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Infektionsmanagement bei Leukämiepatienten

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AGIHO INFEKTIONEN IN DER HÄMATOLOGIE UND ONKOLOGIE
FACHGRUPPE DER DGHO

Disclosures (5 Years)

- Consultant:
  - Gilead; F2G
- Honoraria for lectures:
  - Gilead; Pfizer; Merck-Serono; Celgene; BMS; Basilea; Janssen-Cilag; Astellas; AstraZeneca; Boehringer Ingelheim; AMGEN

How it all started: Tetracyclin *vs* Placebo

FEVER IN MALIGNANT NEOPLASTIC DISEASE: A CONTROLLED STUDY OF TETRACYCLINE THERAPY *

By Dane R. Boggs, M.D.,† Emil Frei, III, M.D., and Charles H. Zierdt, M.S., *Bethesda, Maryland*

We have compared tetracycline and placebo therapy in episodes of fever of undetermined etiology in a heterogeneous group of patients with malignant neoplastic disease: (1) to test the hypothesis that such fever is due to occult bacterial infection; and (2) to investigate the potential benefits or hazards of short-term tetracycline therapy in patients with decreased host resistance.

=> „A trial of antibiotic therapy is not warranted for fever in cancer patients.“

Ann Intern Med 1960;53:754-64

Guidelines of the AGIHO

Ann Hematol (2013) 92:433–442
DOI 10.1007/s00277-013-1698-0

REVIEW ARTICLE

Primary prophylaxis of bacterial infections and *Pneumocystis jirovecii* pneumonia in patients with hematological malignancies and solid tumors

Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO)

S. Neumann · S. W. Krause · G. Maschmeyer · X. Schiel · M. von Lilienfeld-Toal

Ann Hematol
DOI 10.1007/s00277-014-2108-y

REVIEW ARTICLE

Primary prophylaxis of invasive fungal infections in patients with haematologic malignancies. 2014 update of the recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology

Daniela Tacke · Dieter Buchheidt · Meinolf Karthaus · Stefan W. Krause · Georg Maschmeyer · Silke Neumann · Helmut Ostermann · Olaf Penack · Christina Rieger · Markus Ruhnke · Michael Sandherr · Katharina E. Schweer · Andrew J. Ullmann · Oliver A. Cornely

Ann Hematol (2012) 91:1161–1174
DOI 10.1007/s00277-012-1456-8

REVIEW ARTICLE

Antimicrobial therapy of febrile complications after high-dose chemotherapy and autologous hematopoietic stem cell transplantation—guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO)

Florian Weissinger · Holger W. Auner · Hartmut Bertz · Dieter Buchheidt · Oliver A. Cornely · Gerlinde Egerer · Werner Heinz · Meinolf Karthaus · Michael Kiehl · William Krüger · Olaf Penack · Stefan Reuter · Markus Ruhnke · Michael Sandherr · Hans-Jürgen Salwender · Andrew J. Ullmann · Dirk T. Waldschmidt · Hans H. Wolf

n > 45 in PubMed

Annals of Oncology 24: 1189–1202, 2013
doi:10.1093/annonc/mds601
Published online 10 February 2013

Diagnosis and management of gastrointestinal complications in adult cancer patients: evidence-based guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO)

M. J. G. T. Vehreschild[1*], J. J. Vehreschild[1], K. Hübel[1], M. Hentrich[2], M. Schmidt-Hieber[3], M. Christopeit[4], G. Maschmeyer[5], E. Schalk[6], O.A. Cornely[1,7] & S. Neumann[8]

Ann Hematol (2015) 94:1441–1450
DOI 10.1007/s00277-015-2447-3

ORIGINAL ARTICLE

Antiviral prophylaxis in patients with solid tumours and haematological malignancies—update of the Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO)

Michael Sandherr[1] · Marcus Hentrich[2] · Marie von Lilienfeld-Toal[3] · Gero Massenkeil[4] · Silke Neumann[5] · Olaf Penack[6] · Lena Biehl[7,8] · Oliver A. Cornely[7,9]

Annals of Oncology 26: 21–33, 2015
doi:10.1093/annonc/mdu192
Published online 15 May 2014

Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients (allogeneic SCT excluded): updated guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO)†

G. Maschmeyer[1*], J. Carratalà[2], D. Buchheidt[3], A. Hamprecht[4], C. P. Heussel[5], C. Kahl[6], J. Lorenz[7], S. Neumann[8], C. Rieger[9], M. Ruhnke[10], H. Salwender[11], M. Schmidt-Hieber[12] & E. Azoulay[13]

reviews

Annals of Oncology

Annals of Oncology 25: 936–947, 2014
doi:10.1093/annonc/mdt545
Published online 7 January 2014

Central venous catheter-related infections in hematology and oncology: 2012 updated guidelines on diagnosis, management and prevention by the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology

M. Hentrich[1], E. Schalk[2], M. Schmidt-Hieber[3], I. Chaberny[4], S. Mousset[5], D. Buchheidt[6], M. Ruhnke[7], O. Penack[8], H. Salwender[9], H.-H. Wolf[10], M. Christopeit[10], S. Neumann[11], G. Maschmeyer[12] & M. Karthaus[1]

Ann Hematol
DOI 10.1007/s00277-016-2711-1

ORIGINAL ARTICLE

Infectious diseases in allogeneic haematopoietic stem cell transplantation: prevention and prophylaxis strategy guidelines 2016

Andrew J. Ullmann[1] · Martin Schmidt-Hieber[2] · Hartmut Bertz[3] · Werner J. Heinz[1] · Michael Kiehl[4] · William Krüger[5] · Sabine Mousset[6] · Stefan Neuburger[7] · Silke Neumann[8] · Olaf Penack[9] · Gerda Silling[10] · Jörg Janne Vehreschild[11] · Hermann Einsele[1] · Georg Maschmeyer[12] · on behalf of the Infectious Diseases Working Party of the German Society for Hematology and Medical Oncology (AGIHO/DGHO) and the DAG-KBT (German Working Group for Blood and Marrow Transplantation)

Annals of Oncology 25: 1709–17 18, 2014
doi:10.1093/annonc/mdu035
Published online 14 March 2014

Prophylaxis of infectious complications with colony-stimulating factors in adult cancer patients undergoing chemotherapy—evidence-based guidelines from the Infectious Diseases Working Party AGIHO of the German Society for Haematology and Medical Oncology (DGHO)

J. J. Vehreschild[1], A. Böhme[2], O. A. Cornely[1,3,4*], C. Kahl[5], M. Karthaus[6], K.-A. Kreuzer[1], G. Maschmeyer[7], S. Mousset[8], V. Ossendorf[9], O. Penack[9], M. J. G. T. Vehreschild[1] & J. Bohlius[10]

Annals of Oncology 23: 823–833, 2012
doi:10.1093/annonc/mdr407
Published online 23 September 2011

Diagnosis of invasive fungal infections in hematology and oncology—guidelines from the Infectious Diseases Working Party in Haematology and Oncology of the German Society for Haematology and Oncology (AGIHO)

M. Ruhnke[1*], A. Böhme[2], D. Buchheidt[3], O. Cornely[4], K. Donhuijsen[5], H. Einsele[6], R. Enzensberger[7], H. Hebart[8], C. P. Heussel[9], M. Horger[10], H. Hof[11], M. Karthaus[12], W. Krüger[13], G. Maschmeyer[14], O. Penack[15], J. Ritter[16] & S. Schwartz[15]

Annals of Oncology 27: 1207–1225, 2016
doi:10.1093/annonc/mdw105
Published online 6 April 2016

CNS infections in patients with hematological disorders (including allogeneic stem-cell transplantation)—Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO)

M. Schmidt-Hieber[1*], G. Silling[2], E. Schalk[3], W. Heinz[4], J. Panse[2], O. Penack[5], M. Christopeit[6], D. Buchheidt[7], U. Meyding-Lamadé[8,9,10], S. Hähnel[11], H. H. Wolf[12], M. Ruhnke[13], S. Schwartz[14] & G. Maschmeyer[15]

