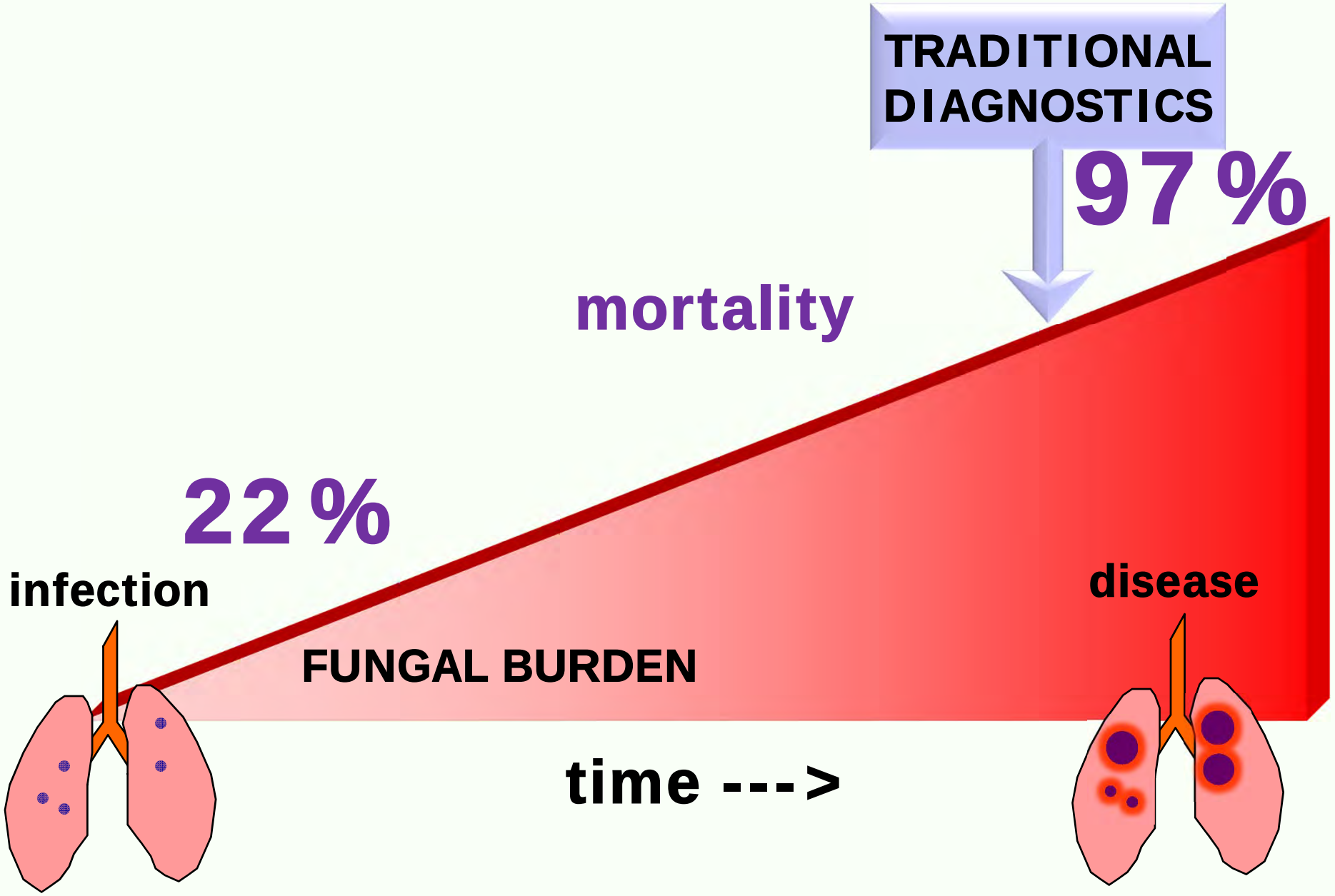
Low:

other organ transplants
burns, malnutrition, post-cardiac surgery
<7 days corticosteroids

EVOLUTION OF MOULD DISEASE



MORTALITY OVER TIME



Strategie di Terapia Antimicrobica nel Neutropenico Febbrile

- **Profilassi**
  - **(Levofloxacina)**
- **Terapia empirica antibiotica**
  - **Neutropenia febbrile (ad alto rischio)**
  - **Escalation Vs. de-escalation therapy**
- **Terapia empirica antifungina**
- **Terapia pre-emptive antifungina**
- **Terapia di infezioni**
  - **Microbiologicamente o clinicamente documentata, ad etiologia batterica o fungina**

BMC Infectious Diseases

BioMed Central
The Open Access Publisher

Epidemiology of bloodstream infections in patients with acute myeloid leukemia undergoing levofloxacin prophylaxis

BMC Infectious Diseases 2013, 13:563 doi:10.1186/1471-2334-13-563

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Caso Clinico 1

- GV, maschio, 31 anni
- Anamnesi remota e familiare NDD
- Gennaio 2012: leucemia acuta mieloblastica
  - AML1/ETO according to WHO classification
  - (AML2 according to FAB classification)
  - Alla diagnosi:

- Aspirato midollare mieloblasti 61% (morphology, cytochemistry, flowcytometry)
- Analisi citogenteica: anomalie cromosomiche in >75% delle metafasi analizzate variante t(8;21) (ETO/AML1 fusion gene on derived 21 chromosome)
- Analisi molecolare: RT-PCR AML1-ETO t(8;21)= positiva; ratio AML1/ETO/ABL >100%

Domanda 1.
E’ indicata una terapia antibiotica nella neutropenia febbrile?

