MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

Updates on invasive fungal disease management: From ECIL 4–6

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ASIA FUNGAL WORKING GROUP
an ISHAM working group

Barts Health NHS Trust

Royal London
and
St Bartholomew's
Hospitals

Updates on Invasive Fungal Disease Management: From ECIL 4–6

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ECIL, European Conference on Infections in Leukaemia

Barts and The London Queen Mary's School of Medicine and Dentistry

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Conflicts of interest

astellas

GILEAD

MERCK

Pfizer

Research grants – advisory boards – speaker

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Updates on IFD Management Guidelines

Topics I will address:

- ***IFD Management – is it important ?***
- *Guidelines , Guidelines, Guidelines !*
- *Improving your practice*

IFD, invasive fungal disease

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Updates on IFD Management Guidelines

IFD management – is it important ?

- **Mortality**: ranges from **40–90%** in high-risk patients[1-5]
  - Invasive candidiasis , aspergillosis , mucormycosis
- **Diagnosis**: is challenging – **Empirical** treatment
- **Antifungal prophylaxis**: common in haematological malignancy and HSCT[6]
- **Impact**?
  - **Exposure** to **unnecessary drugs**[7] , **increased costs**[7] , **missed infections (?)**[8]
  - Increased risk of **antifungal resistance** (an emerging issue)[7,8]
- Can we improve antifungal management?[7]

HSCT, haematopoietic stem cell transplant. 1. Dagenais TR, Keller NP. Clin Microbiol Rev 2009;22:447–65; 2. Wingard J. Adv Stud Med 2006;6:S526–30; 3. Skiada A, et al. Clin Microbiol Infect 2011;17:1859–67; 4. Rüping MJ, et al. J Antimicrob Chemother 2010;65:296–302; 5. Lanternier E, et al. Clin Infect Dis 2012;54(Suppl 1):S35–43; 6. Arvanitis M, et al. J Clin Microbiol 2014;52:3731–42; 7. Muñoz P, et al. J Antimicrob Chemother 2016;71(Suppl 2):ii5–12; 8, Maertens J, et al. Clin Infect Dis. 2005;41(9):1242–50; 9. Fisher MC, et al. Science 2018;360:739–42.

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Updates on IFD Management Guidelines

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IFD, invasive fungal disease

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Updates on IFD Management Guidelines

Guidelines since 2008

Agrawal S, *et al. Crit Rev Microbiol*. 2012;38(3):203–16.

Guideline title	Affiliated associations/society	Year
Australian and New Zealand consensus guidelines	**Australasian** Leukaemia and Lymphoma / Infectious Diseases / NSW Cancer Institute	2008
IFI during therapy for haematological malignancy	**British** Committee for Standards in Haematology (BCSH)	2008
Primary prophylaxis in patients with haematological malignancies	Infectious Diseases Working Party (AGIHO) of the **German** Society of Haem-Onc (DGHO)	2009
Clinical practice guidelines for candidiasis	Infectious Diseases Society of **America** (IDSA)	2009
Treatment of aspergillosis: clinical practice guidelines	IDSA	2008
Antifungal prophylaxis in leukaemia	**European** Conference on Infections in Leukemia (ECIL)-3	2010
Management guideline for *Candida* diseases	**European** Society of Clinical Microbiology and Infectious Diseases (ESCMID)	(2012)

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Updates on IFD Management Guidelines

ECIL development 2005 – 2016[1,2,3]

- **European Conference on Infections in Leukaemia**
  - ECIL-1/2, 2007
    - prophylaxis , empirical , treatment
  - ECIL-3, 2009 & ECIL-5/6, 2016
    - Updates
    - no recommendations on DIAGNOSTICS

1. Eur J Cancer 2007; Suppl 5.
2. Maertens et al. Bone Marrow Transplantation (2011) 46, 709–718
3. Tissot F, Agrawal S, et al. Haematologica. 2017. 102: 433-444

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Updates on IFD Management Guidelines

ECIL development 2005 – 2016[1,2,3]

ECIL-1 and ECIL-3 Prophylaxis

Allogeneic haematopoietic stem cell transplantation
Fluconazole 400 mg qd intavenous (i.v.)/oral
Itraconazole 200 mg IV followed by oral solution 200 mg bid
Posaconazole 200 mg tid oral
Micafungin 50 mg qd i.v.
Polyene[a] i.v.

