CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

Invasive Pilzinfektionen incl. *Pneumocystis*-Pneumonie

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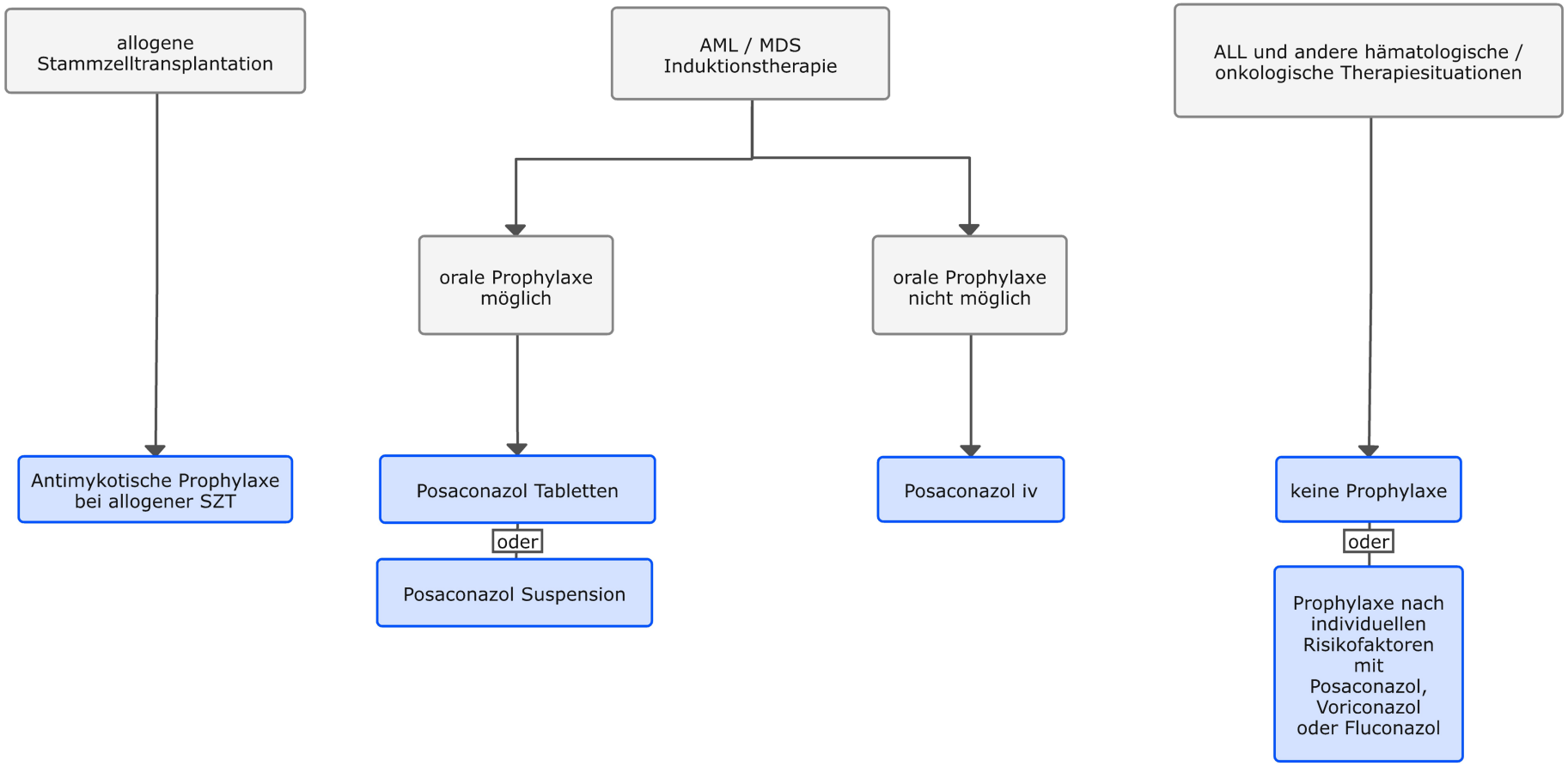
Antimykotische Therapie-Prinzipien

Onkopedia: Antimykotische Prophylaxe



AGIHO INFEKTIONEN IN DER HÄMATOLOGIE UND ONKOLOGIE
FACHGRUPPE DER DGHO

Empirische und präemptive antimykotische Therapie

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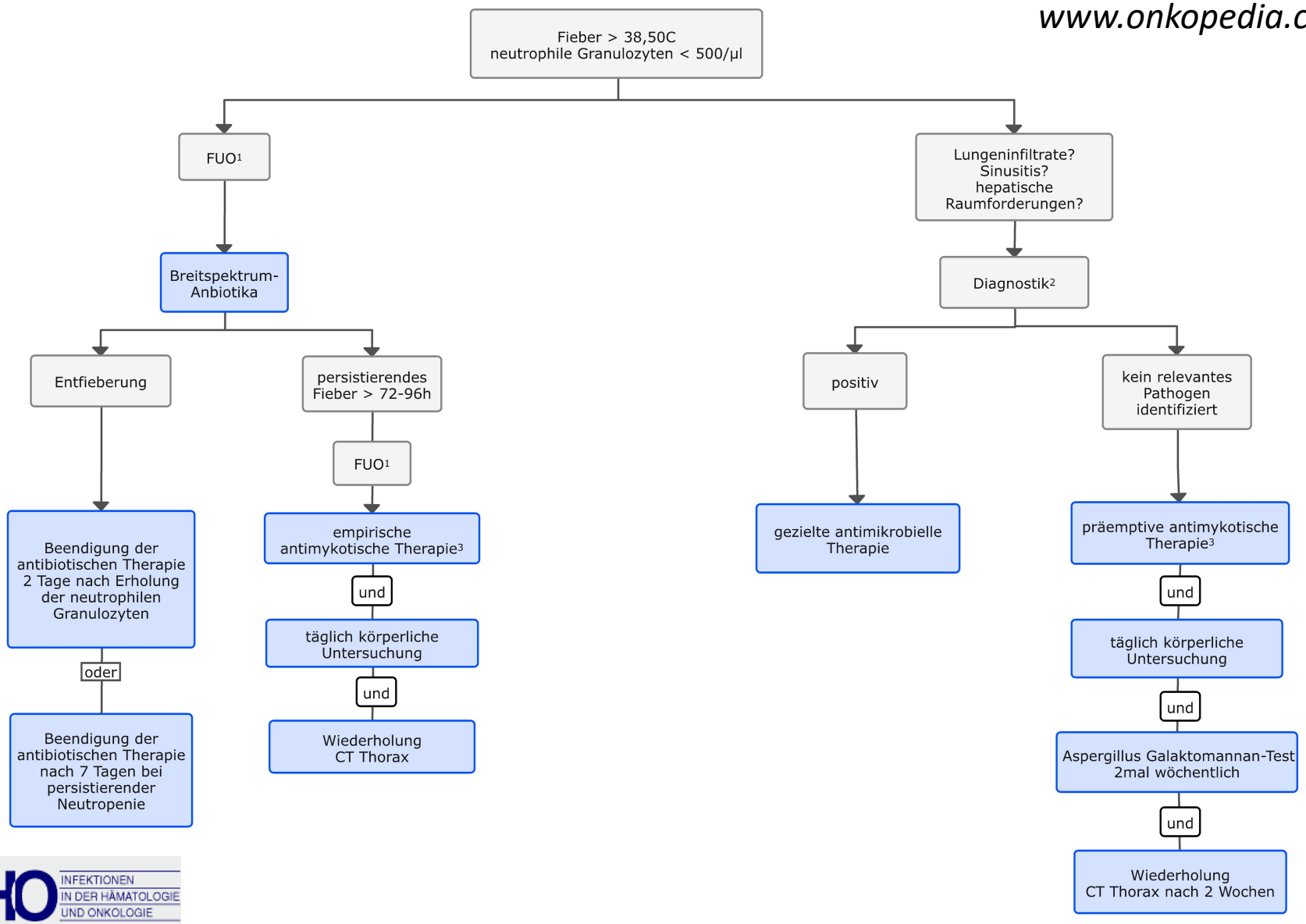

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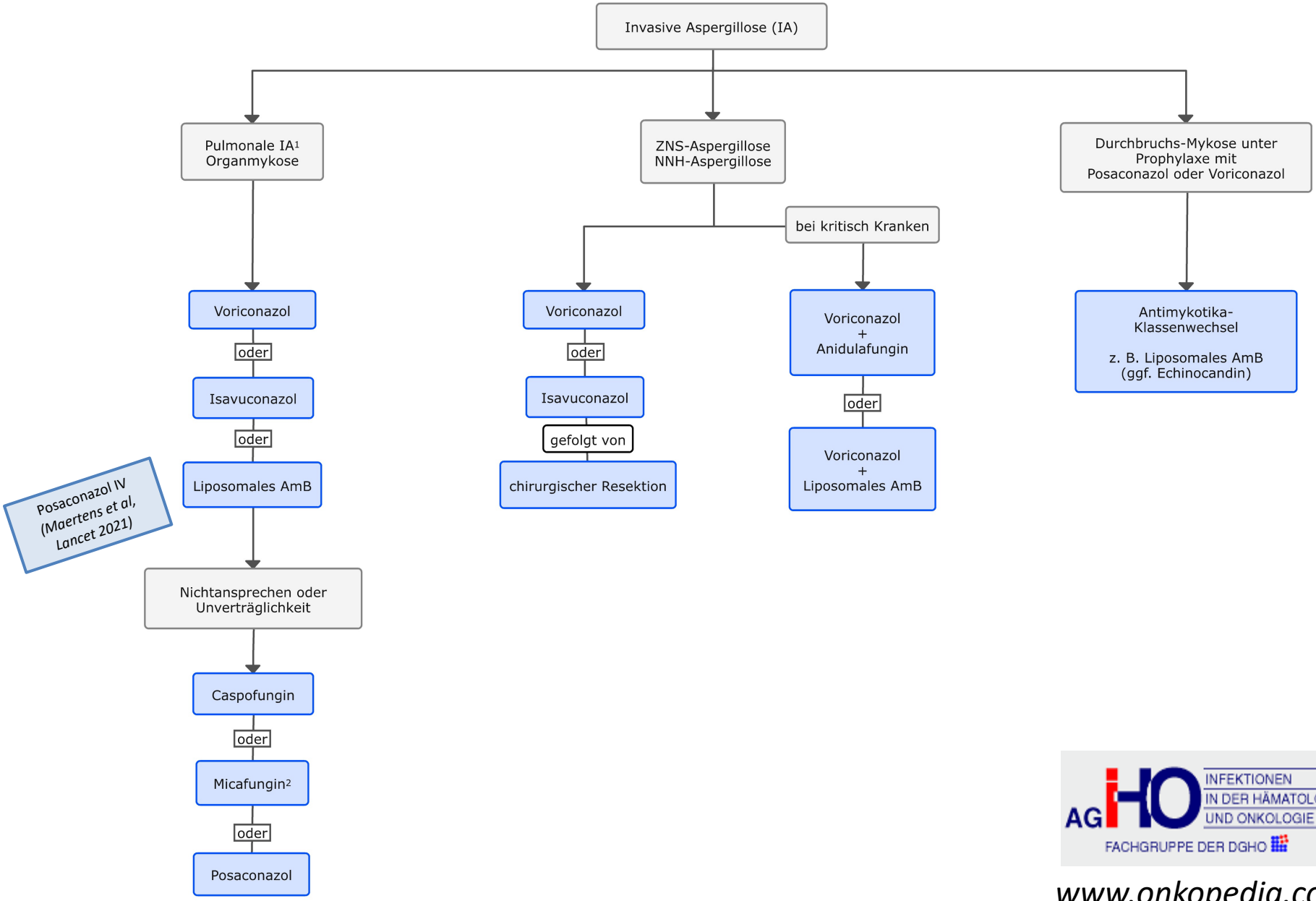
Antimykotische Therapie bei Aspergillosen



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1st-Line Antifungal Therapy for IA

(a) Population	Intention	Intervention	SoR	QoE
Any	To cure	Voriconazole	A	I
Any	To cure	Isavuconazole	A	I
Any	To cure	Liposomal amphotericin B	A	II
Any	To cure	Voriconazole + Anidulafungin combination	B	I
Any	To cure	Posaconazole	C	III
Any	To cure	Caspofungin	C	II
Any	To cure	Micafungin	C	II
Any	To cure	Itraconazole	C	III
Any	To cure	Anidulafungin	D	III
Any	To cure	Amphotericin B lipid complex (ABLC)	D	I
Any	To cure	Amphotericin B Deoxycholate	D	I
Any	To cure	Amphotericin B colloidal dispersion (ABCD)	D	I

