Debate: Empiric *vs* Diagnostic-Driven Therapy in Haemato-Oncology Patients

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Tunis 19th February 2016

What is your strategy to treat refractory febrile neutropenia?

1. Empirical (fever-driven)

2. Preemptive/Screening

3. Diagnostic-driven

Scenario 1

- 32 year old man with recently diagnosed AML
- Received cytarabine plus Idarubicine induction therapy , not housed in a HEPA-filtered room.
- No antifungal prophylaxis, no gut decontamination
- Neutrophil count : $0.1x10^9/l$
- On day 12 of chemotherapy, febrile (T=39°C) for 5 days
- No response to empiric- piperacillin-tazobactam +amikacine (started on day+6) + vancomycine (day+9) (TDM: Amk and Vanco trough levels in the therapeutic ranges)
- Grade4 mucositis and no clinical infectious foci and no severe sepsis

Investigations

Chest X-ray	**normal**
3 sets of blood cultures	**negative**
Urine microscopy and culture	**negative**
Stool culture	**negative**
Renal and liver tests	**normal range**

Table 1. Incidence of mold and yeast infections in patients with different types of hematologic malignancies.

HM	No. of patients	No. of IFI (incidence)	Molds		Yeasts	
			No. cases	Incidence %	No. cases	Incidence %
AML	3012	373 (12%)	239	7.9	134	4.4
ALL	1173	77 (6.5%)	51	4.3	26	2.2
CML	596	15 (2.5%)	14	2.3	1	0.2
CLL	1104	6 (0.5%)	5	0.4	1	0.1
NHL	3457	54 (1.6%)	30	0.9	24	0.7
HD	844	6 (0.7%)	3	0.35	3	0.35
MM	1616	7 (0.5%)	4	0.3	3	0.2
Total	11802	538 (4.6%)	346	2.9	192	1.6

Table 2. Species distribution of invasive fungal infections in patients with hematologic malignancies.

Infections caused by	No. of cases (%)	Incidence %
Molds	**346 (100)**	**2.9**
Aspergillus spp.	310 (90)	2.6
Zygomycetes	14 (4)	0.1
Fusarium spp.	15 (4)	0.1
Others*	7 (2)	0.06
Yeasts	**192 (100)**	**1.6**
Candida spp.	175 (91)	1.5
Cryptococcus spp.	8 (4)	0.07
Trichosporon spp.	7 (4)	0.06
Others°	2 (1)	0.02

*Scedosporium spp. (n=3), Acremonium spp. (n=2), Cladosporium spp.(n=1), Penicillium spp. (n=1); °Rhodotorula spp 1, Hansenula (n=1).

13/16 participating centers used primary prophylaxis with itraconazole or fluconazole

No information about the isolation procedures

Pagano ; Haematologica 2006; 91: 1068

Local data

Invasive aspergillosis

Haematology department of Sfax (2005-2009) : AML (n=75) ALL(n=39)

- **AML**: 24 /75 **(32%) - 7% proven, 40% probable**, 53% possible
- ALL: 8 /39 (20.5%)

By courtesy of Pr S. Hdiji

Invasive candidiasis

Haematology department of Sfax (2001-2002) : AML (n=16) ALL (n=46)

- **AML**: 3/16 **(19%)**
- ALL: 7/46 (15%)

CNGMO- Tunis (1998- 2009)

- Allo HSCT : 16/439 (3.6%)
- Auto HSCT (MM and lymphomas): 13/488 (2.6%)

In your daily practice, what would you do next?

1. Switch to carbapenems
2. Continue the same antibiotics with no further investigations
3. Add empirical mould and yeast active antifungal therapy with no further investigations
4. Add empirical mould and yeast active antifungal therapy and order additional investigations
5. Continue the same antibiotics and order additional investigations

