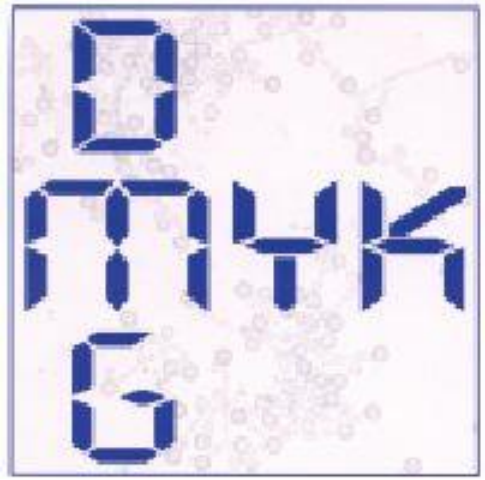

DMykG/PEG – Empfehlungen Invasive *Aspergillus* Infektionen

PEG SAC 2013 – FT

Quality of Evidence – Level Definition

Level of Evidence	Definition
Level I	Evidence from at least 1 properly designed randomized, controlled trial
Level II	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

Strength of Recommendation – Definition *

Grade of Recommendation	Definition
Grade A	DMYKG/PEG **strongly** support a recommendation for use
Grade B	DMYKG/PEG **moderately** support a recommendation for use
Grade C	DMYKG/PEG **marginally** support a recommendation for use
Grade D	DMYKG/PEG support a recommendation **against** use

* ESCMID-ECMM

Added Index – Definition *

Added Index	Source of Level II Evidence
r	Meta-analysis or systematic review of RCT
t	Transferred evidence i.e. results from different patients‘ cohorts, or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trials
a	For published abstract presented at an international symposium or meeting

* ESCMID-ECMM

For Biomarkers only:
Strength of Recommendation – Definition *

Strength of Recommendation	Definition
Highly recommended	Technique is accurate* in >70% of cases
Recommended	Technique is accurate in 50 – 70% of cases
Not recommended	Technique accurate in <50% of cases
No recommendation	No data

$$\text{Accuracy} = \frac{\text{number of true positives} + \text{number of true negatives}}{\text{numbers of true positives} + \text{false positives} + \text{false negatives} + \text{true negatives}}$$

* ESCMID-ECMM

For Biomarkers only:
Quality of Evidence – Definition *

Level of Evidence	Definition
Level I	Evidence from at least 1 properly designed prospective **multicentre** cross-sectional or cohort study
Level II	Evidence from at least 1 well-designed prospective **single-centre** cross-sectional or cohort study, or a properly designed retrospective **multicentre** cross-sectional or cohort study, or from case-control studies
Level III	Opinions of respected authorities, clinical experience, descriptive case studies, or reports of expert committees

* ESCMID-ECMM

Treatment

Treatment Situations - Definitions

- Primary prophylaxis *(not included!)*
- Empirical treatment
- Preemptive (diagnostic driven) treatment
- Treatment of proven/probable infections
  - First line
  - Salvage
  - Oral consolidation / maintenance
- Secondary Prophylaxis

Preemptive (diagnostic driven) vs. Empirical Therapy

Population / Clinical Situation	Intention	Intervention / Method	SoR	QoE	Reference	Comments
Patients with neutropenia, 5 days fever without response to broad-spectrum antbiotics	• To assess the feasibility of a combined EIA/HRCT-based preemptive strategy (while avoiding administration of empirical antifungal therapy) • Cohort study(n=88m 109 epidosdes)	Screening with GM, HR-CT, BAL / peäemptive therapy with L-AMB / cohort study if • Clinical signs + symptoms • Pulmonary infiltrate • Moulds in respiratory specimens • GM 2x positive (cut-off 0.5)	A	IIu	Maertens et al., CID 2005; 41:1242-50	First study on preemptive therapy
	• To compare the incidence of IFIs , the overall and IFI-related mortality in patients after Allo-SCT randomized to PCR based preemptive as opposedto empirical treatment with liposomal amphotericin B • Randomized study (n=409)	• Screening with panfungal PCR 2x/week • Empirical therapy with liposomal AMB • Preemptive when PCR 2x positive or 1x PCR positive plus typical sign for IAI	-	I	Hebard et al, BMT 2009; 43: 553	Mortality (day100): Emp. 16.4% preemptive 16.3%
Patients with neutropenia, 4 days fever without response to broad-spectrum antbiotics plus clinical signs and symptoms or GM	• To compare survival with empirical treatment versus preemptive antifungal treatment. 1st endpoint: Survival at 2 weeks after recovery from neutropenia • Multicenter prospective randomized trial (n=293)	• Screening with GM ELISA 2x/week • Fever ≥ day 4 either empirical therapy (n=150) or preemptive therapy (n=143) if one of the other clinical signs or GM > 1.5 was positive • Therapy: AMB	A	I	Cordonnier et al., CID 2009, 48:1042	1st endpoint: Survival 97.3% (emp. therapy) vs. 96.1 (preemptive therapy)