1. **No, senza altri segni e sintomi di accompagnamento**
2. **Si, sempre**
3. **Si, in presenza di CVC e mucosite**
4. **La terapia antibiotica empirica è parte fondamentale della gestione dei pazienti neutropenici febbrili**

Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recipients: guidelines of the 4th European Conference on Infections in Leukemia (ECIL-4, 2011)

Diana Averbuch,[1] Catherine Cordonnier,[2] David M. Livermore,[3] Malgorzata Mikulska,[4] Christina Orasch,[5] Claudio Viscoli,[4] Inge C. Gyssens,[6,7] Winfried V. Kern,[8] Galina Klyasova,[9] Oscar Marchetti,[5] Dan Engelhard,[1] and Murat Akova[10] on behalf of ECIL4, a joint venture of EBMT, EORTC, ICHS, ESGICH/ESCMID and ELN

[1]Pediatric Infectious Diseases Unit, Hadassah Hebrew University Medical Center, Jerusalem, Israel; [2]APHP Henri Mondor Hospital, Hematology Department and Université Paris Est-Créteil, France; [3]Norwich Medical School, University of East Anglia, Norwich, UK; [4]Division of Infectious Diseases, University of Genova, IRCCS San Martino-IST, Genova, Italy; [5]Infectious Diseases Service, Department of Medicine, Lausanne University Hospital, Switzerland; [6]Department of Medicine and Nijmegen Institute for Infection, Inflammation and Immunity (N4i), Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; [7]Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands; [8]Hasselt University, Diepenbeek, Belgium; [9]Center for Infectious Diseases and Travel Medicine, Department of Medicine, University Hospital, Albert-Ludwigs University, Freiburg, Germany; [10]National Research Center for Hematology, Moscow, Russia; and [11]Department of Medicine, Section of Infectious Diseases, Hacettepe University School of Medicine, Ankara, Turkey

ABSTRACT

The detection of multi-resistant bacterial pathogens, particularly those to carbapenemases, in leukemic and stem cell transplant patients forces the use of old or non-conventional agents as the only remaining treatment options. These include colistin/polymyxin B, tigecycline, fosfomycin and various anti-gram-positive agents. Data on the use of these agents in leukemic patients are scanty, with only linezolid subjected to formal trials. The Expert Group of the 4th European Conference on Infections in Leukemia has developed guidelines for their use in these patient populations. Targeted therapy should be based on (i) *in vitro* susceptibility data, (ii) knowledge of the best treatment option against the particular species or phenotype of bacteria, (iii) pharmacokinetic/pharmacodynamic data, and (iv) careful assessment of the risk-benefit balance. For infections due to resistant Gram-negative bacteria, these agents should be preferably used in combination with other agents that remain active *in vitro*, because of suboptimal efficacy (e.g., tigecycline) and the risk of emergent resistance (e.g., fosfomycin). The paucity of new antibacterial drugs in the near future should lead us to limit the use of these drugs to situations where no alternative exists.

Introduction

There is a growing problem of antimicrobial resistance among the pathogens isolated from hematology patients and hematopoietic stem cell transplant (HSCT) recipients in many centers, and this increasingly influences the choice of empirical therapy.[1] Resistance also affects the choice of 'targeted' therapy once a pathogen has been isolated, identified and subjected to susceptibility testing. In some cases, treatment options are very limited, and the emergence and proliferation of multiresistant Gram-negative organisms – both Enterobacteriaceae and non-fermenters – is forcing the renewed use of old antibiotics, notably colistin/polymyxin B and fosfomycin[2-4] and of tigecycline. Similarly, the emergence of Gram-positive pathogens resistant to β-lactams and glycopeptides is leading to the use of linezolid, daptomycin and tigecycline in hematology patients.

These agents have not been extensively trialed in hematology patients; rather, their use is predicated on the lack of alternatives. Additional concern is that onco-hematological patients, and especially allogeneic HSCT recipients receive a lot of drugs (e.g., cyclosporine, mycophenolate mofetil, triazoles, antivirals) and they are likely more prone to drug-drug interactions than other populations. We should therefore reinforce the caution about the use of these antibiotics. For this reason, the European Conference on Infections in Leukemia (ECIL) group decided to review the published literature on the use of these non-conventional antibacterial agents for use against resistant Gram-negative and -positive pathogens in leukemic patients and HSCT recipients. The resulting draft guidelines, presented here, were discussed by the Expert Group at the ECIL-4 meeting in September 2011 and are based on published studies and expert opinion. Updated slide sets from ECIL-4 covering these aspects are available via the websites of the four organizations involved in ECIL (European Group for Blood and Marrow Transplantation, European Organization for Research and Treatment of Cancer, Immunocompromised Host Society, ECIL and European Leukaemia Net).[5,6]