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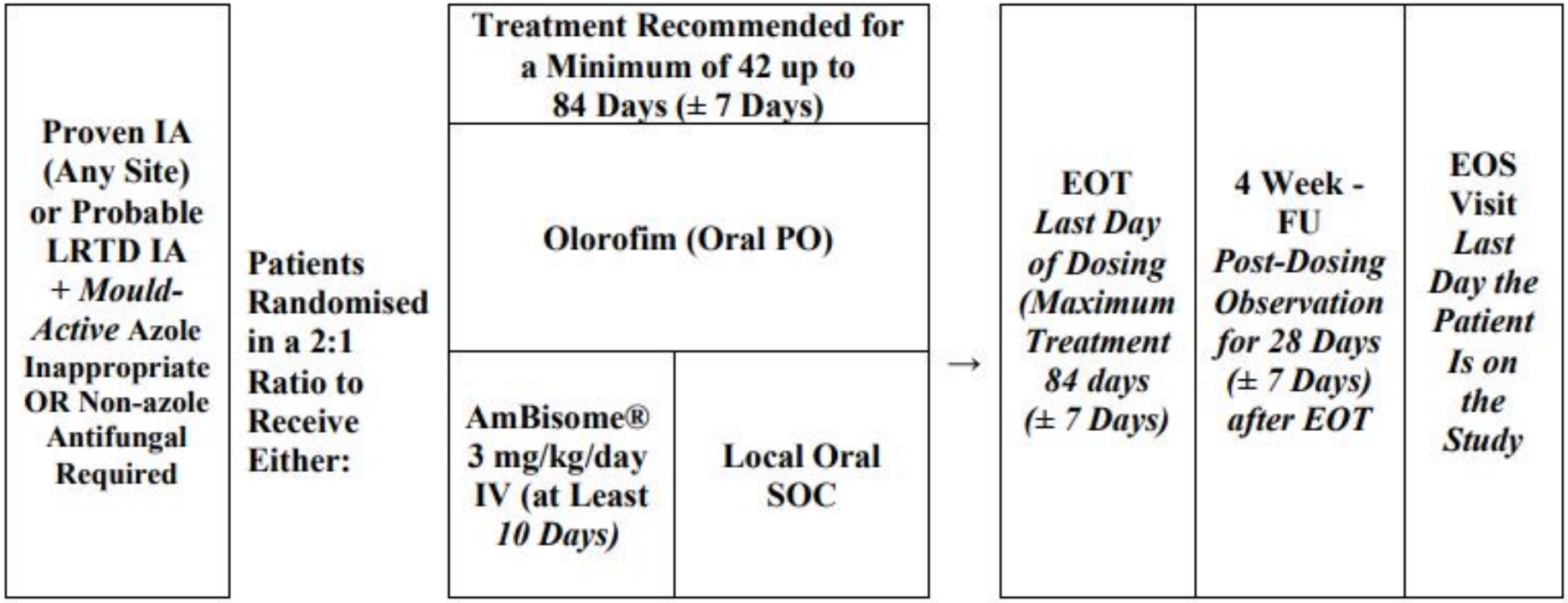
Ruhnke M et al (AGIHO), Mycoses 2020; 63:653-682

OASIS study F901318/0041

Clinical Trial for Patients with Invasive Aspergillosis where Azoles are not a Treatment Option



Ansprechpartner: OA PD Dr. Stefan Schwartz

2nd-Line Antifungal Therapy for IA

(b) Population	Intention	Intervention	SoR	QoE
Any	To cure	Liposomal Amphotericin B	B	II
Any	To cure	Caspofungin	B	II
Any	To cure	Posaconazole	B	II
Any	To cure	Voriconazole	B	II
Any	To cure	Micafungin mono- or combination	C	II
Any	To cure	Voriconazole + Caspofungin mono- or combination	C	II
Any	To cure	Amphotericin B lipid complex	B	III

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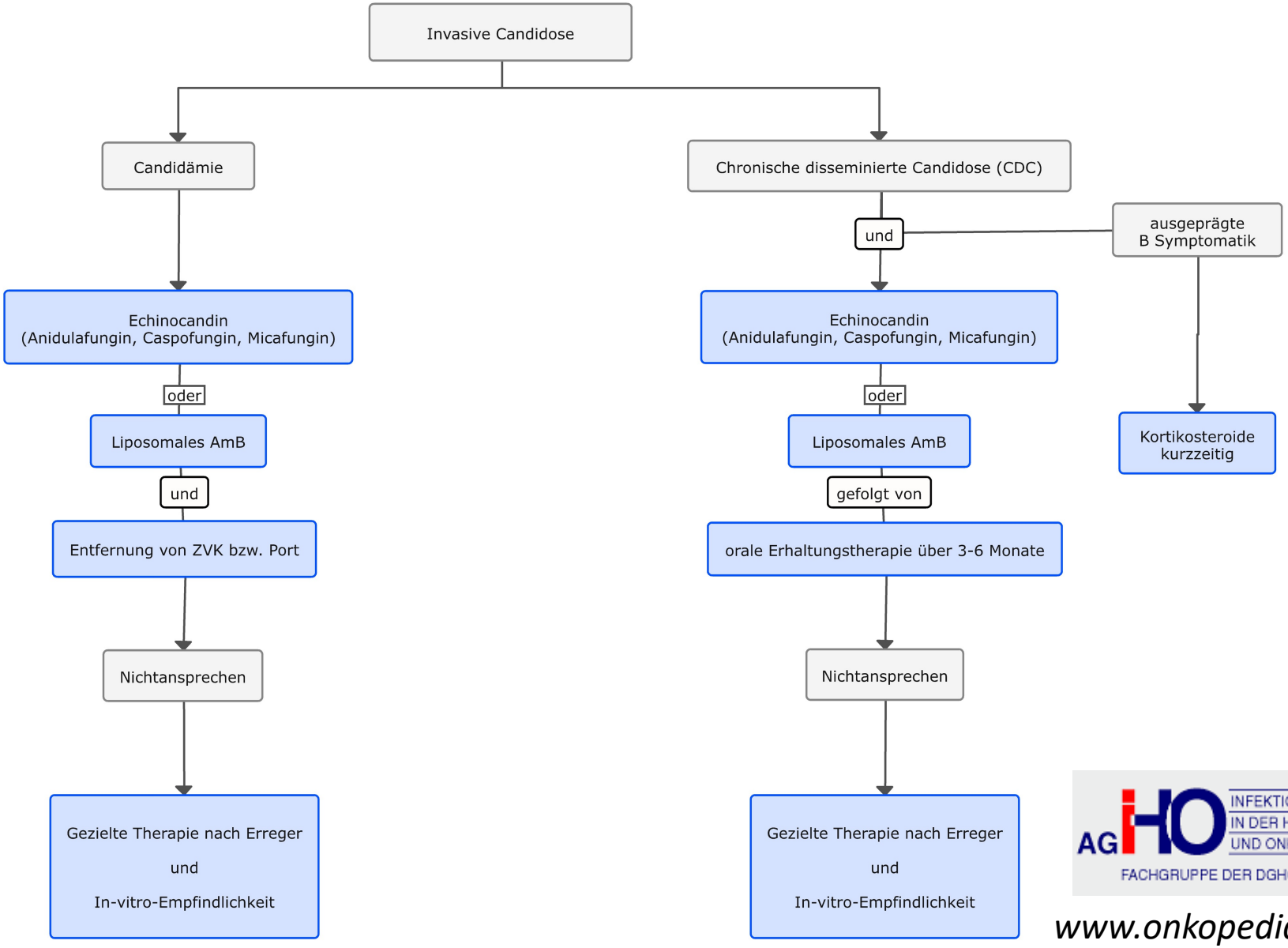
Ruhnke M et al (AGIHO), Mycoses 2020; 63:653-682

Therapie invasiver Candida-Infektionen



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1st-Line Antifungal Therapy for IC

(a) Population	Intention	Intervention	SoR	QoE
All cancer pat.	Cure	Early catheter removal	A	II
Granulocytopenic cancer pat.	Cure	Caspofungin, Micafungin L-AmB Fluconazole/ Voriconazole c-AmB/ABLC/ABCD	A A C D	It It III I
All cancer pat. (non-granulocytopenic)	Cure	Echinocandin L-AmB Azole	A A C	I I I
All cancer pat.	Cure, if clinically no choice other than to retain catheter	Echinocandin L-AmB	A A	III III
All cancer pat.	Switch to oral in responding patients/ step-down strategy	Fluconazole/ Voriconazole	B	IIt
All cancer pat.	Success/cure (chronic diss. Candidosis)	Fluconazole (≥3 mo)	B	III
		Other azoles effective (Vori?)	C	III
		Lipid AmB (8 wk)	B	III
		Echinocandin	B	III
All cancer pat.	Success/cure	Combination antifungal therapy	C	III
	Defervescence	Steroid therapy	C	III

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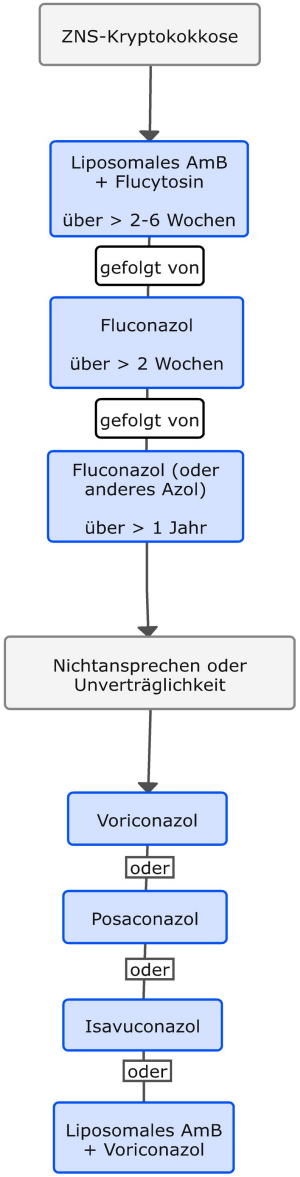
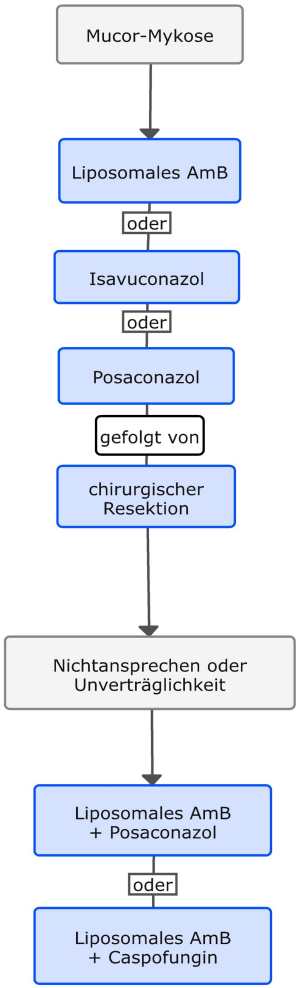
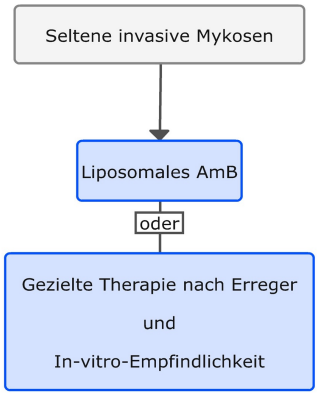
Ruhnke M et al (AGIHO), Mycoses 2020; 63:653-682

Therapie seltener(er) invasiver Mykosen







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1st-Line Therapy for Mucormycosis

(a) Population	Intention	Intervention	SoR	QoE
Any	To cure	Additional surgery (in combination with antifungal therapy)	A	II
Any	To cure	Liposomal amphotericin B	A	II
Any	To cure	Isavuconazole	B	IIu
Any	To cure	Posaconazole	B	IIu
Any	To cure	Combination		
		L-AmB + caspofungin	C	III
		L-AmB + posaconazole	B	IIu
Any	To cure	Amphotericin B lipid complex	D	II
Any	To cure	Amphotericin B formulation + deferasirox	D	II
Any	To cure	Amphotericin B deoxycholate	D	I