Preemptive (diagnostic driven) vs. Empirical Therapy

Population / Clinical Situation	Intention	Intervention / Method	SoR	QoE	Reference	Comments
Patients with episodic neutropenia and cancer treatment	• To assess the feasibility of a diagnostic-driven approach to IFDs based on the identification of the clinical settings requiring intensive diagnostic efforts and without microbiologic screening involving the entire population (n=146, neutropenic episodes n=220)	Weekly microbiological screening In case of fever and other clinical signs and symptoms despite of broad-spectrum AB intensive work up (IWDU) with further cultures, 3x GM-Test and chest-CT Empirical treatment in patients with negative IWDU Preempive treatment in patients with postive IWDU Calculated to possible empirical therapy not given	B	II	Girmenia et al., J Clin Oncology 2010; 28:667	Antifungal therapy in 48/220 episodes, reduction of antifungal therapy by 43% Mortality (3 mo) 24%
Patients with neutropenia and hematological illnesses and BMT, 4-5 days fever without response to broad-spectrum antbiotics	• To assess if serial GM monitoring on the background of effective anti-candidal prophylaxeis obviated the the need of broad-spectrum antifungal treatment • 47 patients representing 52 episodes • GM > 0.5, repetition when positive • Itraconazole sirup 3 x 200 mg, neutro > 0.5 capsules 2 x 200 mg	Block randomization • Group 1: GM twice weekly (27 episodes) 2 cases of IPA • Group 2: antifungal therapy according to established guidelines (25 episodes) – empiric AF therapy started in 10 cases ITT-analysis: 11% patients were saved from empirical treatment Evaluable epidsodes: 14% patients were saved from empirical treatment 12-weeks-survival: 85.2% in group 1, 84% in group 2	B	I	Tan B.H. et al., Int J Infectious Diseases 2011; e350	47 patients randomized, 52 episodes; No difference in survival

PEG Empfehlung

- In einer kürzlich erschienenen Publikation von Maertens heißt es über die präemptive Therapie: "Obwohl es nun mehrere Studien über die präemptive antimykotische Therapie bei Patienten mit neutropenischen Fieber gibt, konnte sich die Expertengruppe nicht auf eine Empfehlung einigen, da es in der einzigen randomisierten Studie eine deutliche wenn auch nicht signifikante Anzahl von invasiven Mykosen bei der Patientengruppe mit präventiver Therapie im Vergleich zur Patientengruppe mit empirischer Therapie gab ...“ (11).
- Basierend auf neuen Daten kann präemptive Therapie kann aber als eine sichere und effektive Vorgangsweise bei Patienten mit Neutropenie und hohem Risiko für invasive Mykosen empfohlen werden. Allerdings sollte bei schwer kranken und klinisch instabilen Patienten die empirische Therapie die Behandlung der Wahl bleiben. (PEG Empfehlungsgrad A).