Methods

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 doi:10.3324/haematol.2013.081339
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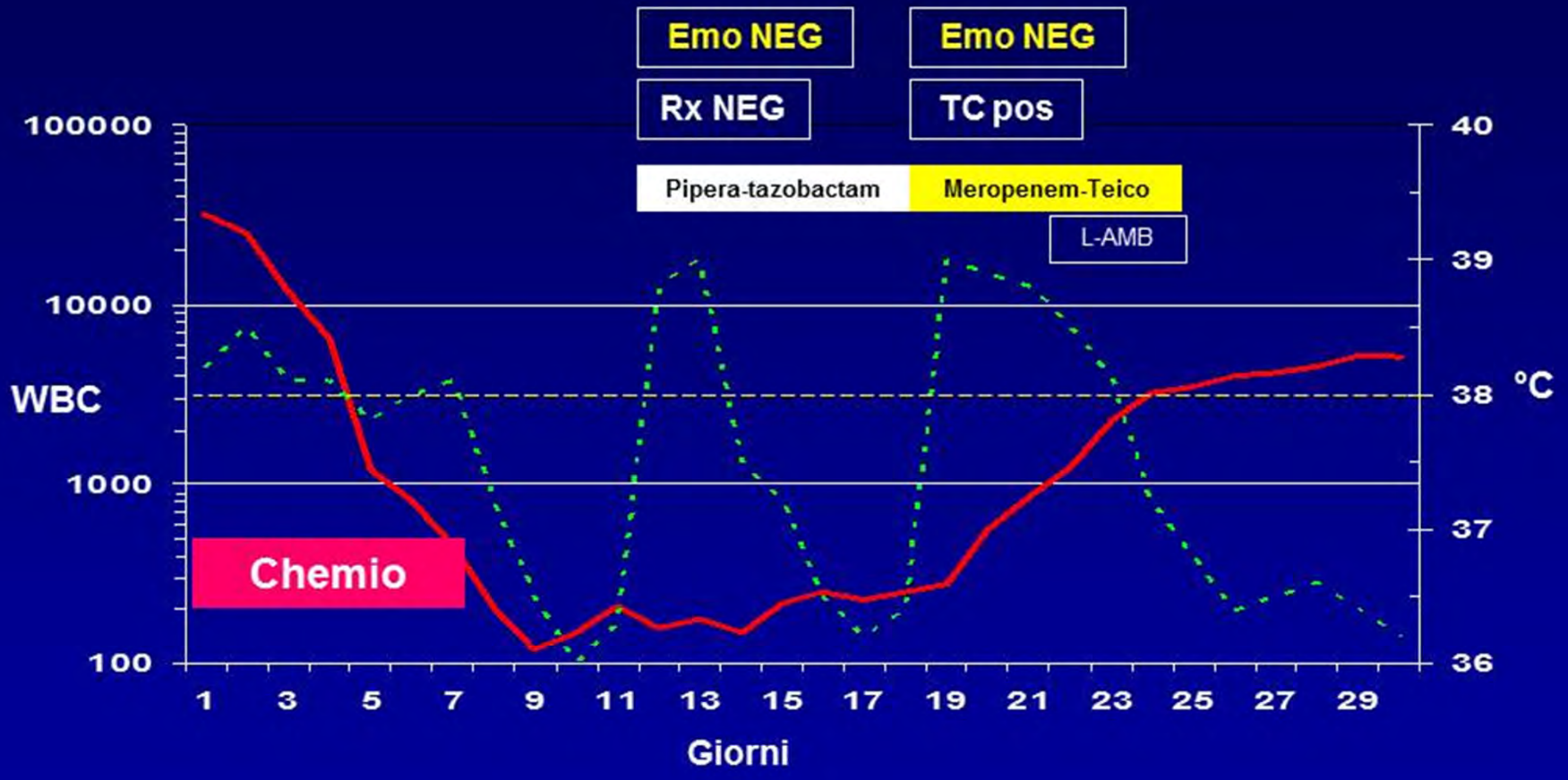
- **Durante le neutropenie:**
  - **Profilassi con fluconazolo**
  - **Terapia empirica con piperacillina / tazobactam se febbre**

- **Gennaio 2012 – Chemioterapia di induzione**
  - **Protocollo “7+3” Ara-C + Doxorubicin**
  - **Febbraio 2012: aspirato midollare**
    - **Mieloblasti = 33% myeloblasts**
    - **No remissione**

Episodi Febbrili in corso di Induzione



LAM in terapia di induzione : 200 pazienti consecutivi (protocolli NILG 01/00 e NILG 02/06)

- Età mediana 53 aa (range 18 – 69)
- Maschi 110 (55%) – Femmine 90 (45%)
- Giugno 2001 → giugno 2007 in reparto aperto (1) : 96 paz (48%)
- Giugno 2007 → oggi in reparto protetto (2) : 104 paz (52%)

	Reparto 1	Reparto 2	Tot
ICE	94 (97.9%)	67 (64.4%)	161 (80.5%)
HDS	2 (5.1%)	37 (35.6%)	39 (19.5%)
	96	104	200