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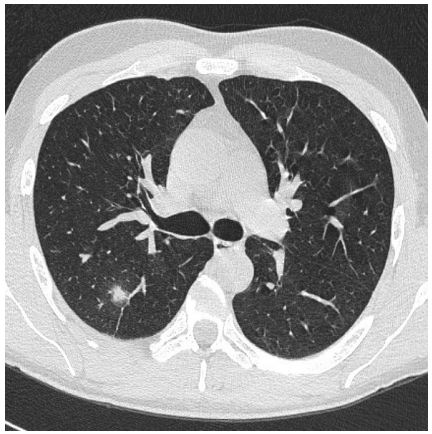
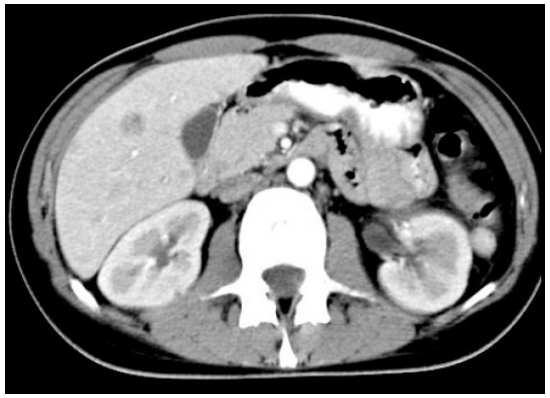
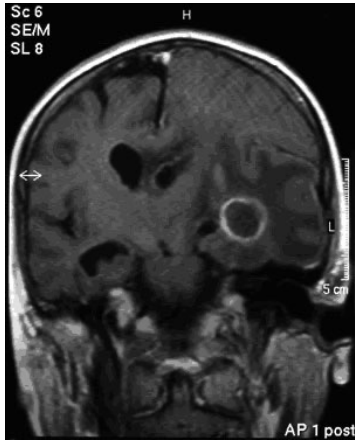
Ruhnke M et al (AGIHO), Mycoses 2020; 63:653-682

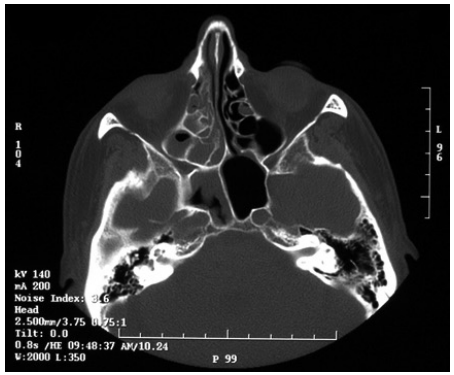
Diagnostic-Driven (**Preemptive**) Antifungal Therapy: Clinical Settings

- Suspect of invasive fungal infection
- Use imaging techniques and non-culture based assays (GM)
- Obtain cultures, take biopsy whenever possible
- Initiate treatment, even before culture results are known
- Adjust antimicrobial therapy accordingly, once (if) results are available









Preemptive Treatment Based on Imaging Findings in Pulmonary Aspergillosis

Imaging finding	No. (%) of patients (N = 235)
Macronodule (⩾1 cm in diameter)[a]	222 (94.5)
Halo sign[b]	143 (60.9)
Consolidation[c]	71 (30.2)
Macronodule, infarct shaped	63 (26.8)
Cavitary lesion[d]	48 (20.4)
Air bronchograms	37 (15.7)
Clusters of small nodules (<1 cm in diameter)	25 (10.6)
Pleural effusion	25 (10.6)
Air crescent sign	24 (10.2)
Nonspecific ground-glass opacification	21 (8.9)
Consolidation, infarct shaped	18 (7.7)
Small-airway lesions[e]	16 (6.8)
Atelectasis	7 (3.0)
Hilar/mediastinal lesion	4 (1.7)
Pericardial effusion	2 (0.9)

NOTE. Patients may have >1 type of lesion.

Greene RE et al, Clin Infect Dis 2007;44:373-9

80% of these nodules represent mould infections

- 61 pts. (hem. NPL, SOTxP) with typical CT findings
- Percutaneous FNB (PLT >50/nl; lesion >1 cm)
- Detection of filamentous fungi (Calcofluor white): 49/61 (80%)

Fungus identified[c]		
Aspergillus fumigatus	13 (36)	…
Aspergillus terreus	21 (58)	…
Aspergillus flavus	2 (6)	…
Mucor species	…	5 (38)
Rhizomucor species	…	3 (23)
Absidia species	…	4 (31)
Cunnighamella species	…	1 (8)

Lass-Flörl C et al (Austria), Clin Infect Dis 2007;45:e101-4

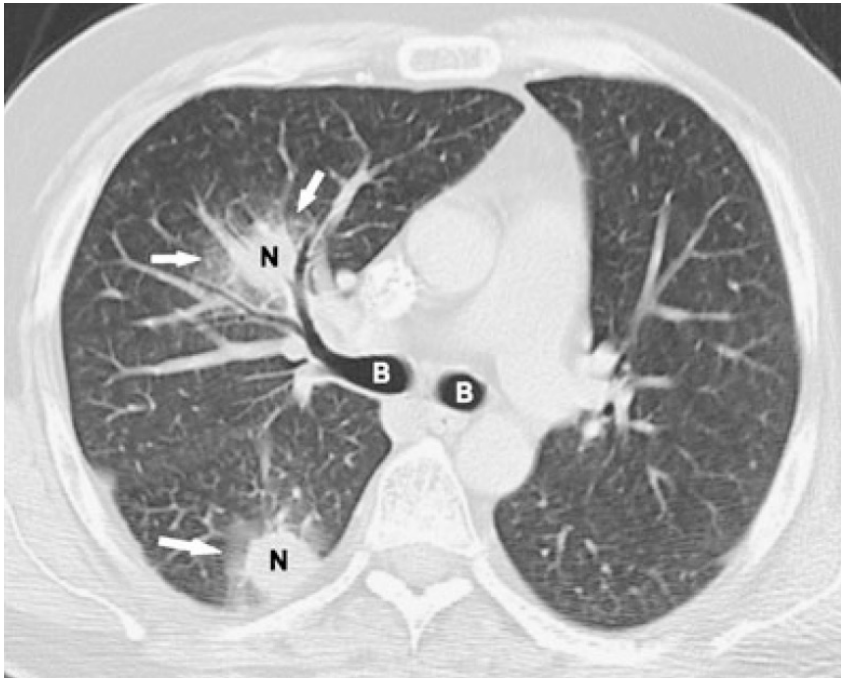
Halo Sign: It's not always *Aspergillus*

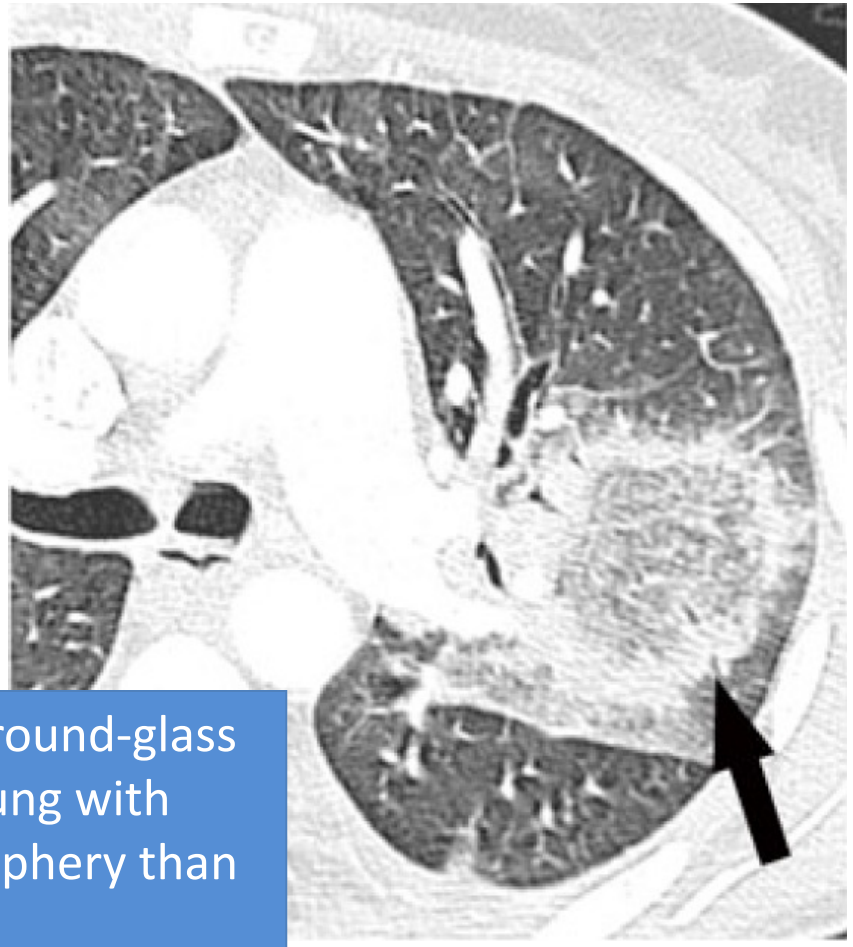
Potential Causes of Halo Sign

- Other Angio-invasive Fungi
  - Zygomycetes, Trichosporon, Penicillium, Fusarium,
- Endemic Fungi, e.g., Coccidioidomyces
- Other Organisms
  - Nocardia, Pseudomonas aeruginosa, Mycobacterium tuberculosis, Cytomegalovirus and Herpes Simplex
- Non-Infectious Conditions
  - Bronchoalveolar cell carcinoma, MALT tumors, Wegener's granulomatosis
- Unsharp margination

Greene R (Boston), 2003

The Diagnostic Value of Halo and Reversed Halo Signs for Invasive Mold Infections in Compromised Hosts

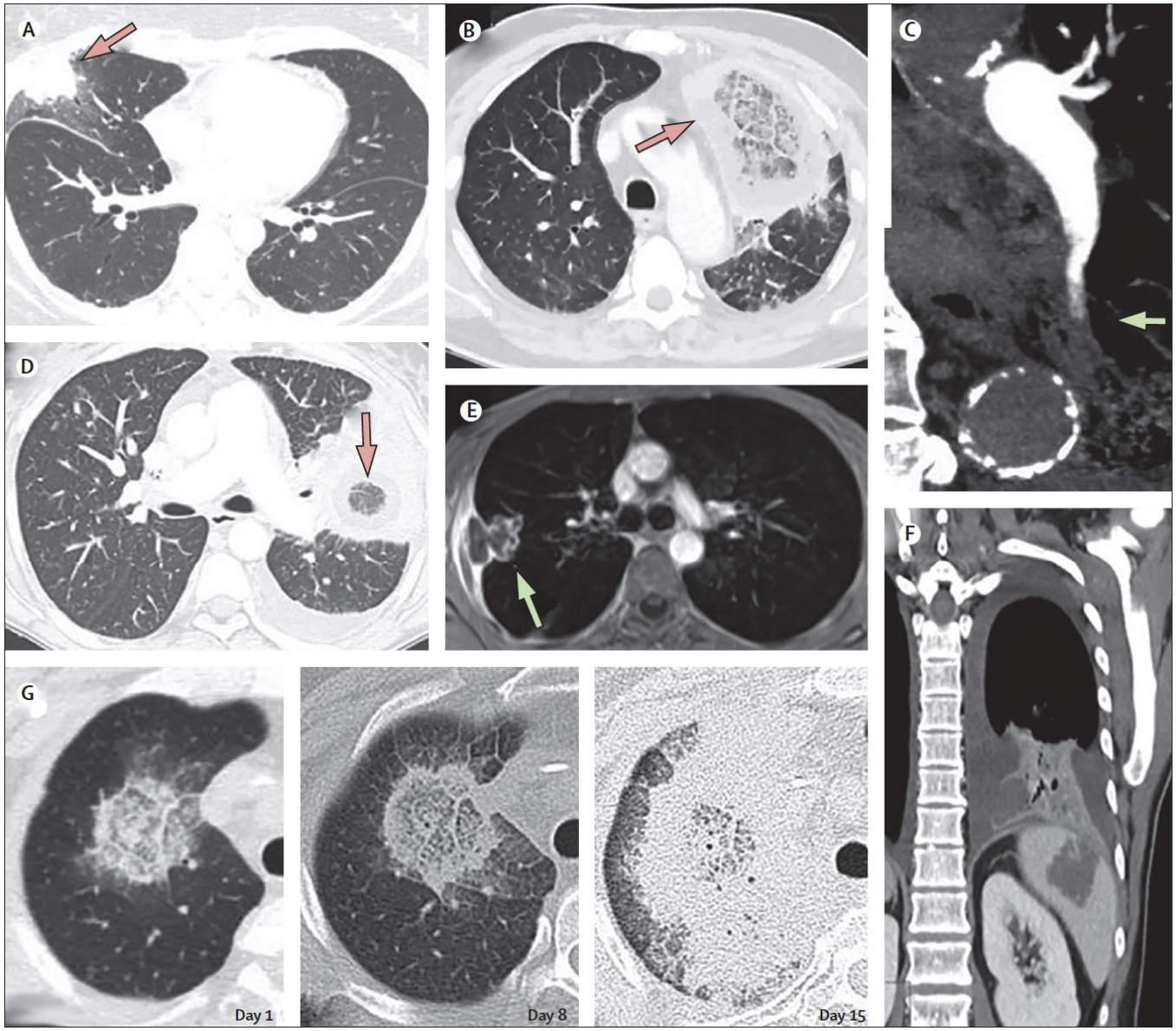




Peripheral consolidation and ground-glass opacities caused by infarcted lung with more hemorrhaging at the periphery than at the center