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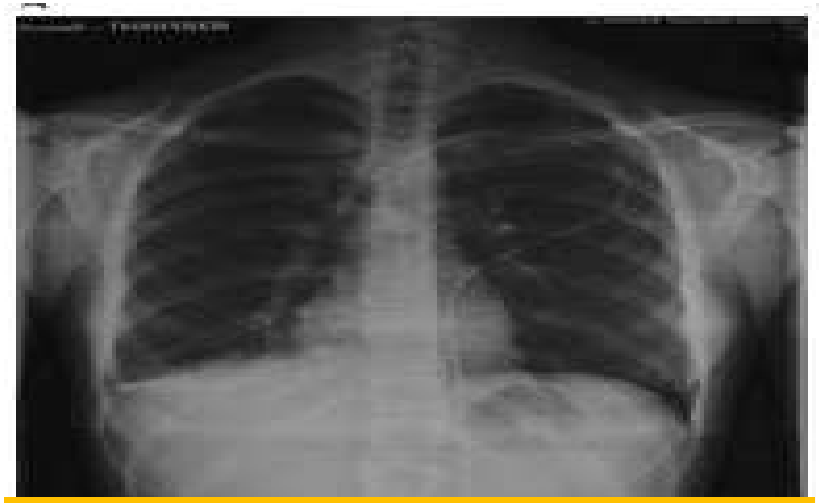
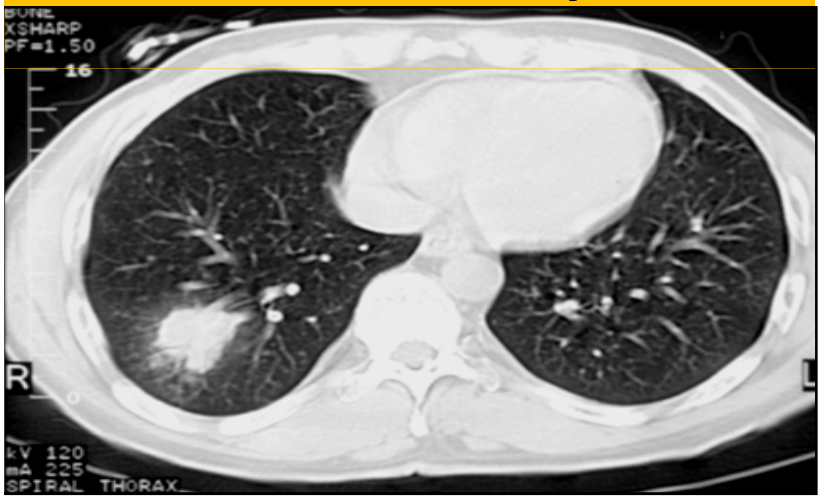
5. Continue the same antibiotics and order additional investigations

In your daily practice, which additional investigations would you order?

1. High resolution CT scan of the chest
2. High resolution CT+ serum galactomannan
3. High resolution CT of the chest+ serum galactomannan + serum 1-3 β-D glucan
4. High resolution CT scan of the chest + real time PCR for aspergillus
5. Bronchoscopy with BAL



The same patient
The same day



No information on fungal aetiology

- CT –scan allows significantly earlier diagnosis and therapy (7 vs 1.9 days)
- Associated with improved overall survival

Caillot et al, JCO, 1997

Heussel et al, JCO, 1999

GM-ELISA assay in serum

Sensitivity	**71%**
Specificity	**89%**
Positive predictive value	**26-53%**
Negative predictive value	**95-98%**

If you order for a HRCT scan of the chest, results are available

1. 24h
2. 48h
3. 72h
4. 3-5 days
5. More than 5 days

If GM-ELISA assay is available, how much time is needed for results to be available?

1. 24h
2. 48h
3. 3-5 days
4. More than 5 days

Bronchoscopy and BAL?

- Indicated , if :
  - positive GM assay and abnormal HRCT with no specific changes according to EORTC criteria or
  - abnormal HRCT-scan of the chest and negative GM assay

- BAL -GM is significantly more sensitive for detection of IPA than serum GM in patients at high risk of IPA (Husain. Clin Vaccine Immunol 2008;15:1760) . Cut-off ODI>1

- Increased performance with combinations of GM, PCR and LFD test (Hoenigl. JCM 2014; 52: 2039) but PCR and LFD not yet available for routine daily practice in Tunisia

Test	Sensitivity	Specificity	PPV	NPV
GM>1	70	98	88	93
PCR	70	100	100	93
LFD test	80	95	80	95
GM + PCR	**100**	**98**	**91**	**100**
GM + LFD	**90**	**93**	**75**	**97**

What is the TAT for bronchoscopy-BAL when available?

1. 24h
2. 48h
3. 3-5 days
4. More than 5 days

The appropriate strategy in this patient?