Ann Hematol (2014) 93:13–32
DOI 10.1007/s00277-013-1867-1

ORIGINAL ARTICLE

Treatment of invasive fungal infections in cancer patients—updated recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO)

Sabine Mousset · Dieter Buchheidt · Werner Heinz · Markus Ruhnke · Oliver A. Cornely · Gerlinde Egerer · William Krüger · Hartmut Link · Silke Neumann · Helmut Ostermann · Jens Panse · Olaf Penack · Christina Rieger · Martin Schmidt-Hieber · Gerda Silling · Thomas Südhoff · Andrew J. Ullmann · Hans-Heinrich Wolf · Georg Maschmeyer · Angelika Böhme

Ann Hematol
DOI 10.1007/s00277-014-2086-0

REVIEW ARTICLE

Management of sepsis in neutropenic patients: 2014 updated guidelines from the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO)

Olaf Penack · Carolin Becker · Dieter Buchheidt · Maximilian Christopeit · Michael Kiehl · Marie von Lilienfeld-Toal · Marcus Hentrich · Marc Reinwald · Hans Salwender · Enrico Schalk · Martin Schmidt-Hieber · Thomas Weber · Helmut Ostermann

European Journal of Cancer 67 (2016) 200–212

Community acquired respiratory virus infections in cancer patients—Guideline on diagnosis and management by the Infectious Diseases Working Party of the German Society for haematology and Medical Oncology

Marie von Lilienfeld-Toal [a,b,c,*], Annemarie Berger [d], Maximilian Christopeit [e], Marcus Hentrich [f], Claus Peter Heussel [g,h,i], Jana Kalkreuth [a], Michael Klein [j], Matthias Kochanek [k], Olaf Penack [l], Elke Hauf [m], Christina Rieger [n], Gerda Silling [o], Maria Vehreschild [k,p], Thomas Weber [q], Hans-Heinrich Wolf [q], Nicola Lehners [r,t], Enrico Schalk [s,t], Karin Mayer [t,t]

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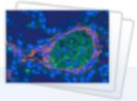
Solide Tumore



Allogene Stammzelltransplantation

Supportive Therapie

Antiemese bei medikamentöser Tumortherapie
Antimikrobielle Therapie infektiöser Komplikationen nach Hochdosistherapie und autologer Stammzelltransplantation
Antimykotische Prophylaxe bei Patienten mit hämatologischen Neoplasien oder nach allogener Stammzelltransplantation
Antivirale Prophylaxe
Bakterielle Infektionen und Pneumocystis jirovecii Pneumonie - Prophylaxe
Diarrhoe und andere gastrointestinale Komplikationen bei Patienten mit hämatologischen und onkologischen Erkrankungen
Febrile Neutropenie mit Lungeninfiltraten nach intensiver Chemotherapie (Fieber in Neutropenie)
Infektionen bei hämatologischen und onkologischen Patienten - Übersicht -
Invasive Pilzinfektionen - Therapie
Invasive Pilzinfektionen – Diagnostik
Pneumokokkenimpfung bei hämatologischen und onkologischen Patienten im Erwachsenenalter
Prävention von Infektionen und Thrombosen nach Splenektomie oder funktioneller Asplenie
Prophylaxe infektiöser Komplikationen durch Granulozyten-Kolonie-stimulierende Faktoren (G-CSF, Pegfilgrastim, Biosimilars)
Respiratory Syncytial Virus (RSV) – Infektionen bei Patienten nach hämatopoetischer Stammzelltransplantation
Sepsis bei neutropenischen Patienten
Thrombozytentransfusion
ZNS-Infektionen bei hämatologischen und onkologischen Erkrankungen, einschl. allogener Stammzelltransplantation
ZVK Infektionen

US American Guidelines

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Prevention and Treatment of Cancer-Related Infections

Version 2.2016

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JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Antimicrobial Prophylaxis and Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology Clinical Practice Guideline

Christopher R. Flowers, Jerome Seidenfeld, Eric J. Bow, Clare Karten, Charise Gleason, Douglas K. Hawley, Nicole M. Kuderer, Amelia A. Langston, Kieren A. Marr, Kenneth V.I. Rolston, and Scott D. Ramsey