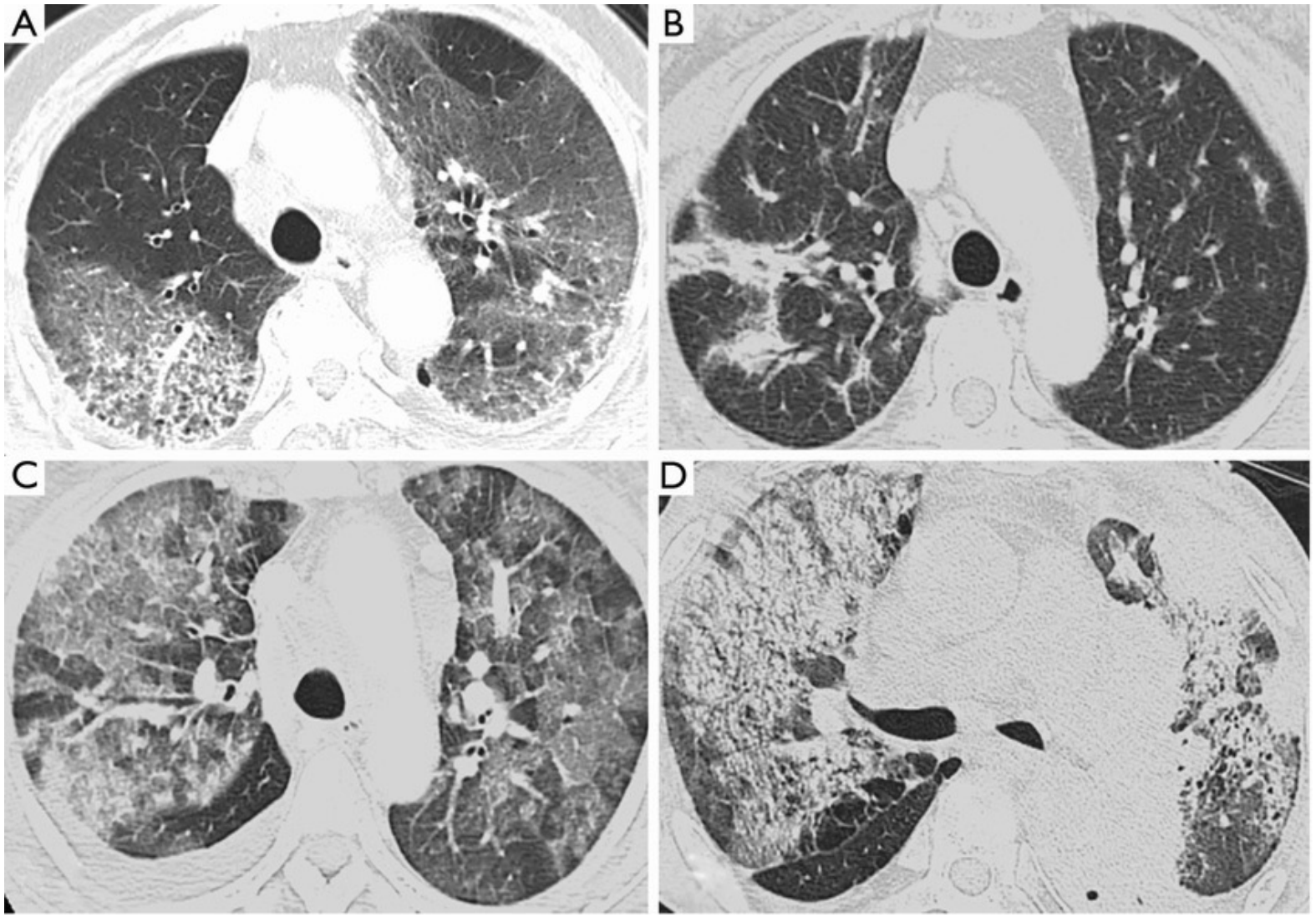
Georgiadou SP et al (MDACC), Clin Infect Dis 2011;52:1144–55

Pulmonary Mucormycoses



Cornely OA et al (ECMM & MSGERC), Lancet Infect Dis 2019;19:e405-21

Drug-Induced Interstitial Lung Disease („DILD“)



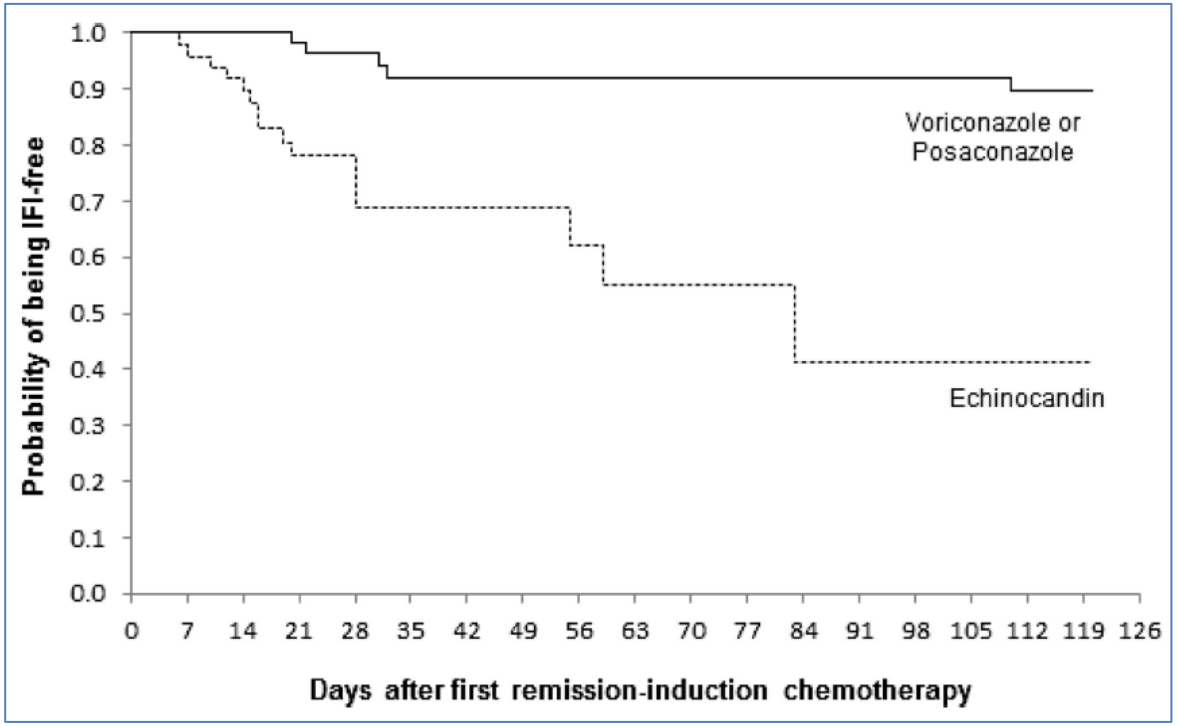
Kim S et al (Korea), J Thorac Dis 2014;6:1209-17

Breakthrough IFD: **Possible causes**

- Second IFI due to pathogens resistant to the antifungal agent given
- Development of resistance in previously sensitive fungi
- Insufficient antifungal drug concentration at the site of infection
  - Poor penetration
  - Drug-drug interactions
  - Incompliance of patients given oral antifungal agents

BT-IFD under Antifungal Prophylaxis in AML

- Total no. of pts under AFP = 152 (2009-2011)



- **Echinocandin** recipients: *Paecilomyces* (1), fusariosis (1), sinopulmonary mold infection (1), probable aspergillosis (6), coccidiomycosis (1), candidemia (3), *Saprochaete capitata* bloodstream infection (1)
- **Posaconazole/voriconazole** recipients: proven mold infection (1), probable aspergillosis (4), probable fusariosis (1)

Gomes MZR et al (MDACC), AAC 2014;58:2775-80

Bottom Line

- Most reasons for changing AF agents are **not rational**
  - Persistent fever
  - Elevated CRP – PCT – IL-6…
  - Enlarging pulmonary infiltrates on CT scan at day 7
  - Fear to make a mistake
  - **New** drug is much more **expensive =>** must be **better**

Breakthrough Aspergillosis: Diagnostic Approach

Investigation	Details
Serum/plasma or blood samples	GM
	β-d-glucan
	PCR
Therapeutic drug monitoring	Titrate drug dose to therapeutic levels
Fibreoptic bronchoscopy	BAL from infected lobe
	Biopsy lesion if practical
	Microscopy (using optical brighteners) and cytology
	Culture
	GM
	LFD
	PCR—positive samples can be tested further for the presence of genetic markers of resistance.
	Antifungal susceptibility on positive cultures
CT-guided biopsy or biopsy of peripheral lesion	Microscopy
	Culture
	Antifungal susceptibility on positive cultures
	Non-culture methods of identification (tissue-based molecular sequencing, immunohistochemistry, cytology)

BAL, bronchoalveolar lavage; GM, galactomannan; LFD, lateral flow device.

Slavin MA et al, J Antimcrob Chemother 2022;77:16-23

Reasons for Changing First-Line Antifungal Therapy

Days since initiation of therapy	Clinical and diagnostic findings compared with baseline
At any time	Identification of a pathogen resistant to primary antifungal therapy
8 to 14	On the basis of changes in GM: (i) Serum: The serum GM index has not fallen by either 1 unit or to <0.5 units based on measurements taken at least 7 days apart (ii) BAL: Positive GM from BAL in a patient with a previous BAL test that did not meet the definition of positive (too low or entirely negative) without regard for the interval of time between samples. Note that there is not a definition for rising GM index values from BAL as these values are subject to sampling error *Or* Clinical deterioration consistent with persisting or progressive invasive fungal disease with no other identifiable aetiology *Or* New distinct site of infection detected clinically or radiologically
≥15	Any of the above criteria *Or* Progression of original lesions on CT (or other imaging) based on >25% growth of initial lesions in the context of no change in immune status

GM, galactomannan.
Please note that equal weighting applies to each factor.

Slavin MA et al, J Antimcrob Chemother 2022;77:16-23

Antifungal Therapy for IA Emerging under Posaconazole or Voriconazole Prophylaxis

- So far, meaningful studies in this field are lacking.
- Breakthrough IFDs have been repeatedly reported under prophylaxis and/ or treatment with either voriconazole or posaconazole.
- These breakthrough IFDs may either due to resistant fungal pathogens (eg Mucor spp.) and/ or low through serum concentration of the triazole.
- The AGIHO recommends the switch to another class of antifungal agents (CIII).