1.	Switch to carbapenems	
2.	Continue the same antibiotics with no further investigations	
3.	Add empirical mould and yeast active antifungal therapy **with no further investigations**	
4.	**Add empirical mould and yeast active antifungal therapy and order in parallel additional investigations to rule out or rule in invasive aspergillosis**	**Yes EAFT permits to buy time and should be adapted to results of the additional investigations**
5.	Continue the same antibiotics and order additional investigations to decide or not to use AFT: **diagnostic driven strategy**	Not in the lack of primary prophylaxis, the absence of appropriate isolation (HEPA) and if additional investigations are not available or results not timely provided Otherwise, Yes

Among antifungal drugs available in Tunisia, which empirical drug would-you use?

1. Caspofungin
2. Voriconazole
3. Amphotericine B deoxycholate
4. Fluconazole
5. Anidulafungine

Our patient

- Amphotericin B deoxycholate: 1 mg/kg started
- CT scanning of the chest was normal (TAT was 4 days)
- GM assay was negative (TAT was 6 days)
- Become afebrile after 72 h of AmB starting

What would you do next?

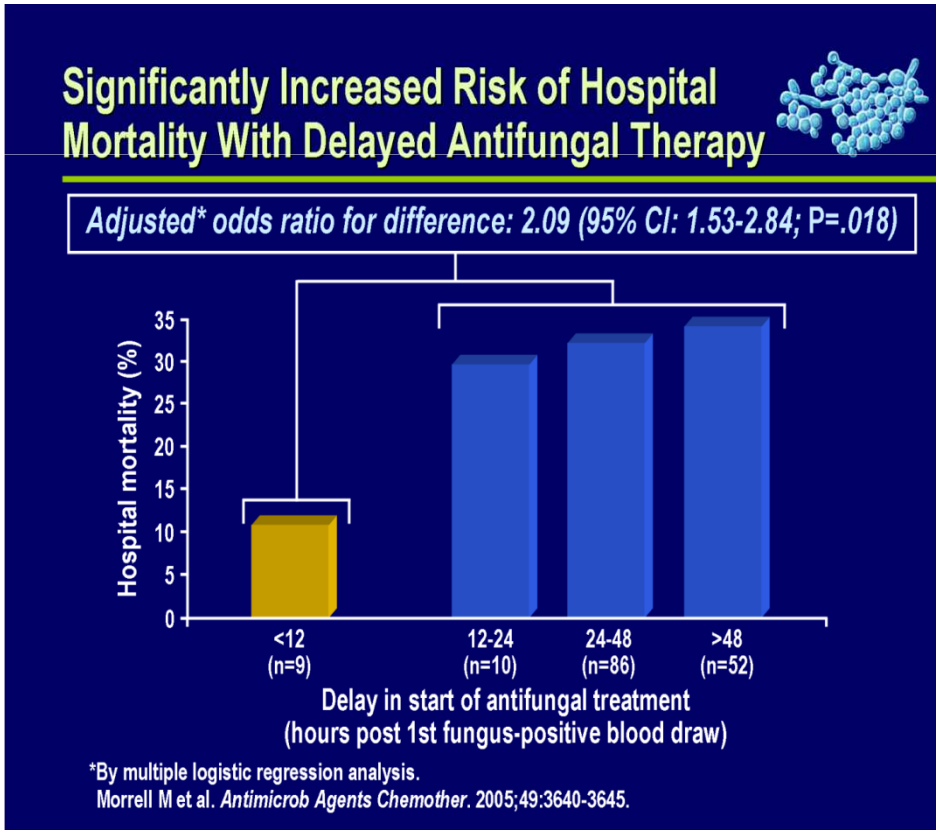
1. Stop AmB on negative results of the additional investigations
2. Stop AmB after resolution of fever
3. Continue AmB until neutrophil recovery