Induction chemotherapy acute leukemia
Fluconazole 50–400 mg qd i.v./oral
Itraconazole oral solution 2.5 mg/kg bid
Posaconazole 200 mg tid oral
Candins i.v.
Polyene[a] i.v.

Antifungal drug	*Grading*
Leukemia patients, induction chemotherapy	
Fluconazole (50–400 mg/day)	CI
Itraconazole oral solution (2.5 mg/kg b.i.d.)	CI
Posaconazole (200 mg t.i.d.)	AI
Echinocandins IV	Insufficient data
Polyenes IV	CI
Aerosolized liposomal ampho B combined with oral fluconazole	*BI*

1. Eur J Cancer 2007; Suppl 5.
2. Maertens et al. Bone Marrow Transplantation (2011) 46, 709–718

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Polyene[a] i.v.

Allogeneic HSCT recipients, initial neutropenic phase	
Fluconazole (400 mg q.d. i.v. or oral)	AI
Allogeneic HSCT recipients, GVHD phase	
Fluconazole (400 mg q.d. i.v. or oral)	CI
Itraconazole (200 mg i.v. followed by oral solution 200 mg b.i.d.)[a]	BI
Posaconazole	AI
Voriconazole (200 mg b.i.d. oral)	*Provisional AI*
Echinocandins i.v.	Insufficient data
Polyenes i.v.	CI
Aerosolized liposomal ampho B combined with oral fluconazole	*Insufficient data*

1. Eur J Cancer 2007; Suppl 5.
2. Maertens et al. Bone Marrow Transplantation (2011) 46, 709–718

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Updates on IFD Management Guidelines

Empirical IFD Treatment – IDSA , ECIL-6 2016[1]

Strategy	Recommendation	Strength of Recommendation	Quality of Evidence
Empirical therapy	L-AmB	Strong	High
	Echinocandin (caspofungin or micafungin)	Strong	High
	Voriconazole	Strong	Moderate
	Strongly suspected IPA: early antifungal therapy + diagnostic evaluation	Strong	Moderate

1 : Patterson, TF, et al. Clin Infect Dis. 2016;63:e1–e60
2: Tissot F, Agrawal S, et al. Haematologica. 2017. 102: 433-444
IDSA, Infectious Dsiease Society of America; IPA, invasive pulmonary aspergillosis; L-AmB, liposomal amphotericin B

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Updates on IFD Management Guidelines

Empirical IFD Treatment – IDSA 2016[1]

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Guidelines for Probable / Proven *Aspergillus* IFD

2016 to 2018:

- IDSA
- ECIL
- ESCMID

IDSA, Infectious Dsiease Society of America; ECIL, European Conference on Infections in Leukaemia ; ESCMID, European Society of Clinical Microbiology and Infectious Diseases

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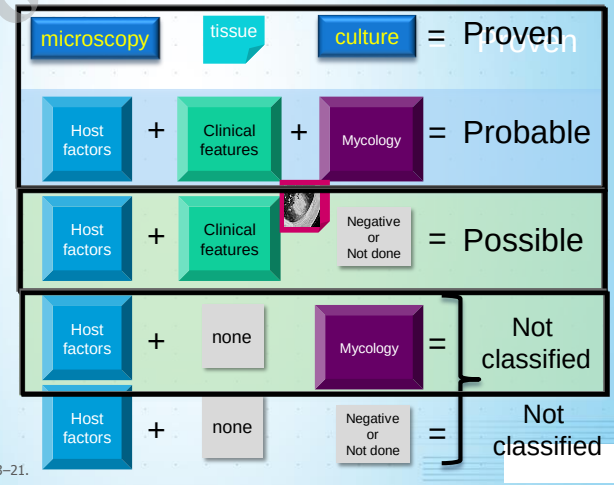
Updates on IFD Management Guidelines

EORTC/MSG 2008: Definitions



1, De Pauw B, et al. Clin Infect Dis. 2008;46:1813–21.

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Updates on IFD Management Guidelines

Probable / Proven *Aspergillus* IFD

- VORICONAZOLE — A
- ISAVUCONAZOLE — A
- LIPOSOMAL AMPHOTERICIN B — A/B*

*ECIL and ESCMID:
not 'A' because AmBiLoad had Liposomal AmB in each arm (3 vs 10 mg/kg)

1. A.J. Ullmann et al. Clinical Microbiology and Infection 24 (2018) e1ee38 (ESCMID-ECMM-ERS)
2. Tissot F, Agrawal S, et al. Haematologica. 2017. 102: 433-444 (ECIL)
3. Patterson TF, et al. Clin Infect Dis. 2016;63:e1-e60. (IDSA)

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Updates on IFD Management Guidelines

Topics I will address:

- *IFD Management – is it imp*
- *Guidelines , Guidelines, Gui*
- ***Improving your practice*** *- Strategy*

Do you have a plan?