Special Sites /
Special Isolates /
Special populations

Chronic (necrotizing) pulmonary aspergillosis

Population / Clinical Situation	Intention	Intervention / Method	SoR	QoE	Reference	Comments
Non neutropenic pts. With COPD, corticosteroid treatment, bronchiectasis, after radiotherapy, prior TB, lung cancer	Chronic aspergillosis – persistently invasive aspergillosis beginning with pyogranulomatous disease and progressing to necrosis and cavitation – no angioinvasion like in neutropenic hosts; - Describe the use of posaconazole in the management of CPA	Retrospective study including patients treatmed with posaconazole 2 x 400 mg po - Primary therapy group: 21 patients - Salvage therapy group: 58 patients (after other antifungal therapy either stopped due to intolerance or because of progression of CPA) Therapy duration 6 months	B	III	Felton T. et al., CID 2010; 51: 1383	Response to posaconazole: 63 % at 6 months, 41% at 12 months
Non neutropenic pts. With GVHD, COPD, AIDS, SOT, CGD, ITP, bronchiectasis, after radiotherapy, prior TB, alcoholism, diabetes mellitus, post-traumatic Etc.	Non-comparative study multicenter-study of the efficacy and safety of voriconazole in chronic IA	Voriconazole 2 x 200 mg po Duration: 4 – 24 weeks Overall 39 patients	B	III	Sambatakou H. et al., American J Med 2006; 119: 527	Response: 3/21 (14%) complete 6/21 (29%) partial 7/21 (33%) stable - 21 patients had subacute non-pulmonary invasive aspergillosis

Chronic (necrotizing) pulmonary aspergillosis/Aspergilloma

Population / Clinical Situation	Intention	Intervention / Method	SoR	QoE	Reference	Comments
Non neutropenic pts. With COPD, bronchiectasis, prior TB, diabetes mellitus, plus complex aspergilloma	- Describe the use of posaconazole in the management of CPA	Prospective trial comparing - micafungin (150- 300 mg/day) versus - intravenous voriconazole (day 2 x 6mg/kg, day2 and following 4 mg/kg every 12h) in 54 patients Duration of therapy: Micafungin 23.6 days Voriconazole 20.6 days	B	I	Kohno S. et al., J Infection 2010; 61:410	ITT- Response to micafungin: 30/53 (56.6%) patients Voriconazole 25/54 (46.3%) patients ,n.s.
Non neutropenic pts. With COPD, bronchiectasis, prior TB, diabetes mellitus, plus complex aspergilloma	To investigate the efficacy and safety of short- and long-term ITCZ therapy in patients with CNPA	Prospective trial Intravenous ITCZ (200 mg) was administrated by injection twice a day for 2 days (400 mg/day) and, subsequently, once a day(200 mg/day) for 3 days or more (2 weeks), then ITCZ capsules 200 mg twice a day for up to 12 weeks	B	IIu	Yoshida K. et al., J Infect Chemother 2012; 18: 378	29 patients enrolled- Overall response 10/23 (43.5 %) – determination of ITCZ blood concentration
Non neutropenic pts. With CPA, with COPD, prior TB,, plus aspergilloma	To complete data on the usefulness of voriconazole for the treatment of CPA and CCPA	Retrospective multi-center study 24 patients included - 13 patients VCZ as first-line therapy - 11 patients : VCZ as salvage therapy Median duration 6.5 months	B	III	Camuset J et al., Chest 2007; 131:1435	Radioclinical improvement 14/24 Mycological eradication 18/19

Chronic (necrotizing) pulmonary aspergillosis

Population / Clinical Situation	Intention	Intervention / Method	SoR	QoE	Reference	Comments
Non neutropenic pts. With COPD, bronchiectasis, prior TB, diabetes mellitus, plus complex aspergilloma	- Describe the use of posaconazole in the management of CPA	Prospective trial comparing - micafungin (150- 300 mg/day) (53 pts.) versus - intravenous voriconazole (day 2 x 6mg/kg, day2 and following 4 mg/kg every 12h) in 54 patients Duration of therapy: Micafungin 23.6 days Voriconazole 20.6 days	B	I	Kohno S. et al., J Infection 2010; 61:410	ITT- Response to micafungin: 30/53 (56.6%) patients Voriconazole 25/54 (46.3%) patients ,n.s.
Non neutropenic pts. With COPD, bronchiectasis, prior TB, diabetes mellitus, plus complex aspergilloma	To investigate the efficacy and safety of short- and long-term ITCZ therapy in patients with CNPA	Prospective trial Intravenous ITCZ (200 mg) was administrated by injection twice a day for 2 days (400 mg/day) and, subsequently, once a day(200 mg/day) for 3 days or more (2 weeks), then ITCZ capsules 200 mg twice a day for up to 12 weeks	B	IIu	Yoshida K. et al., J Infect Chemother 2012; 18: 378	29 patients enrolled- Overall response 10/23 (43.5 %) – determination of ITCZ blood concentration
Non neutropenic pts. With CPA, with COPD, prior TB, plus complex aspergilloma	To complete data on the usefulness of voriconazole for the treatment of CPA and CCPA	Retrospective multi-center study 24 patients included - 13 patients VCZ as first-line therapy - 11 patients : VCZ as salvage therapy Median duration 6.5 months	B	III	Camuset J et al., Chest 2007; 131:1435	Radioclinical improvement 14/24 Mycological eradication 18/19