Arguments for the use of Empirical Antifungal Therapy in this patient

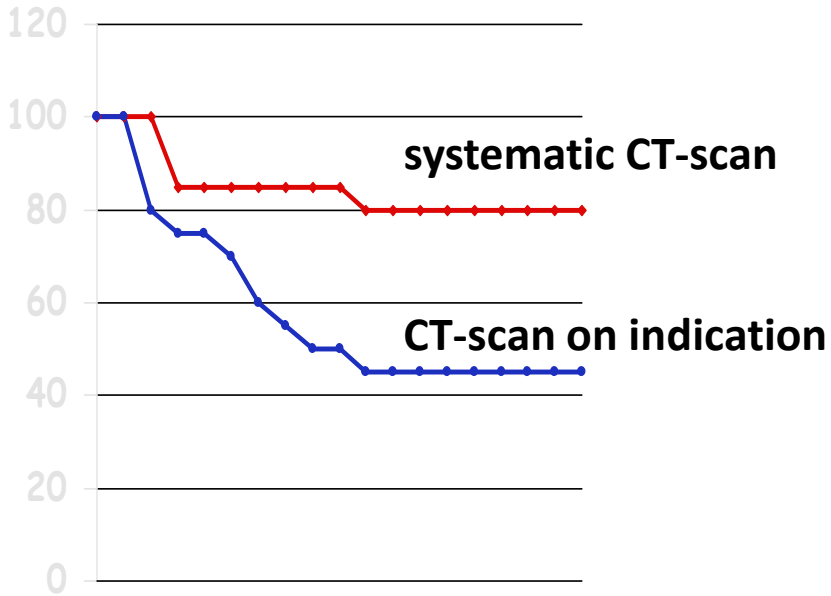
High risk of IA but also of fungemia (no appropriate isolation and no primary prophylaxis for IC)

Delayed diagnosis and delayed treatment increase mortality

Fungemia



Invasive aspergillosis



- CT –scan allows significantly earlier diagnosis and therapy (7 vs 1.9 days)

- Associated with improved overall survival Caillot, JCO, 1997 Heussel JCO, 1999

Arguments for the use of Empirical Antifungal Therapy use in this patient

- If Imaging investigations and biomarkers to exclude IA are unavailable and if results are not timely provided (it is not a rare situation in Tunisia)

- If, TAT for bronchoscopy when indicated is too long (>48h)

- Low sensitivity of blood cultures for the diagnostic of fungemia

- Fungal primary prophylaxis is lacking

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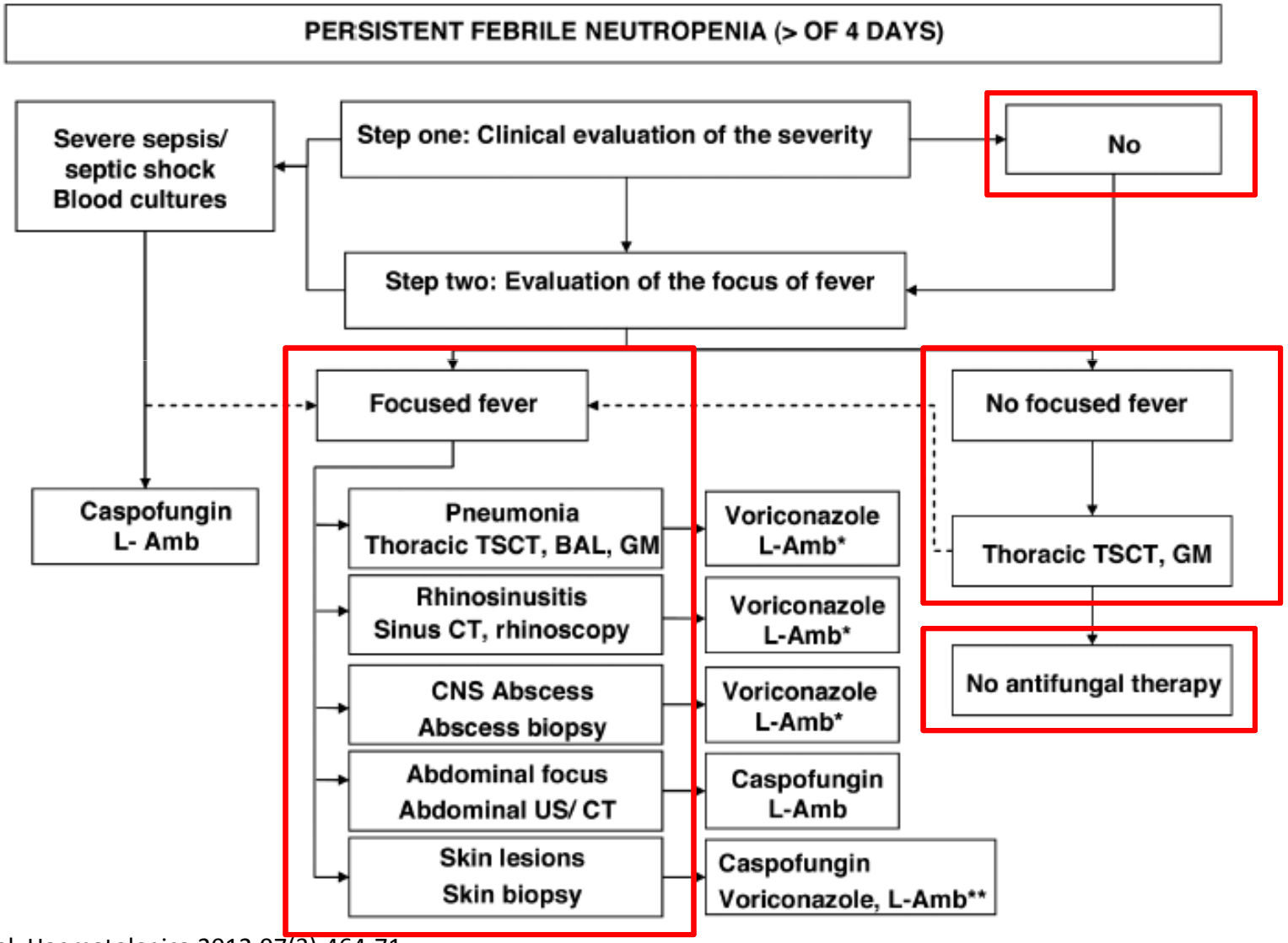
- On day 12 of chemotherapy, febrile (T=39°C) for 5 days
- No response to empiric- piperacillin-tazobactam +amikacine (started on day+6) + vancomycine (day+9) (TDM: Amk and Vanco trough levels in the therapeutic ranges)
- Grade4 mucositis and no other localizing symptoms or signs