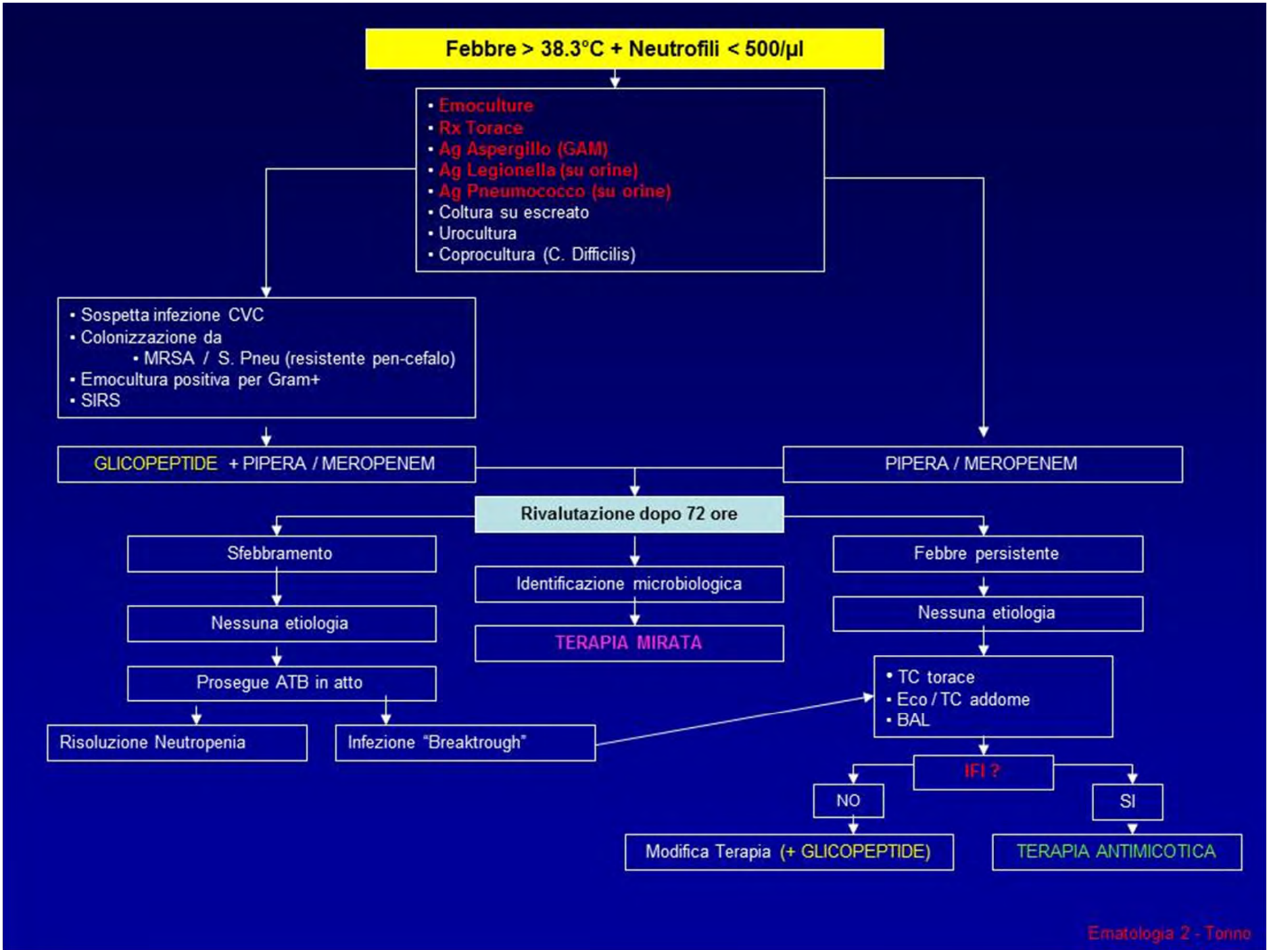
Chemioterapia di Induzione

ICE

Giorni	1	2	3	4	5	6	7
Citarabina 100 mg/m^2 q 12 h	X	X	X	X	X	X	X
Etoposide 100 mg/m^2	X	X	X	X	X		
Idarubicina 12 mg/m^2	X	X	X				

HDS

Giorni	1	2	3	4	5	6	7	8	9	10
Citarabina 2000 mg/m^2 q 12 h	X	X						X	X	
Idarubicina 18 mg/m^2			X							X


Febbre > 38.3°C + Neutrofili < 500/µl
• Emocolture
• Rx Torace
• Ag Aspergillo (GAM)
• Ag Legionella (su orine)
• Ag Pneumococco (su orine)
• Coltura su escreato
• Urocultura
• Coprocultura (C. Difficilis)
• Sospetta infezione CVC
• Colonizzazione da
• MRSA / S. Pneu (resistente pen-cefalo)
• Emocultura positiva per Gram+
• SIRS
GLICOPEPTIDE + PIPERA / MEROPENEM
PIPERA / MEROPENEM
Rivalutazione dopo 72 ore
Sfebbramento
Nessuna etiologia
Prosegue ATB in atto
Risoluzione Neutropenia
Infezione "Breaktrough"
Identificazione microbiologica
TERAPIA MIRATA
Febbre persistente
Nessuna etiologia
• TC torace
• Eco / TC addome
• BAL
IFI ?
NO
SI
Modifica Terapia (+ GLICOPEPTIDE)
TERAPIA ANTIMICOTICA
Ematologia 2 - Torino

Caso Clinico 1

- **Febbraio 2012 Nuova Chemioterapia di induzione:**
  - **Ara-C + Mitoxantrone**

- Aspirato midollare: Mieloblasti <5%

***** HLA: no compatibilità familiare**

- **Marzo e Maggio 2012**
  - **Chemio di consolidamento: Ara-C alte dosi + Mitoxantrone**

- Aspirato midollare: mieloblasti <5%

- **Valutazione molecolare: – positività per malattia minima residua**

*** - Sangue periferico: AML1-ETO/ABL negativo**

*** - Sangue midollare AML1-ETO/ABL ratio 0,17%**

Caso Clinico 1

- **Giugno 2012: Chemioterapia di consolidamento HiDAC**

Aspirato midollare: Mieloblasti <5%

Duante aplasia:

- **Profilassi con fluconazolo**
- **Al terzo giorno di neutropenia → piperacillina / tazobactam per febbre fino a 38,5° C**
- **Espettorato: colture negative**
- **Galattomannano: negativo x 2**
- **Persistentemente febbrile a 72h**
- **Emodinamicamente stabile**

***No donatore HLA compatibile**

Domanda2: Cosa si intende per terapia empirica antifungina nella neutropenia febbrile?

- **1. la somministrazione di un antifungino in un paziente neutropenico e persistentemente febbrile dopo 72 ore di terapia antibiotica empirica**
- **2. la somministrazione empirica di un antifungino in un paziente neutropenico febbrile**
- **3. una strategia terapeutica antifungina, basata sulla somministrazione empirica in pazienti neutropenici con febbre persistente**
- **4. la somministrazione di un antifungino al giorno zero di neutropenia**

Caso Clinico 1

- **Neutropenia grave prolungata con febbre che scompare con terapia antibiotica ad ampio spettro e caspofungina empirica**
- **Colture dell'espettorato: negative**
- **Galattomannano sempre negativo**

Domanda 3. Qual è la durata della terapia antibiotica e antifungina?

- **1. per tutta la durata della neutropenia**
- **2. fino a che il paziente è febbrile o vi è diagnosi di infezione microbiologicamente documentata**
- **3. fino all'esclusione di lesioni polmonari suggestive di *Aspergillus spp.***
- **4. dipende dalla strategia adottata per quanto riguarda la terapia antibiotica: escalation o de-escalation**

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Domanda 4. Si fa sempre riferimento solo alla febbre per quanto riguarda la terapia empirica, antibiotica o antifungina?