J Clin Oncol 2013;31:794-810

Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Alison G. Freifeld,[1] Eric J. Bow,[9] Kent A. Sepkowitz,[2] Michael J. Boeckh,[4] James I. Ito,[5] Craig A. Mullen,[3] Issam I. Raad,[6] Kenneth V. Rolston,[6] Jo-Anne H. Young,[7] and John R. Wingard[8]

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This document updates and expands the initial Infectious Diseases Society of America (IDSA) Fever and Neutropenia Guideline that was published in 1997 and first updated in 2002. It is intended as a guide for the use of antimicrobial agents in managing patients with cancer who experience chemotherapy-induced fever and neutropenia.

Recent advances in antimicrobial drug development and technology, clinical trial results, and extensive clinical experience have informed the approaches and recommendations herein. Because the previous iteration of this guideline in 2002, we have a developed a clearer definition of which populations of patients with cancer may benefit most from antibiotic, antifungal, and antiviral prophylaxis. Furthermore, categorizing neutropenic patients as being at high risk or low risk for infection according to presenting signs and symptoms, underlying cancer, type of therapy, and medical comorbidities has become essential to the treatment algorithm. Risk stratification is a recommended starting point for managing patients with fever and neutropenia. In addition, earlier detection of invasive fungal infections has led to debate regarding optimal use of empirical or preemptive antifungal therapy, although algorithms are still evolving.

What has not changed is the indication for immediate empirical antibiotic therapy. It remains true that all patients who present with fever and neutropenia should be treated swiftly and broadly with antibiotics to treat both gram-positive and gram-negative pathogens.

Finally, we note that all Panel members are from institutions in the United States or Canada; thus, these guidelines were developed in the context of North American practices. Some recommendations may not be as applicable outside of North America, in areas where differences in available antibiotics, in the predominant pathogens, and/or in health care–associated economic conditions exist. Regardless of venue, clinical vigilance and immediate treatment are the universal keys to managing neutropenic patients with fever and/or infection.

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Clinical Infectious Diseases 2011;52(4):e56–e93

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1058-4838/2011/524-0001$37.00
DOI: 10.1093/cid/cir073

EXECUTIVE SUMMARY

Fever during chemotherapy-induced neutropenia may be the only indication of a severe underlying infection, because signs and symptoms of inflammation typically are attenuated. Physicians must be keenly aware of the infection risks, diagnostic methods, and antimicrobial therapies required for management of febrile patients through the neutropenic period. Accordingly, algorithmic approaches to fever and neutropenia, infection prophylaxis, diagnosis, and treatment have been

www.idsociety.org

ESMO Guidelines 2016

clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v111–v118, 2016
doi:10.1093/annonc/mdw325

Management of febrile neutropaenia: ESMO Clinical Practice Guidelines†

J. Klastersky[1], J. de Naurois[2], K. Rolston[3], B. Rapoport[4], G. Maschmeyer[5], M. Aapro[6] & J. Herrstedt[7] on behalf of the ESMO Guidelines Committee*

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Predominant Pathogens

Neutropenia:	ESBL	Gram-negative aerobes
	MRSA	*S.aureus,* streptococci, enterococci, anaerobes
		Coagulase-neg. staphylococci (CVC)
		Fungi, primarily *Aspergillus*, *Candida,* zygomycetes
T cell suppression:		Viruses (CMV, Herpes, VZV)
		Pneumocystis jirovecii
		Fungi (as above, plus cryptococci)
		Mycobacteria
		Parasites (e.g. *Toxoplasma gondii*)
		Bacteria (a.a.), plus *Listeria*
Humoral immunodeficiency:		Bacteria (a.a.), plus pneumococci
		Viruses (a.a.)
		(rarely:) Fungi