What could be the cause of fever?

1. Gram –ve bacteria
2. Gram +ve bacteria
3. Viruses
4. Fungi – moulds
5. Fungi – yeasts
6. Antibiotic/drug fever
7. Tumour-associated fever
8. Parasites
9. Other

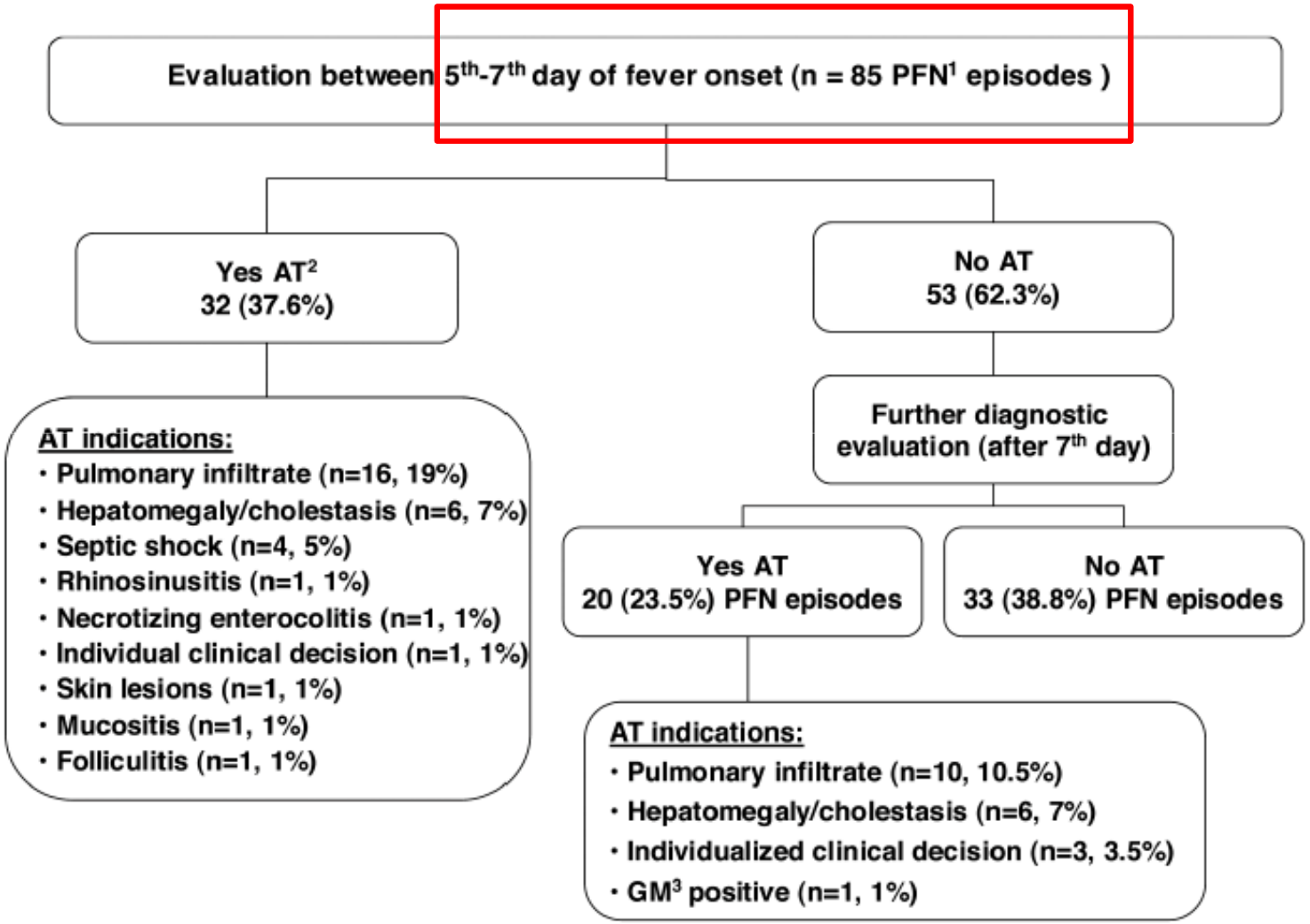
Multiple choices are permitted !