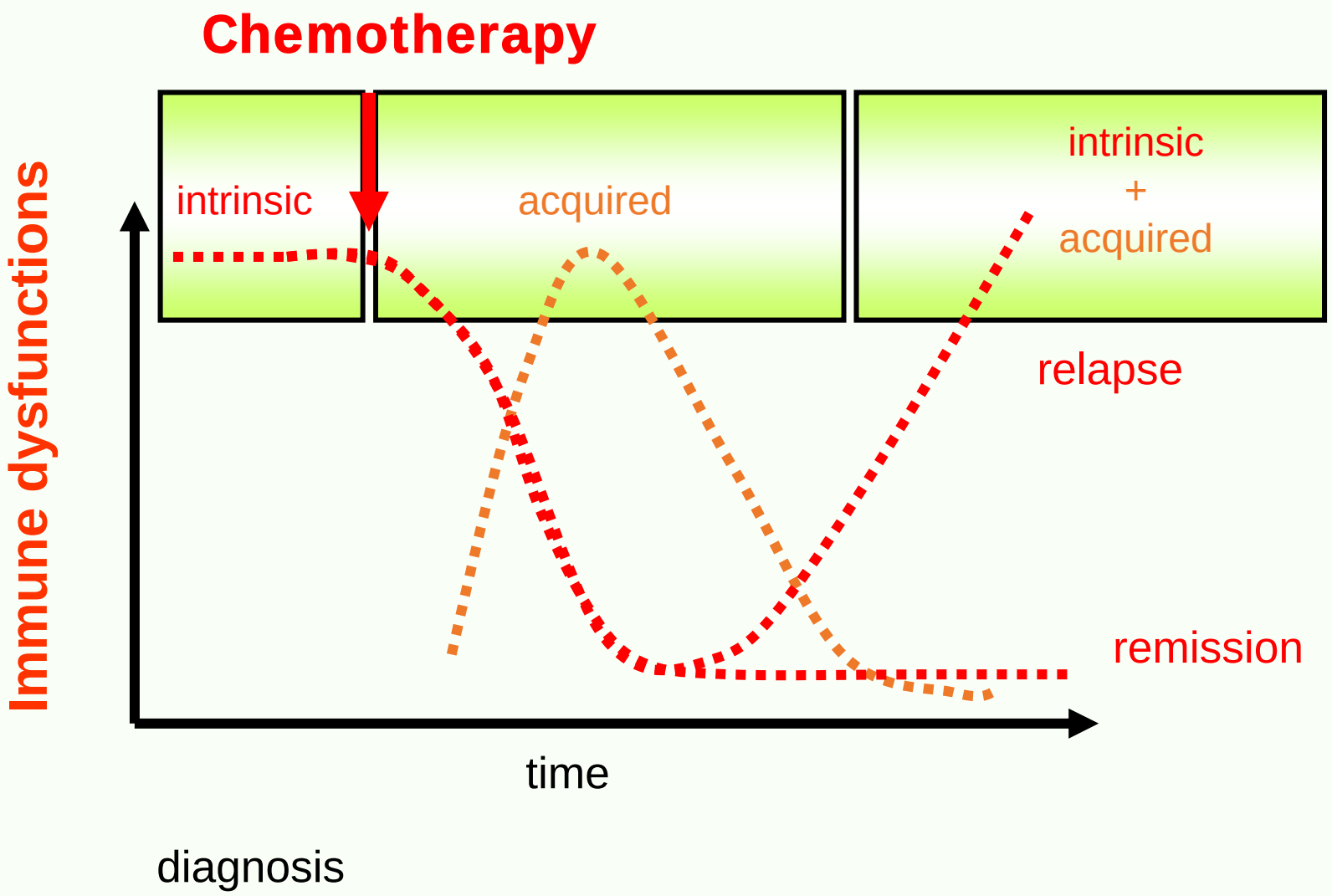
- **1. No**
- **2. Si**
- **3. No: i pazienti ipotermici vanno trattati con le stesse doverose considerazioni. Il termine di neutropenia febbrile può essere poi ulteriormente caratterizzato**
- **4. No: a parte l'ipotermia, ci sono infezioni clinicamente o microbiologicamente documentate**

Caso Clinico 1

- **Giugno 2012:**
  - **Chemioterapia di consolidamento (HiDAC)**

- **Terapia antibiotica ad ampio spettro e caspofungin per 14 giorni**

(Al momento non c'è donatore HLA compatibile)


Chemotherapy
intrinsic
acquired
intrinsic
+
acquired
relapse
remission
Immune dysfunctions
time
diagnosis