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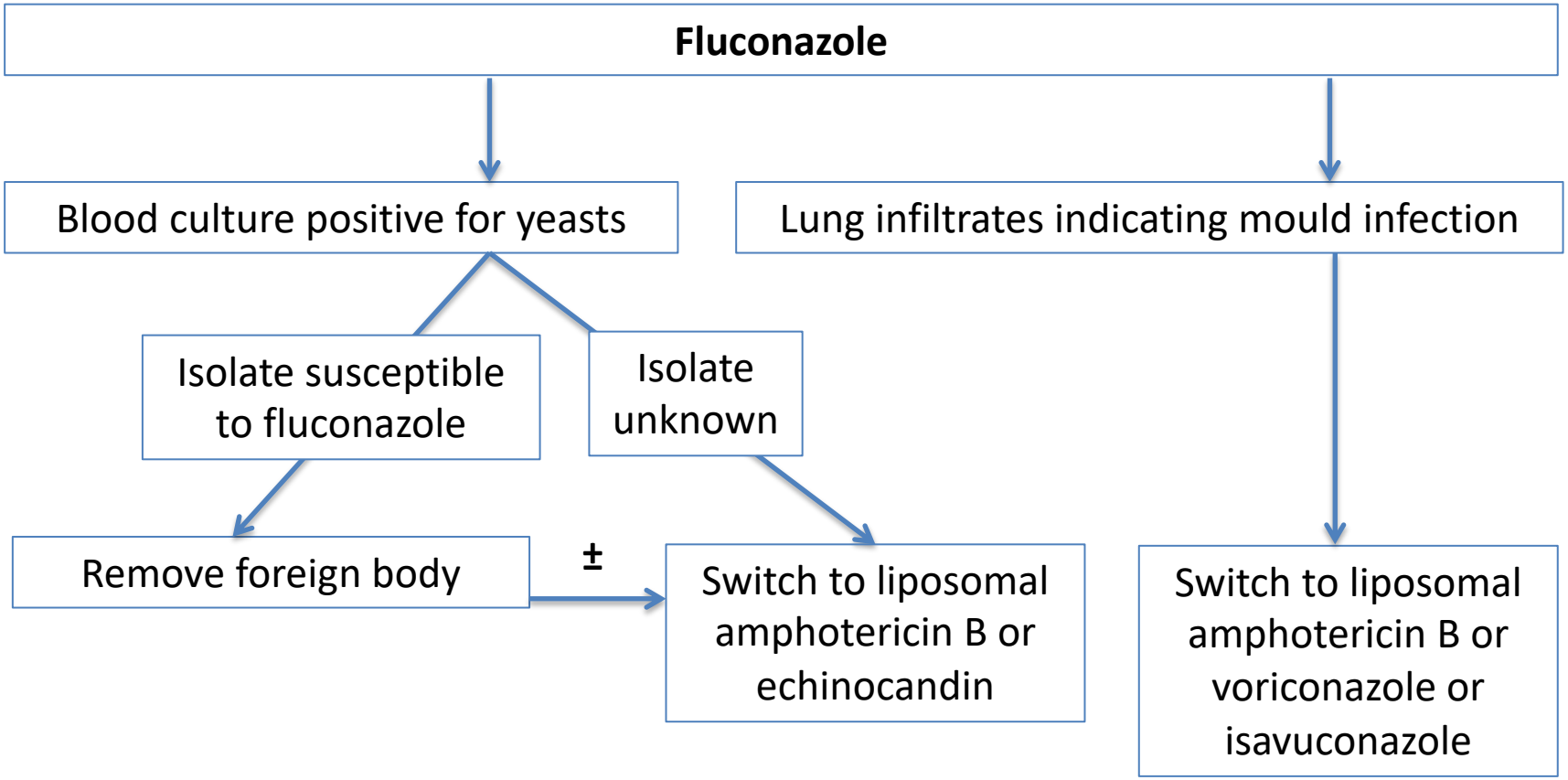
Ruhnke M et al (AGIHO), Mycoses 2020; 63:653-682

AGIHO: Antifungal TDM in Hematology

Intention	Drug	SoR	QoE	Comment
Definition of serum levels for optimal therapy	Posaconazole	B	IIt/r	• 700-1830 ng/mL (prophylaxis) • 800-2100 ng/mL (prophylaxis and therapy) • >1 mg/L (therapy)
	Voriconazole	B	IIr	• 2-5 mg/L • sustained high concentration associated with hepatotoxicity
	Isavuconazole	C	III (not yet well defined)	• 2-4 mg/L
	Flucytosine	B	IIt	• 30-80 mg/mL

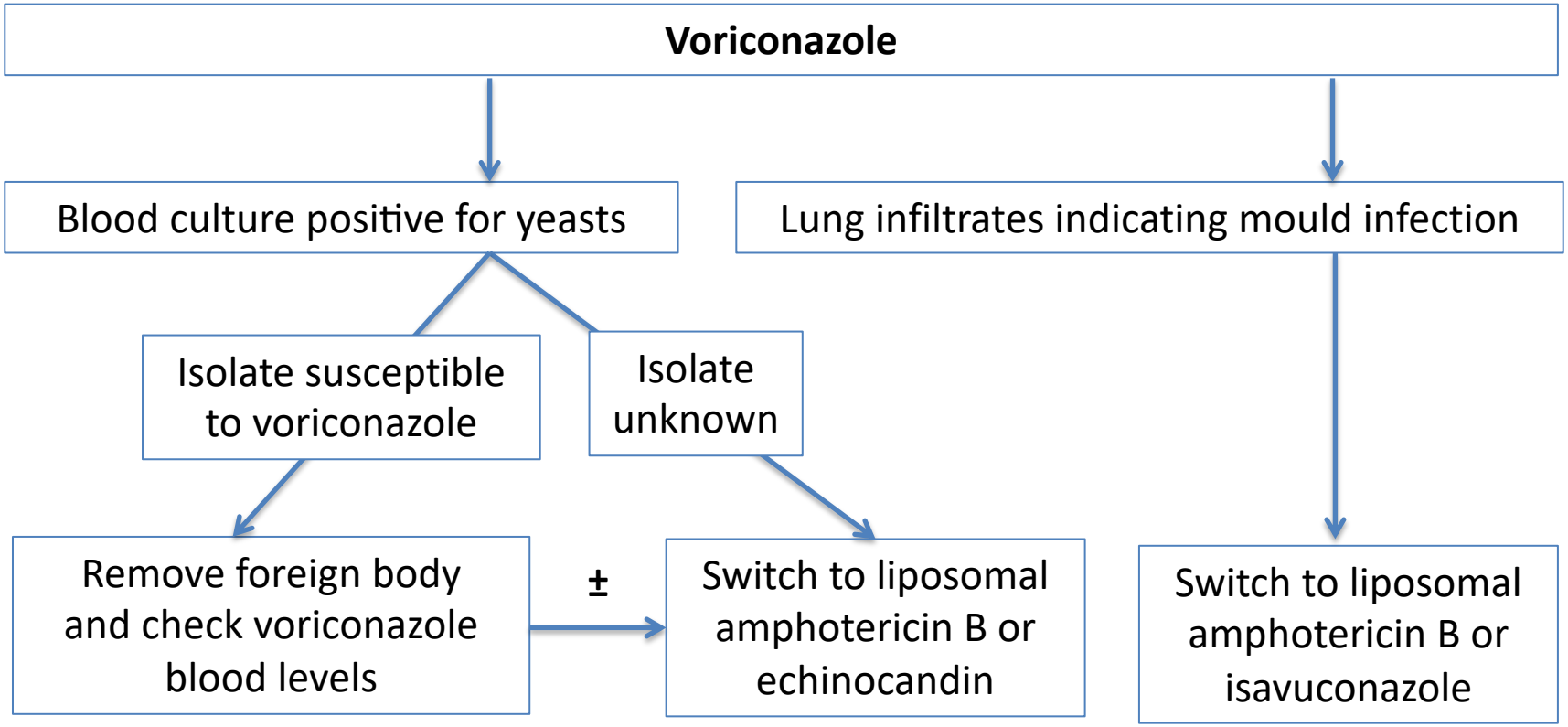
Ruhnke M et al (AGIHO), Mycoses 2020; 63:653-682

Fluconazole:
How to Handle Breakthrough Fungal Infection?



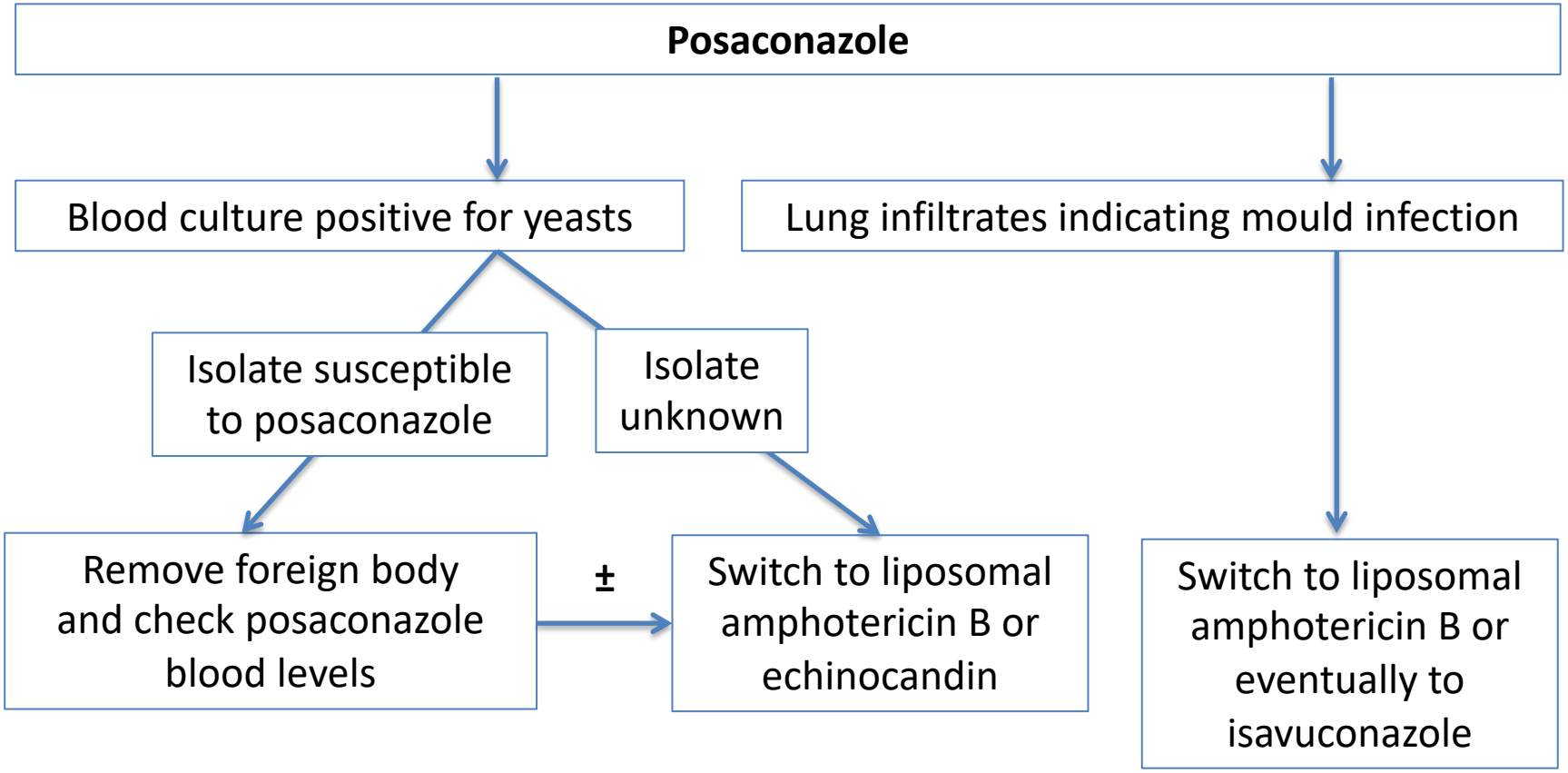
Adapted from: Maschmeyer G & Patterson TF, Mycoses 2014;57:645-51

Voriconazole:
How to Handle Breakthrough Fungal Infection?