Chronic (necrotizing) pulmonary aspergillosis/ Allergic bronchopulmonary aspergillosis

Population / Clinical Situation	Intention	Intervention / Method	SoR	QoE	Reference	Comments
Non neutropenic pts., chronic granulomatous disease, hematological disease including BMT and AIDS	To determine the efficacy and safety of this iv/oral itraconazole dosing regimen in the treatment of pulmonary aspergillosis in immunocompromised patients and to evaluate plasma concentrations of itraconazole	Prospective open international multicenter trial 31 patients received 2 days of iv itraconazole 400 mg/day, 12 days of iv itraconazole 200 mg/day, and then 12 weeks of oral itraconazole capsules, 400 mg/day.	A-B	IIu	Caillot et al., CID 2001; 33:83	EOT: 15/31 (48%) had complete (n=8) or partial (n=7) response
Allergic bronchopulmonary aspergillosis	To confirm the results of non-randomized trials that reported that treatment led to a lowering of the corticosteroid dose; improved pulmonary function, exercise tolerance, symptoms, and radiographic features; and reduced IgE concentrations.	randomized, double-blind, placebo-controlled clinical trial - 28 patients received itraconazole (2 x 200 mg po for 16 weeks) - 27 patients received placebo	B	I	Stevens et al., NEJM 2000; 342:756	Overall response: ITCZ 13/28 Placebo 5/27; p 0.04
Allergic bronchopulmonary aspergillosis	To complete data on the usefulness of voriconazole for the treatment of CPA and CCPA	- See above study of Camuset, also included patients with ABPA	B	III	Camuset J et al., Chest 2007; 131:1435	

Invasive bronchial aspergillosis – Aspergillus tracheobronchitis

Population / Clinical Situation	Intention	Intervention / Method	SoR	QoE	Reference	Comments
Aspergillus tracheobronchits SOT	Use of systemic antifungal agents or nebulized AMB	- No randomized trials - Patients included in invasive aspergillosis studies of non-neutropenic patients	B	III		Expert statement
Non neutropenic pts., SOT recipients	To assess feasibility, tolerability, and outcomes of nebulized liposomal amphotericin B as prophylaxis for Aspergillus infection in lung transplant recipients	Prospective observational study - 104 consecutive patients received 25 mg (6 ml) of n-LAB 3 times per week for the first 60 days after transplantation, 25 mg 1 time per week between 60 and 180 days, and 25 mg once every 2 weeks thereafter - Historical control group of 49 patients without nebulization	C	III	Monforte V. et al., J Heart Lung Transplant 2010;	Aspergillosis developed in 8/104 (7.7%) patient with n-lAMB and in 5/49 control (10.2%), not significant

Invasive bronchial aspergillosis – Aspergillus tracheobronchitis

Population / Clinical Situation	Intention	Intervention / Method	SoR	QoE	Reference	Comments
Non neutropenic pts., SOT recipients	Conventional AMB inhalation plus IV AMB	Inhalataion, IV plus topical	D	III	Boettcher et al., Heart Lung Transplant. 2000;19(12):1224-7	3 patients
Non neutropenic pts., SOT recipients	Amphotericin Lipid complex inhalation	Aerosol deposition testing: 6 single and 6 double lung recipients 1 x 7 mL (35 mg) nebulized dose of Technetium-labeled ABLC . In single lung recipients, the average deposited doses were 3.9 +/- 1.6 mg (mean +/- S.D.) in the allograft versus 2.1 +/- 1.1 mg in the native lung. Double lung recipients deposited on average 2.8 +/- 0.8 mg (left lung) and 4.0 +/- 1.3 mg (right lung).	D	III	Corcoran et al., Am J Transplant. 2006;6(11):2765-73	No reference to efficacy.

Vielen Dank für die Aufmerksamkeit