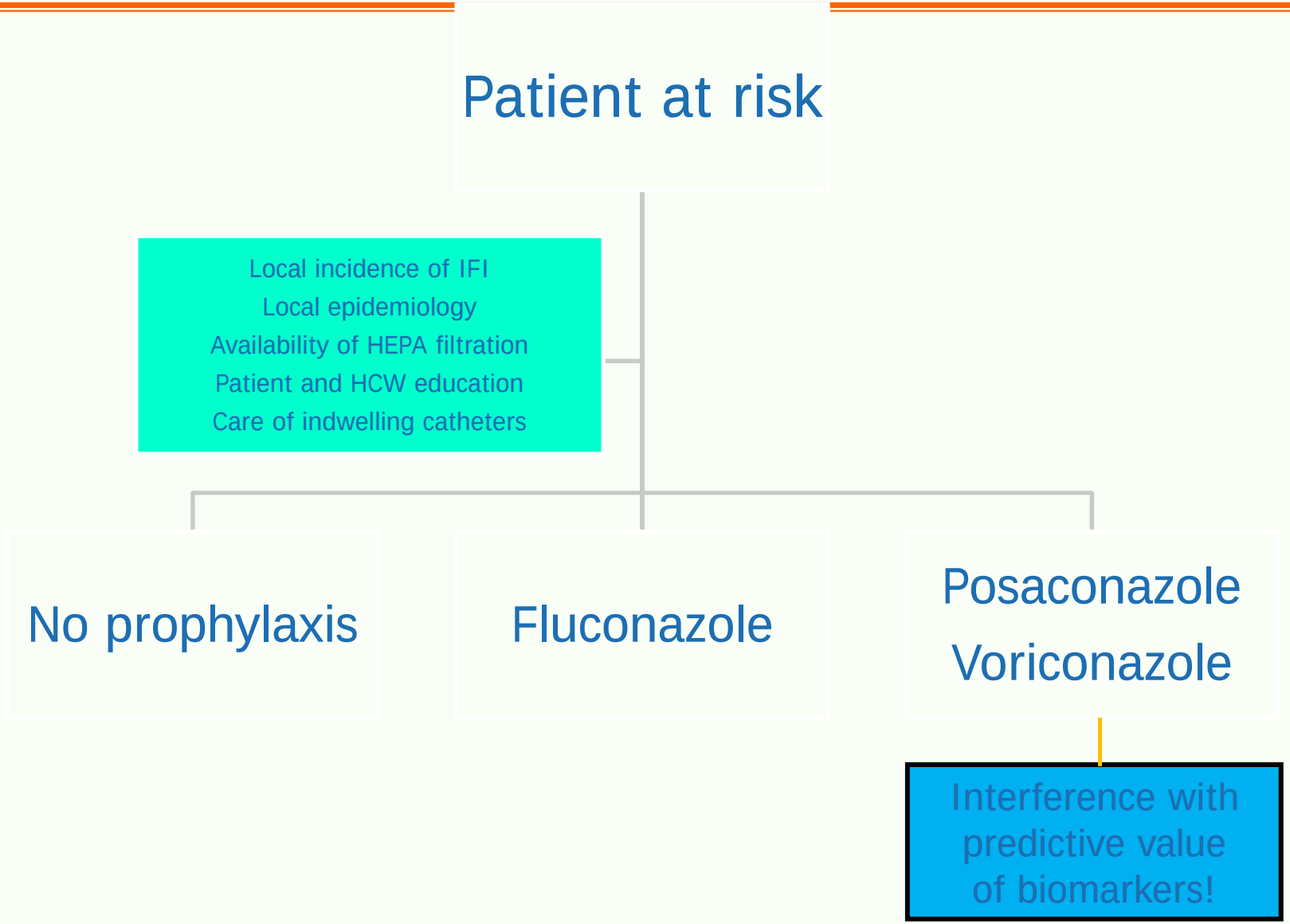
- **Luglio 2012**
  - **Chemioterapia di consolidamento HiDAC**
- **Fluconazolo in profilassi**
- **Terapia empirica con piperacillina/tazobactam da 10 giorni (neutropenia febbrile, regredita)**
  - Esame obiettivo: stabile, tosse, dolore toracico pleuritico al fianco destro, senza rumori aggiunti polmonari
  - Esami microbiologici negativi
- **Emocromo: Neutropenia severa (WBC=100/mm³)**
  - **Inizia terapia empirica antifungina con caspofungin**
  - **Espettorato: colture negative**
- **Galattomannano: negativo x 1; 0,8 secondo campione**

Domanda 5

A questo punto conviene insistere con una terapia empirica antifungina o piuttosto richiedere una TC torace?

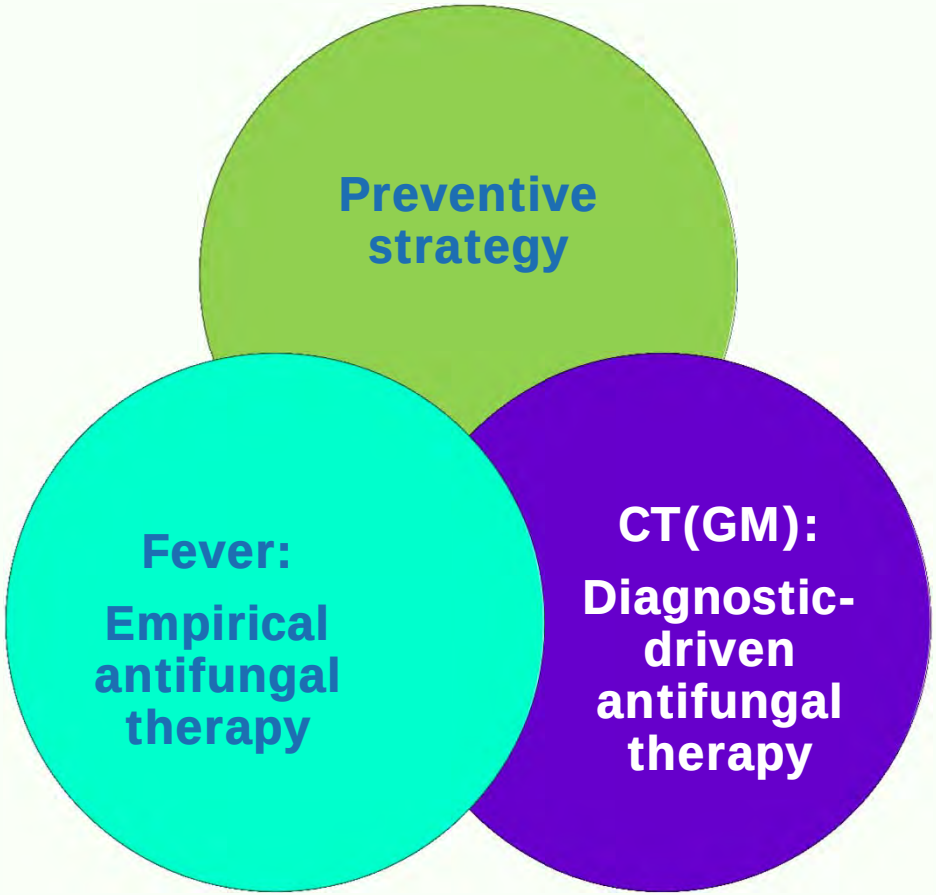
- **1. continuo una terapia empirica antifungina (caspofungin o amfotericina liposomiale)**
- **2. richiedo TC torace per escludere un'infezione aspergillare**
- **3. cambio terapia da caspofungin a voriconazolo**
- **4. Cambio terapia da caspofungin ad amfotericina liposomiale**