IFD, invasive fungal disease

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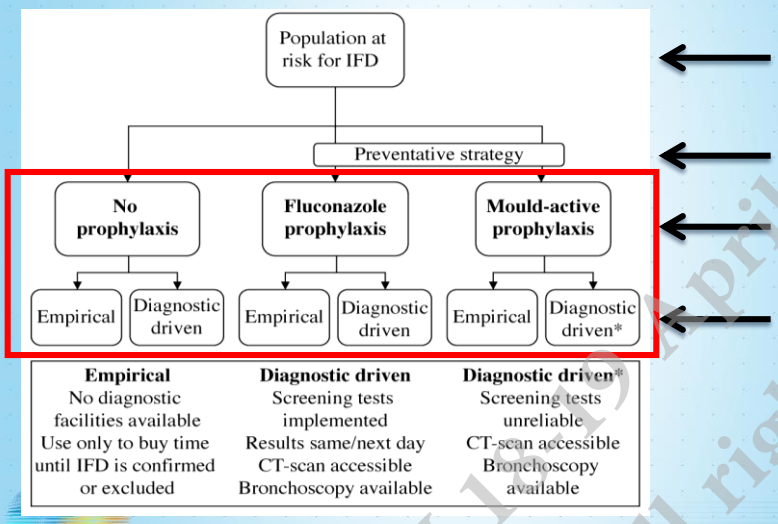

Agrawal S, *et al*. J Antimicrob Chemother 2011; 66 Suppl 1: 145–53

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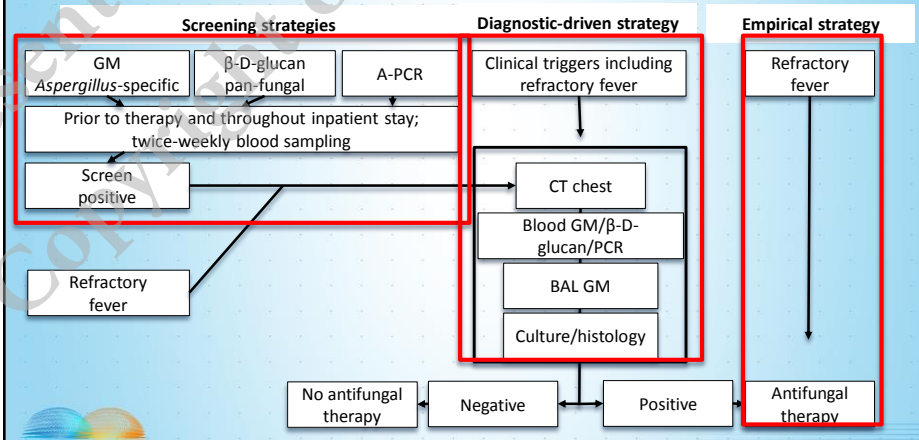
Strategies for IMD management



BAL, bronchoalveolar lavage; CT, computerised tomography; GM, galactomannan; IMD, invasive mould disease; A-PCR, *Aspergillus* polymerase chain reaction

Agrawal S, *et al*. *Crit Rev Microbiol*. 2012;38(3)(Suppl.):203–16.

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Strategies for IFD management

- **What is usual in your centre?**
  - True empiric
  - Empiric 'plus' (CT)
  - Pre-emptive/screening
  - Diagnostic
  - PROPHYLAXIS (mould-active)

CT, computerised tomography; IFD, invasive fungal disease; IMD, invasive mould disease