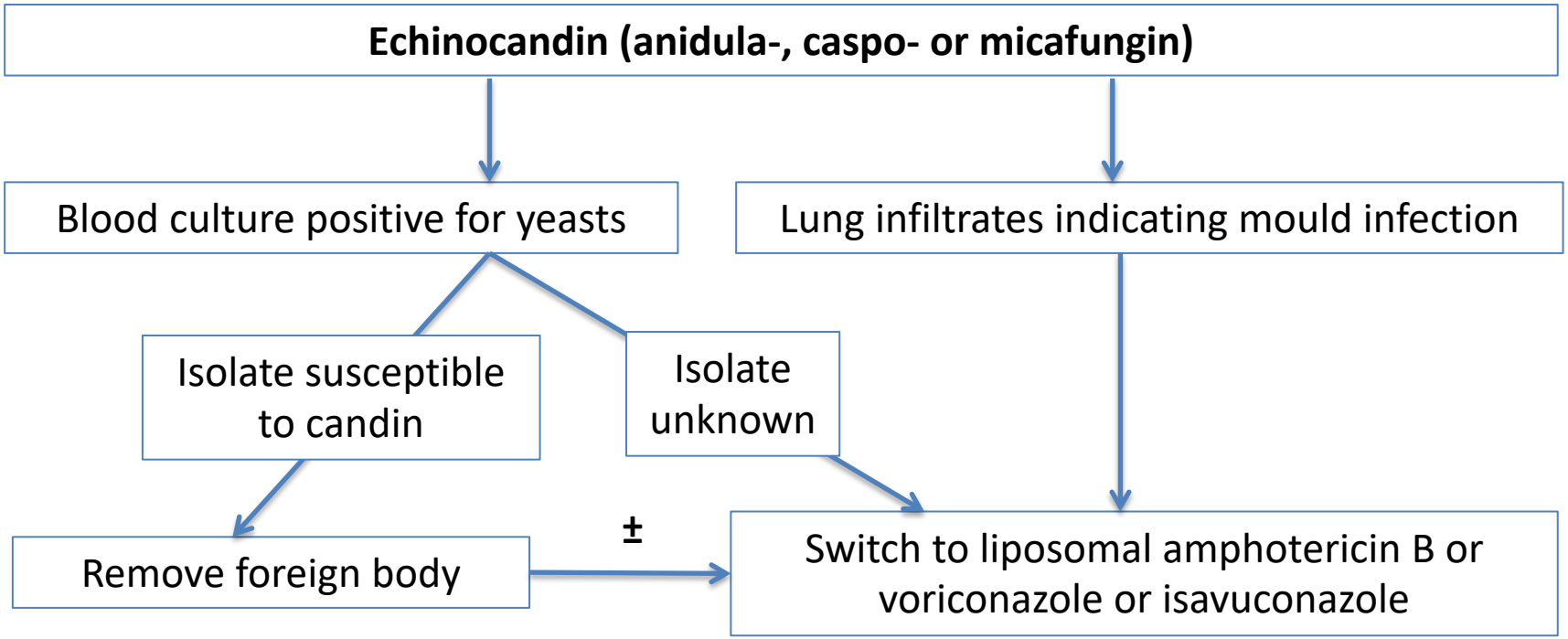
Maschmeyer G & Patterson TF, Mycoses 2014;57:645-51

Posaconazole:
How to Handle Breakthrough Fungal Infection?



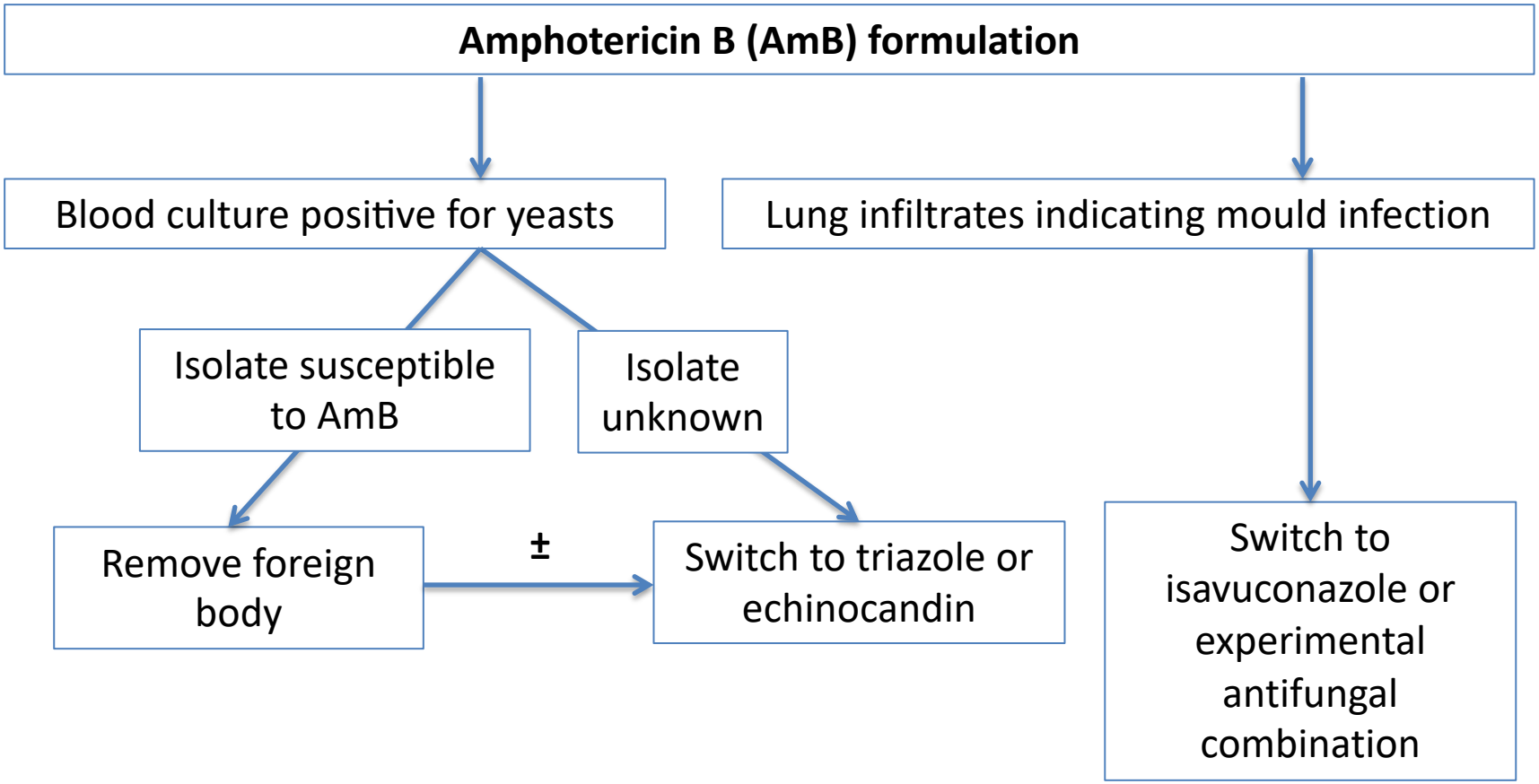
Adapted from: Maschmeyer G & Patterson TF, Mycoses 2014;57:645-51

Echinocandin:
How to Handle Breakthrough Fungal Infection?



Adapted from: Maschmeyer G & Patterson TF, Mycoses 2014;57:645-51

Amphotericin B:
How to Handle Breakthrough Fungal Infection?



Adapted from: Maschmeyer G & Patterson TF, Mycoses 2014;57:645-51

Pneumocystis-Pneumonie

Pneumocystis jirovecii infections in (non HIV-infected) hematology patients: *Part A: Biological aspects*

Alexandre Alanio (France)
Philippe M. Hauser (Switzerland)
Katrien Lagrou (Belgium)
Willem Melchers (The Netherlands)
Jannik Helweg-Larsen (Denmark)
Olga Matos (Portugal)
Stéphane Bretagne (France, chair)

ECIL 5 meeting
Juan-les-Pins, France
Sept. 19-21, 2013

Pneumocystis jirovecii infections in (non HIV-infected) adult and pediatric hematology patients: *Part B: Clinical aspects* "risk factors, presentation and prevention"

Johan Maertens (Belgium, chair)
Catherine Cordonnier (France)
Georg Maschmeyer (Germany)
Hermann Einsele (Germany)
Simone Cesaro (Italy)

ECIL 5 meeting
Juan-les-Pins, France
Sept. 19-21, 2013

Pneumocystis jirovecii Pneumonia (PcP) in non HIV-Infected Hematology Patients: *Treatment Guidelines*

Georg Maschmeyer (Germany, chair)
Jannik Helweg-Larsen (Denmark)
Livio Pagano (Italy)
Christine Robin (France)
Peter Schellongowski (Austria)

ECIL 6 meeting
Juan-les-Pins, France
Sept. 11-12, 2015

Pneumocystis Epidemiology

- *Pneumocystis jirovecii*: specific to humans
- Transmission by **airborne route**
- Acquisition in humans most likely by person-to-person spread *(Thomas et al. NEJM 2004)*
- Nearly **universal** seropositivity in immunocompetent children 2 years of age *(Vargas et al. Clin Infect Dis 2001)*
- **Primary infection** is generally an asymptomatic or mild, self-limiting upper respiratory tract infection

Patients with Hematological Malignancies: Risk Factors for Developing PcP

- **High risk**:
  - Treatment for ALL / relapsed aggressive lymphoma
  - Receipt of an allogeneic hematopoietic stem cell transplant
  - High-dose corticosteroid treatment (> 20 mg prednisone equivalent per day for > 1 month)
  - T cell depleting agents (e.g., alemtuzumab, nucleoside analogs); FCR for B-CLL
  - Antecedent PcP
- **Moderate risk**:
  - Receipt of an autologous hematopoietic stem cell transplant
  - Higher-intensity chemotherapy regimens (RCHOP-14, BEACOPP, high-dose MTX)
- **Low risk**:
  - Lower-intensity chemotherapy (RCHOP-21), gemcitabine
- **Absence or poor compliance to PcP prophylaxis in patients at risk**

PcP: Individual Risk Factors in Adults with Hematological Disorders

- Co-existing pulmonary infection, e.g., CMV
- Pre-existing lung disease
- *P. jirovecii* carriage
- Patient-to-patient transmission
- Genetic risk factors:
  - Dectin-1 polymorphisms
- Use of TNF antibodies: infliximab, adalimumab, etanercept etc.
- Use of temozolomide

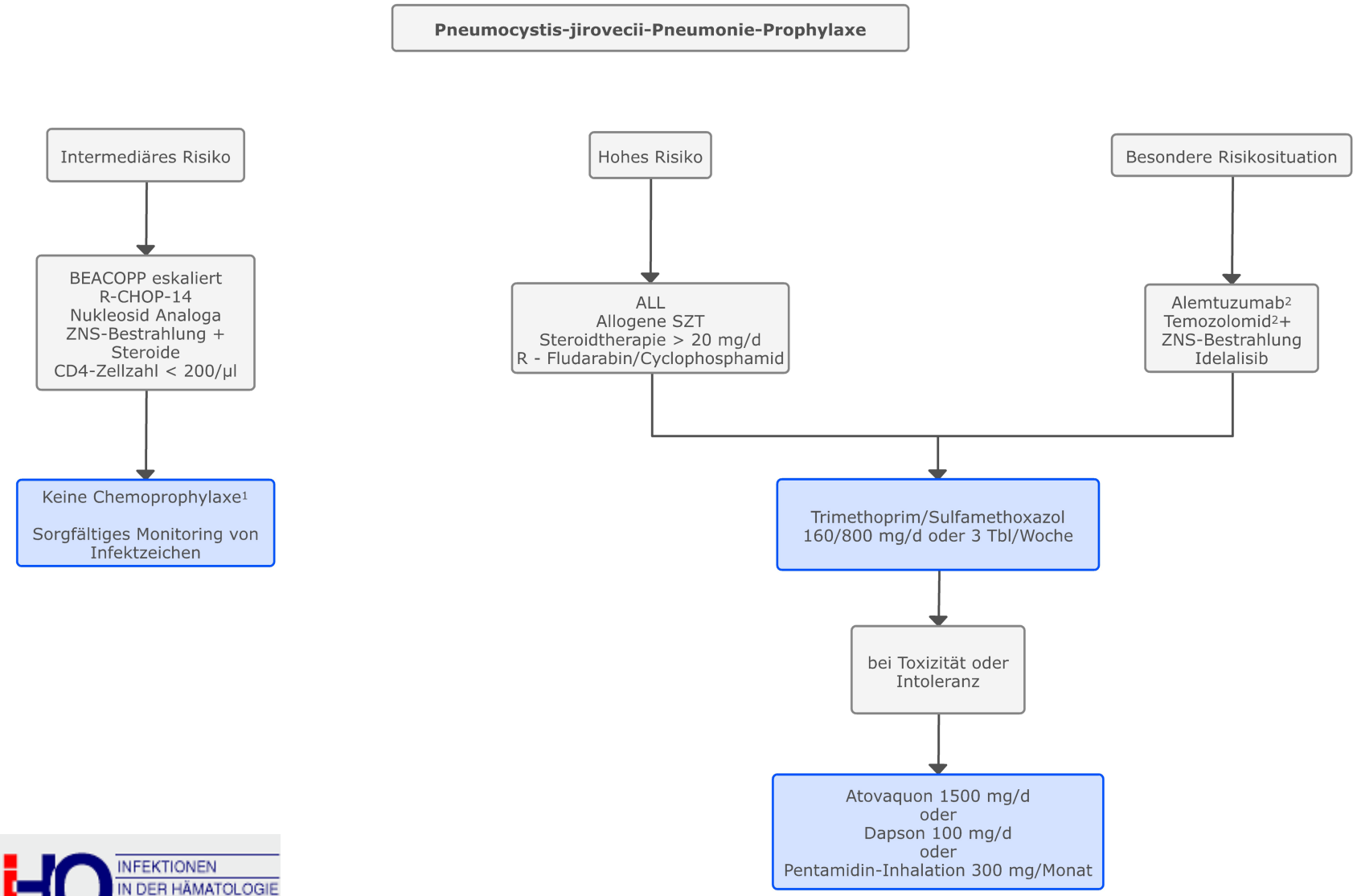
Maini EID 2013, Manoloff EID 2003, Ricks I&I 2013, Schoffelen AIDS 2013, Watanabe Mod Rheumatol 2013, Kim SJID 2012, Haeusler EJH 2013, Yu CO 2007

Infection Control
PcP: Preventing Exposure

ECIL expert opinion

- **Severely immunocompromised patients should avoid exposure to patients with documented PcP. C-III**
  - Infected patients should be preferably hospitalized in single rooms.