Step 2: Choice of preventive strategy

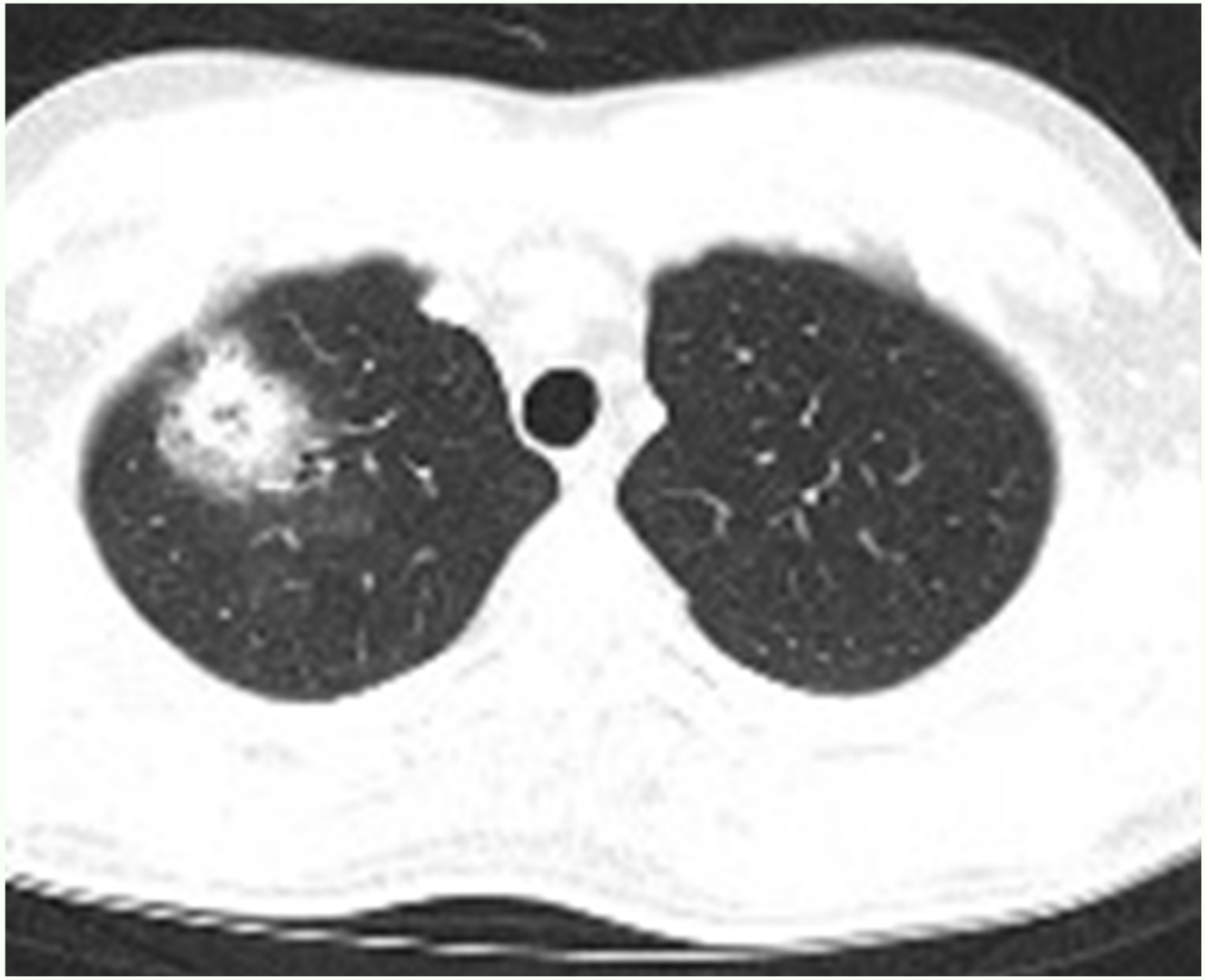


Strategia Empirica o Pre-emptive

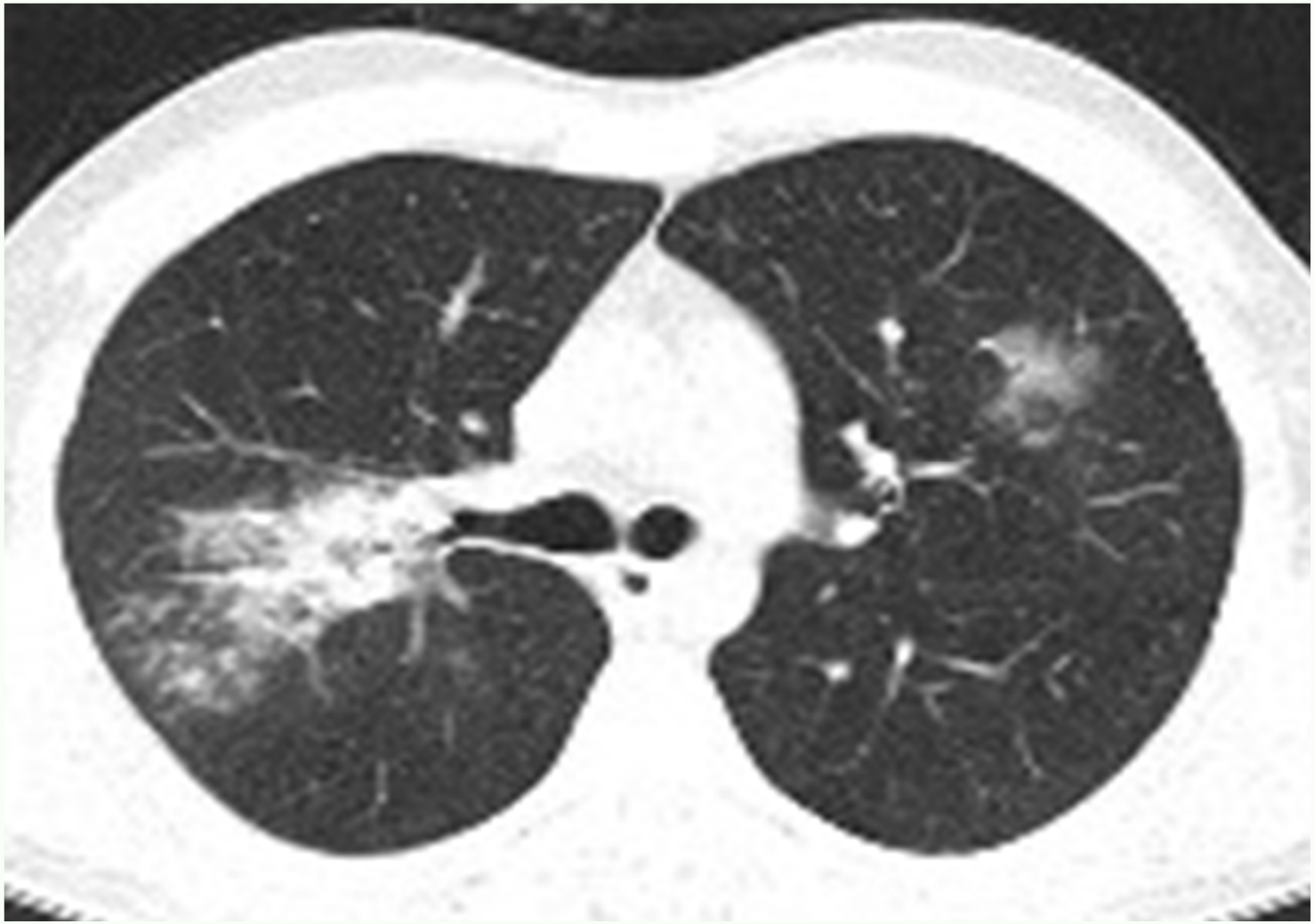
…solo per neutropenici…



TC Torace



TC Torace



- **Quantiferon TB test – negativo**
- **Espettorato per BK – negativo**
- **No broncoscopia per aplasia midollare**

Domanda6: Quale terapia?

- 1. Amfotericina liposomiale
- 2. Amfotericina in complessi lipidici
- 3. Voriconazolo
- 4. Caspofungin
- 5. Posaconazolo

- **Quantiferon TB test – negativo**
- **Espettorato per BK – negativo**
- **No broncoscopia per aplasia midollare**

- **Inizia voriconazolo: aspergillosi polmonare probabile**
- **(durata terapia: indefinita)**
- **Novembre 2012: trapianto allogenico e continua voriconazolo**

Caso Clinico 2

- MS, femmina, 30 anni
- No comorbidità
- Aprile 2012 – Leucemia acuta promielocitica

- Aprile-Maggio 2012 – Inizia anche Chemioterapia "7+3"
- Sindrome ATRA during la chemio di induzione
- Esame obiettivo: incremento ponderale di 5-6kg, lieve dispnea, tosse, no febbre, MV diminuito bilateralmente
- WBC: 64.000/mm^3
- Rx torace; versamento basale destro
- Desametasone 16 mg/die
- Outcome favorevole, riduzione e interruzione dopo due settimane

Caso Clinico 2

- **Durante l'aplasia conseguente alla chemioterapia di induzione:**

- **Neutropenia grave e prolungata di 14 giorni**
- **EO: mucosite orale e febbre fino a 38,2 C per tre giorni**
- **Colture: tutte negative (espettorato, urine, sangue)**
- **Galattomannano negativo x 3 v**
- **In terapia empirica con piperacillina / tazobactam**