VRE

When to Start Empirical Antimicrobial Therapy in Cancer Patients

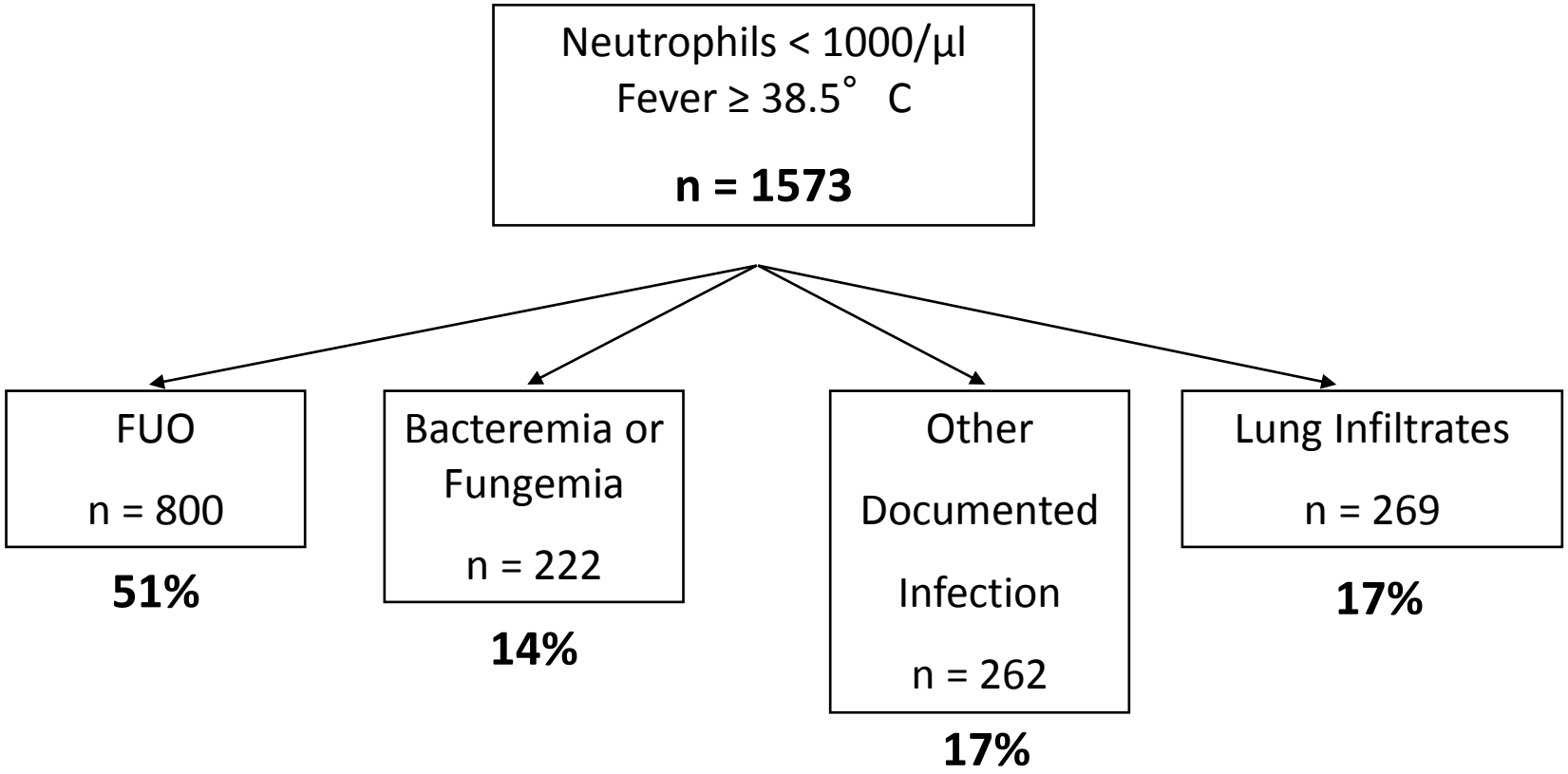
- Granulocyte count < 500/µl or < 1000/µl with predicted decline to ≤ 500/µl
- Single oral temperature of > 38.3° C
  - or ≥ 38.0° C x 2 within 12 h
  - or ≥ 38.0° C over ≥ 1 h
- No obvious non-infectious origin
  - Adverse reaction to blood products, cytokines, other drugs

Pathogens Associated With Characteristic Clinical Symptoms in Febrile Neutropenic Pts