Prospective study of persistent, febrile neutropenia in patients with hematologic malignancies or HSCT recipients



Aguilar-Guisado M et al. Haematologica 2012;97(3):464-71

Seville approach



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Seville approach

Final diagnosis of PFN episodes	Antifungal therapy N. (%)	No antifungal therapy N. (%)	
Infection	43 (82.7)	25 (75.7)	= 68
Invasive fungal infection	22 (42.3)	0	= 22
Proven IFI	3 (5.8)	0	
Probable IFI	9 (17.3)	0	
Possible IFI	10 (19.2)	0	
Non-fungal infection	21 (40.4)	25 (75.7)	= 46
Not infection	9 (17.3)	7 (21.2)	= 16
Tumor fever	5 (9.6)	5 (15.1)	
Drug fever	2 (3.8)	2 (6.1)	
Pulmonary thromboembolism	1 (1.9)	0	

Fever: IFD 22 vs Non IFD 62

After 5 days of antibiotics

Aguilar-Guisado M et al. Haematologica 2012;97(3):464-71

What is the most likely cause of fever?

1. Gram –ve bacteria
2. Gram +ve bacteria
3. Viruses
4. Fungi – moulds
5. Fungi – yeasts
6. Antibiotic/drug fever
7. Tumour-associated fever
8. Parasites
9. Other

Local data

Invasive aspergillosis

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No primary prophylaxis, No HEPA filtered-rooms, AML (n=75) ALL(n=39)

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- **AML**: 3/16 **(19%)**
- ALL: 7/46 (15%)

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CNGMO- Tunis (1998- 2009)

- Allo HSCT : Ψ with fluconazole and HEPA-filtered rooms : 16/439 (3.6%)
- Auto HSCT (MM and lymphomas): No primary prophylaxis, No HEPA-filtered-rooms: 13/488 (2.6%)

Local data

Audit of 531 AML/allograft episodes

- Using EORTC/MSG criteria
  - Evidence of IFD, 39 (7.4%)
  - Probable/proven, 11 (2.1%)
- 44% of patients treated for “IFD”
- = Empirical management
- BUT low rates of IFD = Empirical/Screening NOT viable
- = Diagnostic-driven approach

BAL, bronchoalveolar lavage; CT, computed tomography; ID, infectious disease; IFD, invasive fungal disease

Tsitsikas DA, *et al*. *Med Mycol*. 2012;50:538-42.

Investigations

Chest X-ray	**normal**
3 sets of blood cultures	**negative**
Urine microscopy and culture	**negative**
Stool culture	**negative**

In your daily practice, what would you do next?

1. Switch to carbapenems
2. Continue same antibiotics – no investigations (Ix)
3. Add empirical mould+yeast antifungal therapy – no Ix
4. Add empirical mould+yeast antifungal therapy AND Ix
5. Continue the same antibiotics AND Ix

Which additional investigations would you order?