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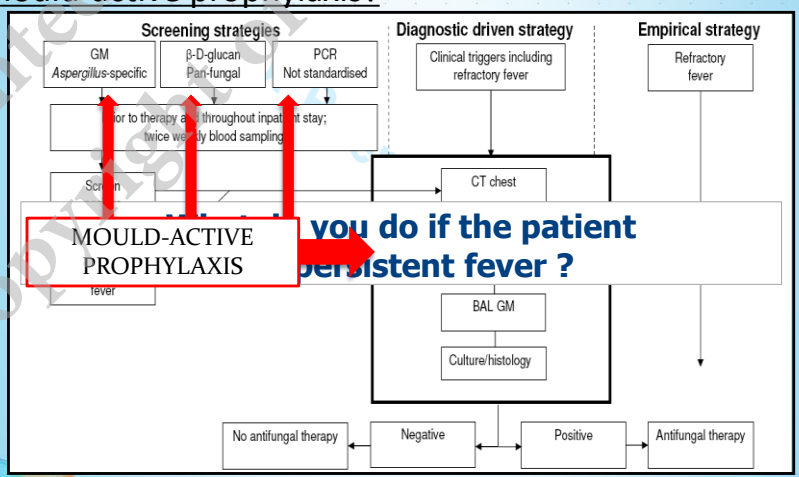
Updates on IFD Management Guidelines

Mould-active prophylaxis?



BAL, broncho-alveolar lavage; CT, computerised tomography; GM, galactomannan; IFD, invasive fungal disease; IMD, invasive mould disease; PCR, polymerase chain reaction

1. Mennink-Kersten MA, *et al. Lancet Infect Dis*. 2004;4(6):349–57;
2. Eigl S, *et al. Int J Antimicrob Agents*. 2015;46(4):401–5;
3. Barnes RA. *J Antimicrob Chemother*. 2008;61(Suppl. 1):i3–i6.

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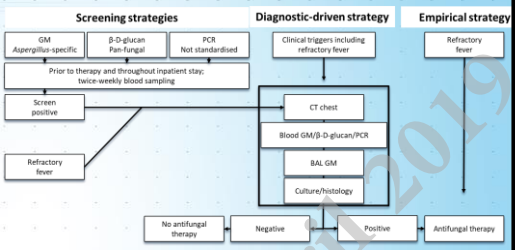
Updates on IFD Management Guidelines

Mould-active prophylaxis?

- Expose large numbers of patients to drug
- Therapeutic drug monitoring
  - Voriconazole, posaconazole suspension, itraconazole
- Resistance?
- Treatment drug?



IDSA 2016:
'…switch to IV therapy, and/or another drug class.'[1]

BAL, bronchoalveolar lavage; CT, computerised tomography; GM, galactomannan; IDSA, Infectious Diseases Society of America; IMD, invasive mould disease; IV, intravenous; PCR, polymerase chain reaction

1. Patterson TF, *et al. Clin Infect Dis*. 2016;63(4):e1–60;

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Updates on IFD Management Guidelines

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- *IFD Management – is it imp*
- *Guidelines , Guidelines, Gui*
- ***Improving your practice*** *- Diagnostics*

Do you have biomarkers in your centre?

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Updates on IFD Management Guidelines

Commercially available assays

- Galactomannan – *Aspergillus* spp. (not mucor)
- β-D-glucan – pan-fungal (not mucor)
- PCR – *Aspergillus* spp. (and resistance genes)
- **Rapid antigen tests** – lateral flow devices

IMD, invasive mould disease; PCR, polymerase chain reaction

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Updates on IFD Management Guidelines

Studies in haem-onc using GM/A-PCR[1–3]

- 2013 empirical 'plus' vs GM + A-PCR
  - 50% mould prophylaxis
  - Decreased AF 32% vs 15% (p=0.002); Mortality same
- 2015 GM vs GM + A-PCR
  - No mould prophylaxis
  - Decreased empirical AF 29% vs 17% (p=0.038); Mortality same
- 2005 prospective feasibility study using GM, CT, BAL
  - Fluconazole prophylaxis
  - Decreased AF 35% vs 8%
  - **10 pts (7%) started AF based on biomarker (no fever)**

AF, antifungal drugs; A-PCR, *Aspergillus* PCR; BAL, broncho-alveolar lavage; GM, galactomannan; IMD, invasive mould disease; PCR, polymerase chain reaction

1. Morrissey CO, *et al. Lancet Infect Dis.* 2013;13(6):519–28;
2. Aguado JM, *et al. Clin Infect Dis.* 2015;60(3):405–14;
3. Maertens J, *et al. Clin Infect Dis.* 2005;41(9):1242–50.