Onkopedia: *Pneumocystis*-Prophylaxe



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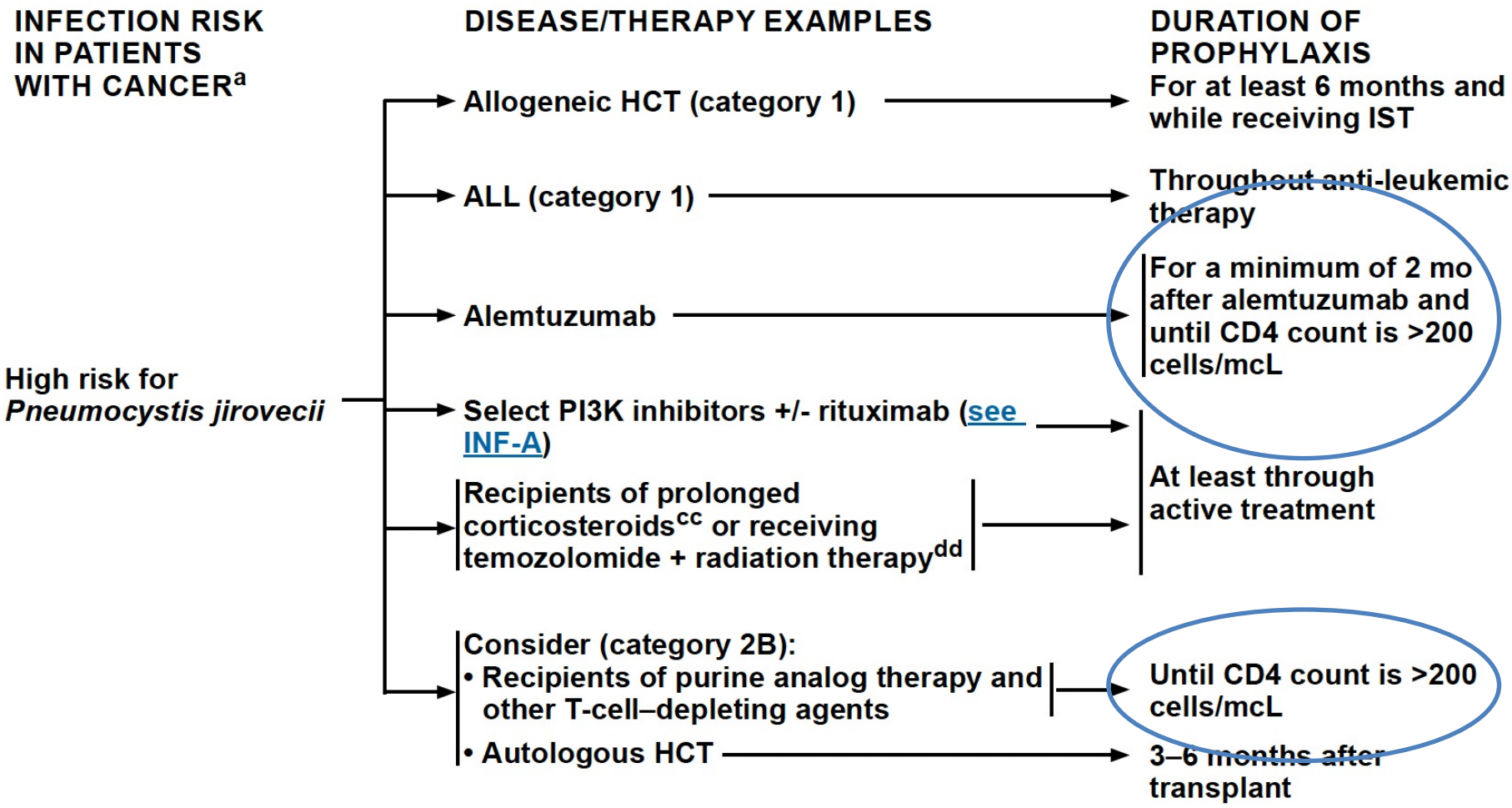
ECIL guidelines for PcP prophylaxis: Indications and Duration

Indication	Adults		Children	
	Disease/condition	**Duration**	**Disease/condition**	**Duration**
Main	**ALL**	From induction to end of maintenance	**ALL**	From induction to end of maintenance
	AlloHSCT	From engraftment to ≥ 6 months, and as long as IS is ongoing	**AlloHSCT**	From engraftment to ≥ 6 months, and as long as IS is ongoing
	Alemtuzumab		**Alemtuzumab**	
	FCR		SCID, WAS, X-linked Hyper-IgM, X-linked agammaglobulinemia HLA-II combined immunodeficiency	Life-long or until restoration of underlying defect
	Steroids (> 20mg/d prednisone for 7 weeks)		**Steroids (>0.4 mg/kg or 16 mg/d for ≥ 1 month)**	
Optional	**R-CHOP14 or BEACOPPesc**		**AML**	Duration of chemo
	Nucleoside analogs		**Solid tumors**	Duration of chemo

Maertens J et al, J Antimicrob Chemother 2016;71:2397-404

PcP Chemoprophylaxis

NCCN Guidelines 3.2022



www.nccn.org

PcP: Symptoms in Hematological Patients

- n = 55 (1990-99)
- Acute onset
- **Fever (86%), dyspnoea (78%), non-productive cough (71%), severe hypoxaemia (71%)**, thoracic pain (14%) and chills (5%).

Pagano et al. Br J Haematol 2002

- n = 56, 44 patients (78.6%) with hematologic malignancies (18 SCT recipients) and 12 patients with solid tumors
- Time from symptom onset: 7 days (3-14)
- **Fever (85.7%), dyspnea (78.6%), cough (57.1%)**
- Severe pneumonia (PaO_2, 58 mm Hg [50-70]) with bilateral interstitial infiltrates (80.4%) and bilateral ground-glass attenuation (89.3%) on CT scans

Bollée et al. Chest 2007

PcP in non-HIV Patients:

Co-Infections

- Co-infections in 28 to 71% of patients, especially pulmonary
- Multiple pathogens: *S. aureus*, Gram-negative bacteria, *Aspergillus sp*., CMV…
- In allogeneic HSCT recipients, PcP is associated with CMV pneumonia in around 50% of cases

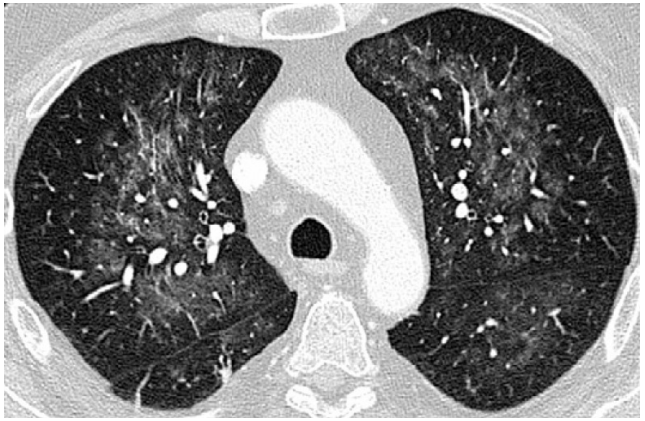
Ewig et al. Eur Respir J 1995
Toper et al. Rev Pneumol Clin 2011
Torres et al. Eur J Clin Microbiol Infect Dis 2006
Yale & Limper. Mayo Clin Proc 1996

PcP: Imaging in non-HIV^{+} Patients

Multislice chest CT: **gold standard.** Diffuse interstitial pneumonia is highly evocative of PcP in patients at risk, but no aspect is specific.

Main imaging patterns:

- ***bilateral interstitial pneumonia*** (60-80%)
- ***alveolar*** (10-20%)
- ***alveolo-interstitial*** pattern (10-20%)

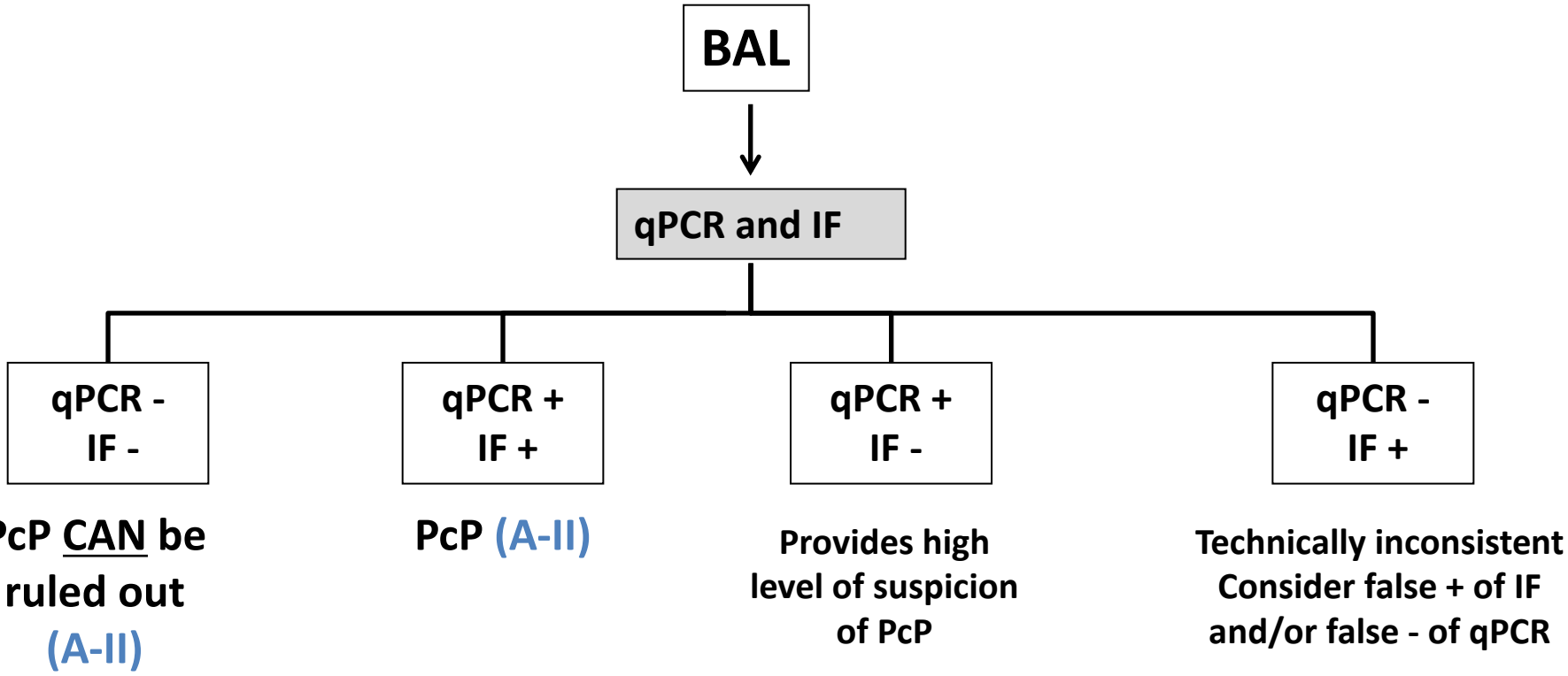


Vogel et al. EJR 2012

Rare:

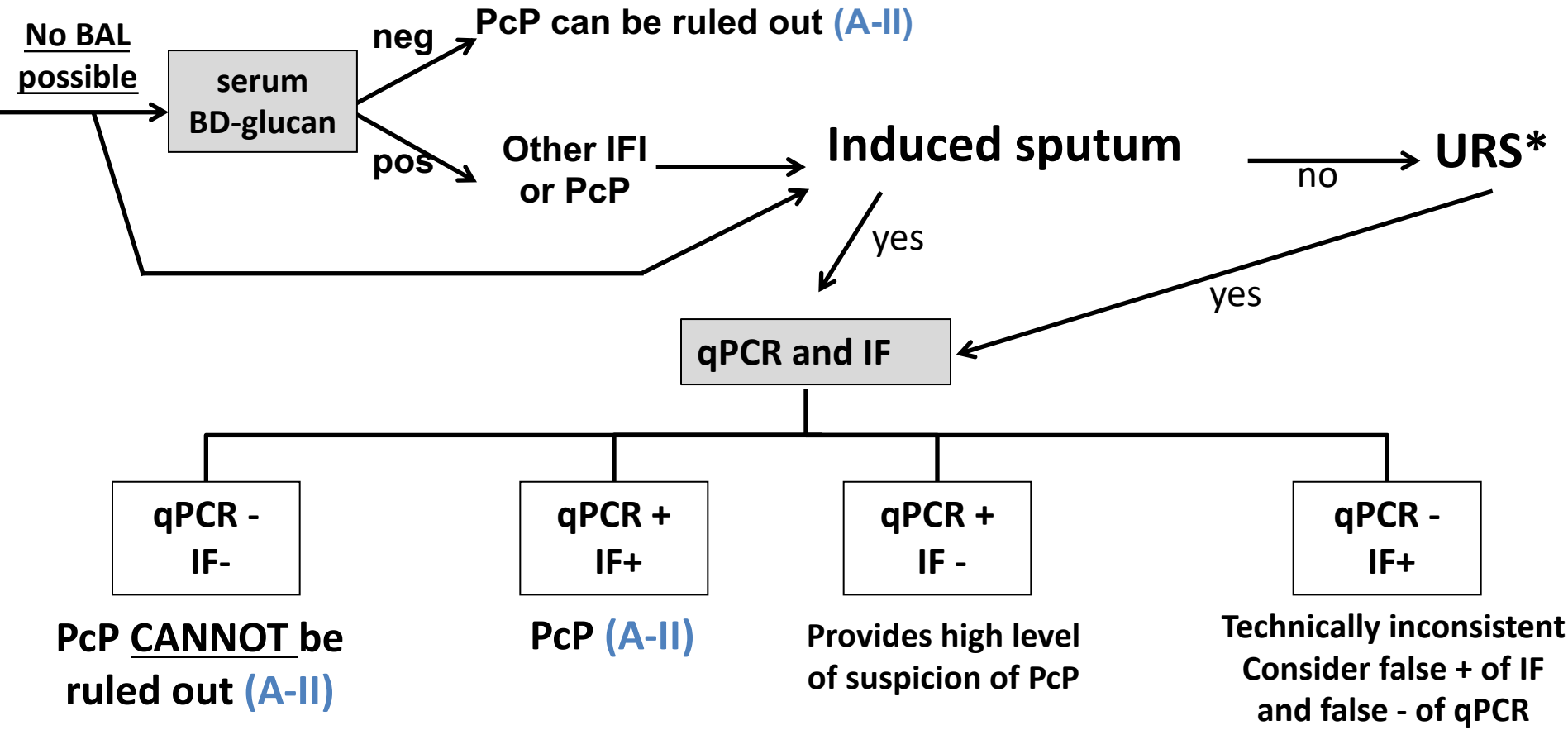
- spontaneous ***pneumothorax*** complicating cystic lesions, especially in HSCT recipients *(Kovacs et al. AIM 1984, Chow et al. AJR 1993, Torres et al. EJCMID 2006, Hardak et al. Lung 2010)*
- ***pleural effusion,*** up to 39% of HSCT recipients *(Torres)*

PcP: Diagnosis with Bronchoalveolar Lavage (BAL)



Alanio A et al (ECIL), J Antimicrob Chemother 2016;71:2386-96

PcP: What if BAL is not possible?



*URS: upper respiratory specimen

Alanio A et al (ECIL), J Antimicrob Chemother 2016;71:2386-96

Indication for Antimicrobial Treatment

As no single clinical criterion to proof PcP is available, timely diagnostic efforts and prompt antimicrobial treatment against *P.jirovecii* **should be triggered by composite criteria (A-III):**

- Patient at risk

  with
- Clinical signs and symptoms
  - Dyspnea and/or cough
  - Fever (may be absent)
  - Hypoxemia (may not yet be present)
  - Chest pain (rare; from pneumothorax)

  with
- Suggestive radiology compatible with PcP (preferably thoracic CT scan)

  with or without
- Unexplained LDH elevation

Maschmeyer G et al (ECIL), J Antimicrob Chemother 2016;71:2405-13

PcP in Non-HIV Patients:
Start of Antimicrobial Treatment

- **Appropriate systemic antimicrobial treatment should be started as early as possible (A-II*u*)**
  - Bronchoscopy and BAL may also provide reliable results several days after start of antimicrobial therapy

    Roger et al. Clin Infect Dis 1998
  - Any delay in starting the specific treatment has negative impact on prognosis

    Roux et al. Emerg Infect Dis 2014
    Li et al. J Microbiol Immunol Infect 2014
    Guo et al. PloS One 2014
    Asai et al. J Infect Chemother 2012

Maschmeyer G et al (ECIL), J Antimicrob Chemother 2016;71:2405-13

PcP – Recommendations for Front-line Treatment

Population	Intention	Intervention	SoR	QoE	*References*	Comment
HMs, SOTxP, cancer, autoimmune / inflammat diseases	**To cure**	**TMP-SMX* 15-20 mg/kg (TMP) 75-100 mg/kg (SMX) for ≥14 days**	**A**	**IIr**	*Céron 2014* *Kim 2014* *Ko 2014* *Kofteridis 2014* *Matsumura 2011* *Moon 2011* *Pagano 2002* *Roblot 2002*	**No randomized trials; high number of cases; low toxicity**
		Pentamidine iv 4 mg/kg/d	**C**	**IIt**	*Matsumura 2011*	**No randomized trials; low number of non-HIV pts**
		Primaquine + clindamycin 30 mg/d + 600 mg x 3/d**	**C**	**IIt**	*McKinnell 2012*	**Low number of non-HIV pts**
		Atovaquone 750 mg x 2(-3)/d	**C**	**IIt**	*McKinnell 2012* *Roblot 2002*	**Low number of non-HIV pts**

* Avoid MTX co-medication (toxicity)

** Check for G-6-PD deficiency prior to the use of primaquine

Maschmeyer G et al (ECIL), J Antimicrob Chemother 2016;71:2405-13

PcP – Recommendations for Second-line Treatment

Population	Intention	Intervention	SoR	QoE	*References*	Comment
HMs, SOT Cancer , autoimmune diseases	**To cure**	**Primaquine* (30 mg) + clindamycin (600 mg x 3)**	**B**	***IIt***	*Boornsarngsuk 2009* *Kim 2009* *Kim 2014*	**Few cases**
		Pentamidine IV 4 mg/kg/day	**B**	**III**	*Kim 2009* *Kim 2014* *Ko 2014* *Pagano 2002*	**Few cases**
		TMP-SMX (15-20 mg/kg) + caspofungin (70-50 mg/day)	**C**	***IIu***	*Armstrong-James 2011* *Tu 2013* *Utili 2007*	**Few cases**
		Echinocandin alone	**D**	***IIu***	*Annaloro 2007* *Hof 2008* *Kim 2013*	**Only case reports**

*Check for G-6-PD deficiency prior to the use of primaquine

N.B. In a large series of HIV+ pts, Helweg-Larsen et al *(JAC 2009)* showed that 2nd-line with prima+clinda was superior to penta with a lower mortality (non-randomized study)

Maschmeyer G et al (ECIL), J Antimicrob Chemother 2016;71:2405-13

PcP Treatment: Main Drug-Related Adverse Events

TMP-SMX	Clindamycin-primaquine	Pentamidine
• Rash and fever • Nephrotoxicity • Electrolyte disorders • Bone marrow depression • Hepatotoxicity	• Nausea and vomiting • Neutropenia • *Clostridium difficile*-associated diarrhea • Primaquine may cause hemolysis in patients with G-6PD deficiency	• Bone marrow suppression • Nephrotoxicity • Electrolyte disorders • Dysglycemia, IDDM • Pancreatitis • Q-T prolongation

PcP in non-HIV Patients: Assessment of Treatment Response

- **Efficacy has to be assessed daily, evaluation after 8 days is recommended (A-III)**
  - Early deterioration (3-5 days) is common
  - Radiological improvement (CT scan) under treatment expected in 57% of patients *(Vogel et al. EJR 2012)*
- **Clinical failure: lack of improvement or worsening of respiratory function documented by arterial blood gases after 8 days of adequate anti-PcP treatment.**
  - Failure attributed to lack of drug efficacy occurs in approximately 10% of those with mild-to-moderate disease in HIV-positive patients

Cooley et al. Intern Med J 2014
Kaplan et al. MMWR 2009
Limper et al (ATS). AJRCCM 2011
Maschmeyer et al (AGIHO). Ann Oncol 2015

Maschmeyer G et al (ECIL), J Antimicrob Chemother 2016;71:2405-13

PcP: Recommendations for Management of Clinical Failure (1)

Clinical **failure at day 8** => we recommend to do:

- **A new bronchoscopy and BAL to look for co-infections (A-III)**
  - Co-infections are common: 20% at time of ICU admission
  - ICU-acquired infections: 22%

Lemiale et al. Respir Res 2013

  - The **persistence of positive PCR is no criterion for treatment failure - should not be used for treatment assessment (D-II*t*)**

Roger et al. Clin Infect Dis 1998

- **A new thoracic CT scan to check for complications (A-III)**
  - Spontaneous pneumothorax
  - Pleural effusion

Torres et al. EJCMID 2006

Maschmeyer G et al (ECIL), J Antimicrob Chemother 2016;71:2405-13

PcP: Recommendations for Management of Clinical Failure (2)

- **Unnecessary switch to 2nd-line PcP treatment in patients receiving high-dose TMP-SMX should be avoided (A-II*t*)**
  - Efficacy of 2nd-line treatment is less well documented than that of front-line TMP-SMX => switch to 2nd-line treatment should be considered after exclusion of a co-infection or another cause of deterioration
  - DHPS mutations are not associated with failure of high-dose TMP-SMX treatment

Maschmeyer G et al (ECIL), J Antimicrob Chemother 2016;71:2405-13

PcP: Recommendations for Treatment Duration

- **Standard treatment duration: 3 weeks (B-II*t*)**
- **Mild cases: at least 2 weeks (A-II*t*)**
- **Slow clinical improvement: at least 3 weeks (A-II*u*)**

Maschmeyer G et al (ECIL), J Antimicrob Chemother 2016;71:2405-13

PcP:
Adjunctive Glucocorticosteroids in Non-HIV Patients

- **The *routine* adjunctive use of glucocorticosteroids in non-HIV patients with PcP and respiratory failure is not recommended. The decision to add glucocorticosteroids in a non-HIV patient with PcP and respiratory failure has to be made on an individual basis (B-II*h*)**
  - **Conflicting data on the benefit** from adjunctive CS in non-HIV patients with PcP in general (and specifically in hematology patients)
  - In patients treated with CS prior to PcP onset, it is unclear how to treat these patients (maintaining the dose *vs.* escalation *vs.* tapering)

Maschmeyer G et al (ECIL), J Antimicrob Chemother 2016;71:2405-13

PcP: Secondary Prophylaxis

- **Non-HIV patients who have been successfully treated for PcP should be given secondary prophylaxis (A-II*h*).**
  - Preferred and alternative regimens for secondary PcP prophylaxis should be chosen as for primary prophylaxis *(see ECIL-5 guideline by Maertens et al.).*
  - A stopping rule for secondary PcP prophylaxis in patients whose immune system is recovering has not yet been defined; therefore the decision to discontinue secondary PcP prophylaxis has to be made on an individual basis.
  - Co-medication of MTX may cause substantial toxicity.

Maschmeyer G et al (ECIL), J Antimicrob Chemother 2016;71:2405-13