1. High resolution CT scan of the chest
2. High resolution CT+ serum galactomannan
3. High resolution CT of the chest+ serum galactomannan + serum 1-3 β-D glucan
4. High resolution CT scan of the chest + real time PCR for aspergillus
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Barts Health NHS Trust

ANTIMICROBIAL POLICY FOR HAEMATO-ONCOLOGY PATIENTS

A) Prophylaxis for high-risk patients (AML, ALL, Auto/Allo)

See APPENDIX 1: Prophylaxis Summary:

- Ciprofloxacin prophylaxis 750mg bd – while neutrophils <0.5x10*9/L
- Fluconazole 400 mg od – while neutrophils <0.5x10*9/L
- Aciclovir 400 mg bd – variable duration see prophylaxis guidelines
- Penicillin V 250 mg bd life-long (Post-Allo patients only)

B) Empiric therapy for Febrile Neutropenic patients:

1st line antimicrobials
Piperacillin & Tazobactam 4.5g tds **AND** **Amikacin 15mg/kg od (maximum 1.5g daily) [if normal renal function i.e. CrCl>50ml/min]**
2nd line antimicrobials (on-going fever after 48 hours)
Consultant decision to change before 48 hours in an ill patient: **Meropenem 1g tds** *Consider;* **Vancomycin** - dose as per Vancomycin guidelines (available on trust fileshare) -If positive blood cultures (with Gram positive organisim that are resistant to 1st line agents) -Colonised with MRSA

Diagnostic Strategy 2012 with CT + GM; no screening

At risk

Primary Prophylaxis

AML/ALL
Auto/Allograft
R-CODOX-M/ IVAC

- Fluconazole 400mg PO daily

UKALL 14 induction I only

- AmBisome 50mg IV daily
- 2nd choice- micafungin 50mg IV daily

72 Hours

CT / GM

Clinical suspicion of IFI;

- Persistent >72 hrs or relapsing fever +/- clinical signs AND
- No other positive cultures

- Order CT Chest
- Other imaging, e.g. sinus/head/abdomen, if clinically indicated
- Order Serum Galactomannan (GM) for *2 consecutive days*

Awaiting results

GM –
CT normal/non-sp

- Do not treat

GM +
CT normal

- Investigate

GM –
CT +

- Investigate

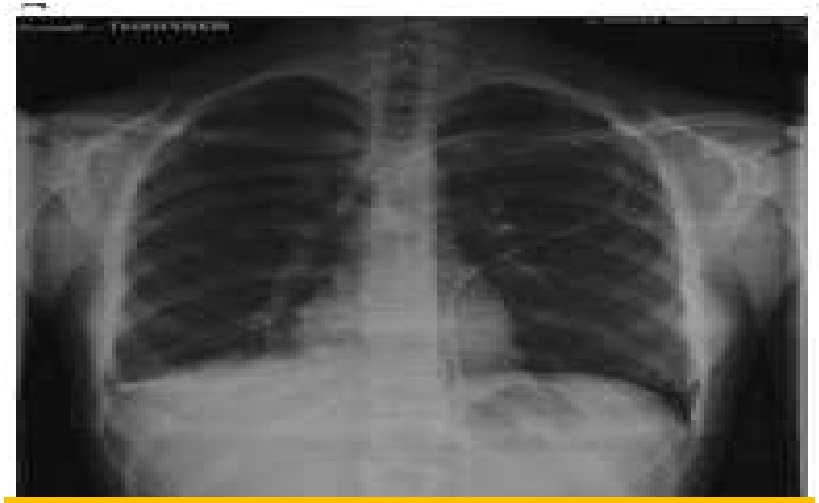
GM +
CT + or non-sp

- Treat

Non pulmonary IFI?
- Imaging -sinus/head/abdomen

Pulmonary IFD?
- Bronchoscopy
- BAL

Barts Health NHS Trust



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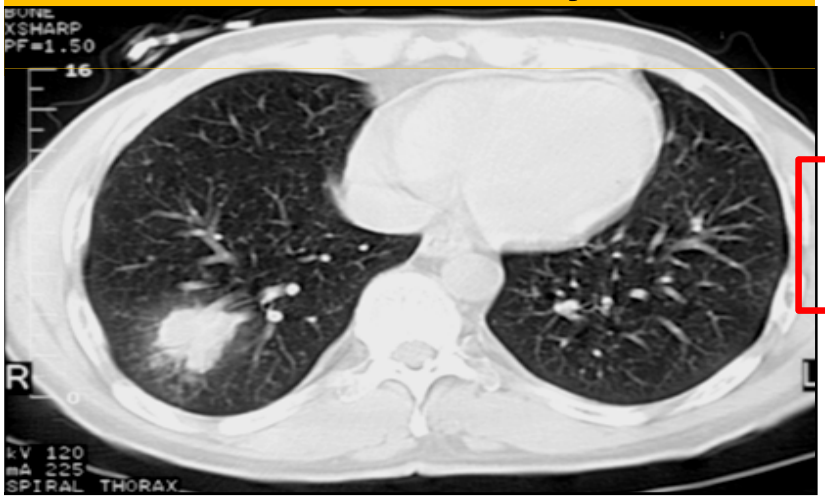

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GM + PCR	**100**	**98**	**91**	**100**
GM + LFD	**90**	**93**	**75**	**97**

If you had bronchoscopy-BAL available, what TAT would be acceptable?