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Updates on IFD Management Guidelines

Studies in haem-onc using rapid tests

- Current biomarkers
  - Not available in all centres
  - Turn-around times?
- Lateral flow tests
  - Aspergillus-specific antigens
  - Single-sample tests
  - Fast – 15 min to 1 hour
  - Point-of-care for BAL

OLM LFD IMMY LFA

BAL, broncho-alveolar lavage; IMD, invasive mould disease; LFA, lateral flow assay; LFD, lateral flow device

1. Heldt S, *et al. J Infect*. 2018;77(3):235–41;
2. Mercier T, *et al. J Clin Microbiol*. 2019. [Epub ahead of print];
3. Jenks JD, *et al. J Infect*. 2019;78(3):249–59;
4. Jenks JD, *et al. Mycoses*. 2019;62(3):230–6.

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- ***Improving your practice***

Real world cases…implementing a strategy

IFD, invasive fungal disease

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Case 1

- 62-year-old man with CLL
- #1 and #2 chemo-immunotherapy (FCR)
- Neutropenia, fever, cough, dyspnoea
  - On aciclovir/fluconazole/co-trimoxazole
  - Piperacillin–tazobactam + gentamicin
  - Remains febrile for >72 hours
  - Caspofungin

CLL, chronic lymphocytic leukaemia; FCR, fludarabine/cyclophosphamide/rituximab

Agrawal S, personal data.

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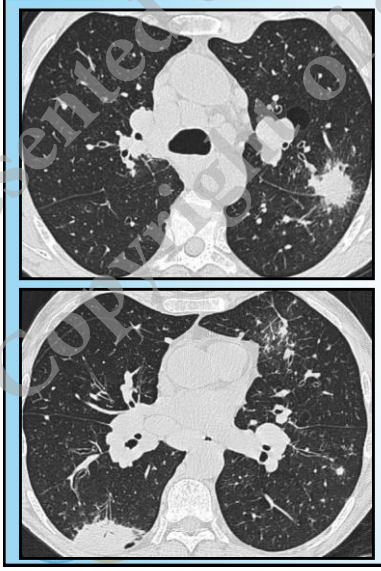
Case 1: Would you give empirical Caspofungin ?



EORTC/MSG criteria[1]

- CT/no micro = **Possible IFD**
- *EMPIRICAL?*
- Change antibiotics?
- Change antifungals?
- Investigations?

CT, computerised tomography; EORTC/MSG, European Organisation for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group; IFD, invasive fungal disease; L-AMB, liposomal amphotericin B

1. De Pauw B, *et al*. *Clin Infect Dis*. 2008;46(12):1813–21; Agrawal S, personal data. .

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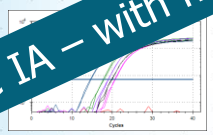
Case 1: What happened…

- Serum GM – <0.5
- BAL:
  - GM 0.9
  - [illegible]
  - LFD



Probable IA – with multiple biomarkers

Diagnostic driven

A-PCR, *Aspergillus* PCR; BAL, broncho-alveolar lavage; GM, galactomannan; IA, invasive aspergillosis; L-AMB, liposomal amphotericin; LFD, *Aspergillus* lateral flow device

Agrawal S, personal data.

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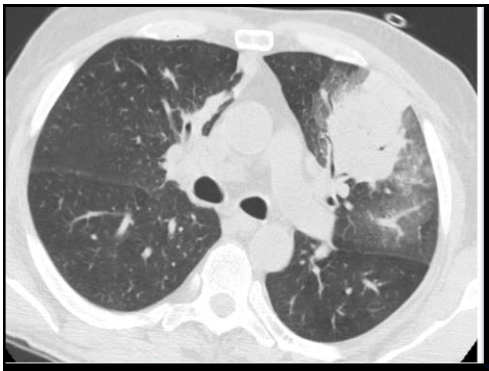
Case 2: Diagnosis made easy!

- 59-year-old man
- Acute myeloid leukaemia
- Allogeneic stem cell transplant

- Presents Day 120 – cough, dyspnoea, fever
- Co-trimoxazole, aciclovir, reducing cyclosporin
- No GVHD
- **CT chest…**

CT, computerised tomography; GVHD, graft-versus-host disease

Agrawal S, personal data.



Treatment?
Investigations?

CTPA

Vessel occlusion sign
(yellow arrow)

Stanzani M, *et al. Clin Infect Dis.* 2015;60(11):1603–10.

CT, computerised tomography; CTPA, CT pulmonary angiography

Agrawal S, personal data.