- **Profilassi antifungina con posaconazolo**
- **Profilassi antivirale con acyclovir**

Chemioterapia di Consolidamento

- Giugno-Agosto: due cicli di Chemioterapia di consolidamento
- Ottobre 2012: Terzo ciclo di Chemioterapia di consolidamento
- (no neutropenia febbrile; posaconazolo in profilassi)

- Durante l'aplasia midollare:
- Ascesso perianale all'esame obiettivo, senza febbre
- WBC: grave neutropenia per 14 giorni
- Inizia meropenem ev sostituendo la piperacillina/tazobactam

Ottobre 2012

- **Durante l’aplasia:**
- **Esame obiettivo: tosse produttiva, febbre, all’ascoltazione non rilievi patologici**
- **Emocromo: aumento della PCR**
- **Emocolture negative**
- **Espettorato: colturale positivo per *Aspergillus spp.***

Domanda7: Quale strategia antifungina?

- **1. Continuo posaconazolo**
- **2. continuo posaconazolo ma controllo i livelli plasmatici**
- **3. Inizio una terapia empirica antifungina con amfotericina liposomiale o caspofungin**
- **4. Scelgo di completare una strategia pre-emptive: TC torace e dosaggio del galattomannano plasmatico**

- **Strategia pre-emptive:**
- **Febbre persistente in corso di profilassi con posaconazolo**
- **Galattomannano positivo X 2**
- **TC torace: .....**
  - Noduli e segno dell'alone radiotrasparente

- **Test Quantiferon negativo**
- **Espettorato negativo per BK**
- **No bronoscopia per aplasia midollare**

Outcome

- Inizia Voriconazolo a dose standard
- La febbre scompare in 24 ore ma gli effetti collaterali visivi inducono alla sospensione
- Stop voriconazolo e inizia amfotericina liposomiale

STOP