1. 24h
2. 48h
3. 3-5 days
4. More than 5 days

Barts Cancer Institute
Queen Mary, University of London

Barts and The London
School of Medicine and Dentistry

Aspergillus LFD and qPCR testing in BAL Fluid: Combination Biomarker Detection for Clinical Diagnosis of Pulmonary Aspergillosis

Johnson G…Agrawal, S. J Clin Microbiol. 2015 Apr 22. pii:JCM.00110-15. [Epub ahead of print]

PCR, GM and LFD
For *Aspergillus* Detection

BAL vs Blood/Serum – paired samples

BAL, bronchoalveolar lavage; GM, galactomannan; LFD, lateral-flow device; PCR, polymerase chain reaction

Bronchoscopy and BAL?

- 5/25 BALs
  - PCR +ve
  - GM+ / LFD+

  } = ***IPA***

- Blood/serum - 3/5 PCR and 4/5 GM/LFD - negative

- **Time from AF to BAL**
  - median 6d (4–8)
  - culture / calcofluor - negative

BAL, bronchoalveolar lavage; D, days; EORTC, European Organisation for Research and Treatment of Cancer; IPA, invasive pulmonary aspergillosis; GM, galactomannan; LFD, lateral flow device; MDS, myelodysplastic syndrome; MSG, Mycoses Study Group; PCR, polymerase chain reaction

Johnson G, et al. J Clin Microbiol. 2015 Apr 22. pii:JCM.00110-15. [Epub ahead of print]

Bronchoscopy and BAL?

- 20/25 BALs - PCR negative
  - no GM+/LFD+
  - 2 GM+
  - 1 LFD+
- Corresponding blood/serum
  - negative

} = ***no IPA***

- Time from AF to BAL
  - median 6d (4–8)
  - culture -ve, calcofluor -ve

BAL, bronchoalveolar lavage; D, days; EORTC, European Organisation for Research and Treatment of Cancer; IPA, invasive pulmonary aspergillosis; GM, galactomannan; LFD, lateral flow device; MDS, myelodysplastic syndrome; MSG, Mycoses Study Group; PCR, polymerase chain reaction

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4.	**Add empirical mould and yeast active antifungal therapy and order in parallel additional investigations to rule out or rule in invasive aspergillosis**	**Yes EAFT permits to buy time and should be adapted to results of the additional investigations**
5.	Continue the same antibiotics and order additional investigations to decide or not to use AFT: **diagnostic driven strategy**	Not in the lack of primary prophylaxis, the absence of appropriate isolation (HEPA) and if additional investigations are not available or results not timely provided Otherwise, Yes

Among antifungal drugs available in Tunisia, which **empirical** drug would-you use?

- Caspofungin - A , but NOT for *Aspergillus*
- Voriconazole - A (IDSA) , but NOT licensed
- Ampho B - NOT recommended
  - A , Liposomal
- Fluconazole - NOT recommended

Our patient

- Amphotericin B deoxycholate: 1 mg/kg started
- CT scanning of the chest was normal (TAT was 4 days)
- GM assay was negative (TAT was 6 days)
- Become afebrile after 72 h of AmB starting

What would you do next?

1. Stop AmB on negative results of the additional investigations
2. Stop AmB after resolution of fever
3. Continue AmB until neutrophil recovery

Conclusion - drawbacks of EAFT

- Blind strategy
- Treating patients who do not need treatment
- Drug toxicity (especially, AmB-D)
- Drug-drug interactions (Azoles)
- Costly + adverse events
- Fungal resistance

However

Empirical ATF treatment is indicated

- High risk of IA and yeast infections
- No primary fungal prophylaxis ents under induction chemotherapy
- Additional (HRCT and GM assay) availabl ent in Tunisia exclude only IA and ar available and results are often not tin ided