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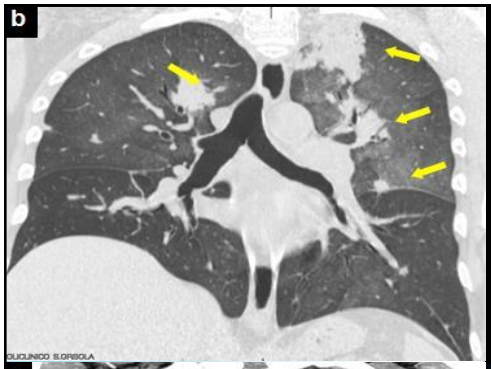
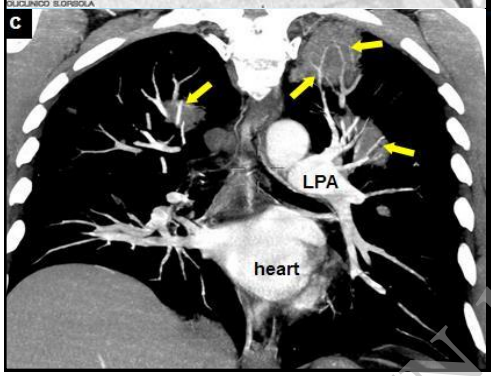
Case 3: Diagnosis made easy?

- 53-year-old man
- Acute myeloid leukaemia
- Consolidation chemotherapy
- Persistent neutropenic fever
- CT chest…

CT, computerised tomography

Agrawal S, personal data.





Treatment?

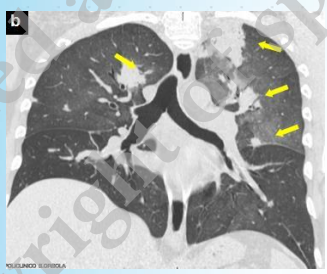
Investigations:
Biomarkers?
Blood/BAL?
CTPA?

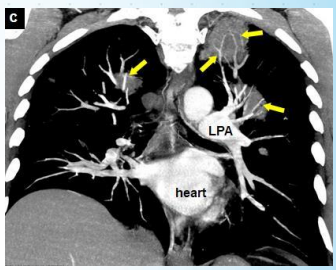
CTPA

BAL, broncho-alveolar lavage; CT, computerised tomography; CTPA, CT pulmonary angiography; LPA, left pulmonary artery

Agrawal S, personal data.

This is ***not*** pulmonary IMD!





- GM – negative blood/BAL
- CTPA – no vessel occlusion sign
- Multidrug-resistant *Pseudomonas aeruginosa* from blood/BAL
- **Antifungals stopped**

BAL, broncho-alveolar lavage; CT, computerised tomography; CTPA, CT pulmonary angiography; GM, galactomannan; IMD, invasive mould disease

Stanzani M, *et al. Clin Infect Dis.* 2015;60(11):1603–10; Agrawal S, personal data.

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Updates on IFD Management Guidelines

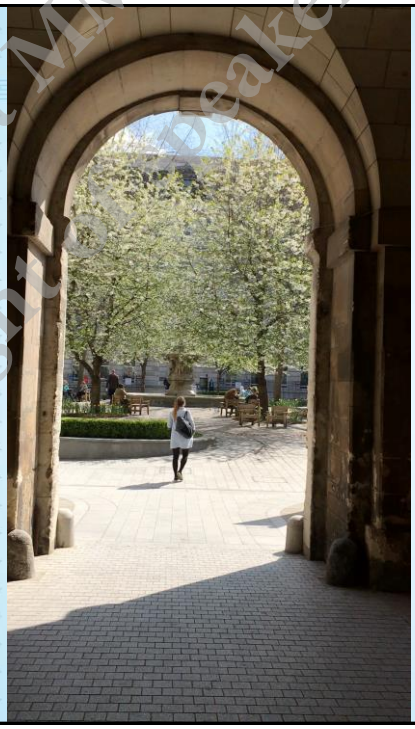
Summary:

- *IFD Management is Important !*
- *Guidelines…*
- ***…Improving Your Practice…***

LOCAL POLICIES:

- *Risk*
- *Mould-active prophylaxis*
- *Treatment drug*
- *Empirical vs diagnostic*
- *Screening*
- *Biomarkers*
- *New rapid assays*
- *CT*
- *CTPA*
- *COLLECT YOUR DATA !*

IFD, invasive fungal disease



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Central London

13th and 14th March 2020

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Podcasts