Clinical Symptoms	***Typical Pathogens***
Erythema/pain at venous access	Coagulase-negative staphylococci
Mucosal ulcers	Alpha-hemolytic streptococci, *Candida* spp.
Single point-like erythemas	Gram-positive cocci, *Candida* spp.
Necrotizing skin lesions	*Pseudomonas aeruginosa*, *Aspergillus* spp.
Retinal infiltrates	*Candida* spp.
Diarrhea, meteorism	*Clostridium difficile*
Enterocolitis, perianal lesion	Polymicrobial incl. anaerobes
Lung infiltrates ± sinusitis	*Aspergillus* spp., mucorales, *P.jirovecii*

=> A thorough clinical examination is mandatory!

Infections in Febrile Neutropenic Patients



Link H et al (Paul Ehrlich Society Study), Ann Hematol 1994;69:231-43

β lactam monotherapy versus β lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis

Mical Paul, Karla Soares-Weiser, Leonard Leibovici **BMJ** VOLUME 326 24 MAY 2003

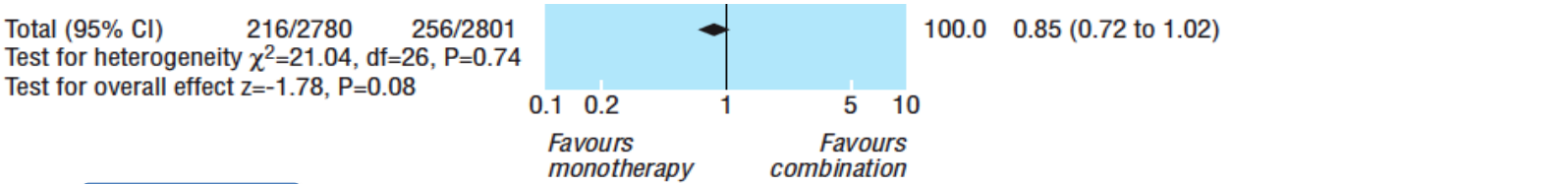


Fig 2 All cause fatality

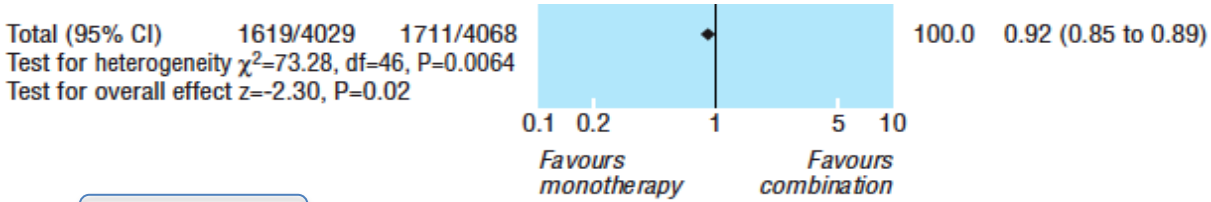


Fig 3 Treatment failure

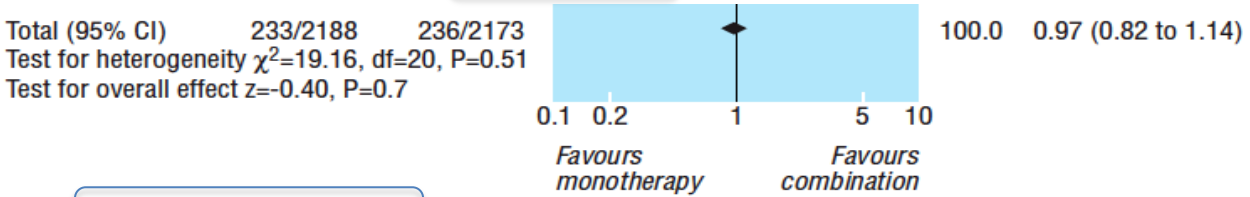


Fig 4 Bacterial superinfections

Ceftazidime/Amikacin ± Vancomycin Upfront in Febrile Neutropenic Patients

- n = 747; initial empirical therapy for fever

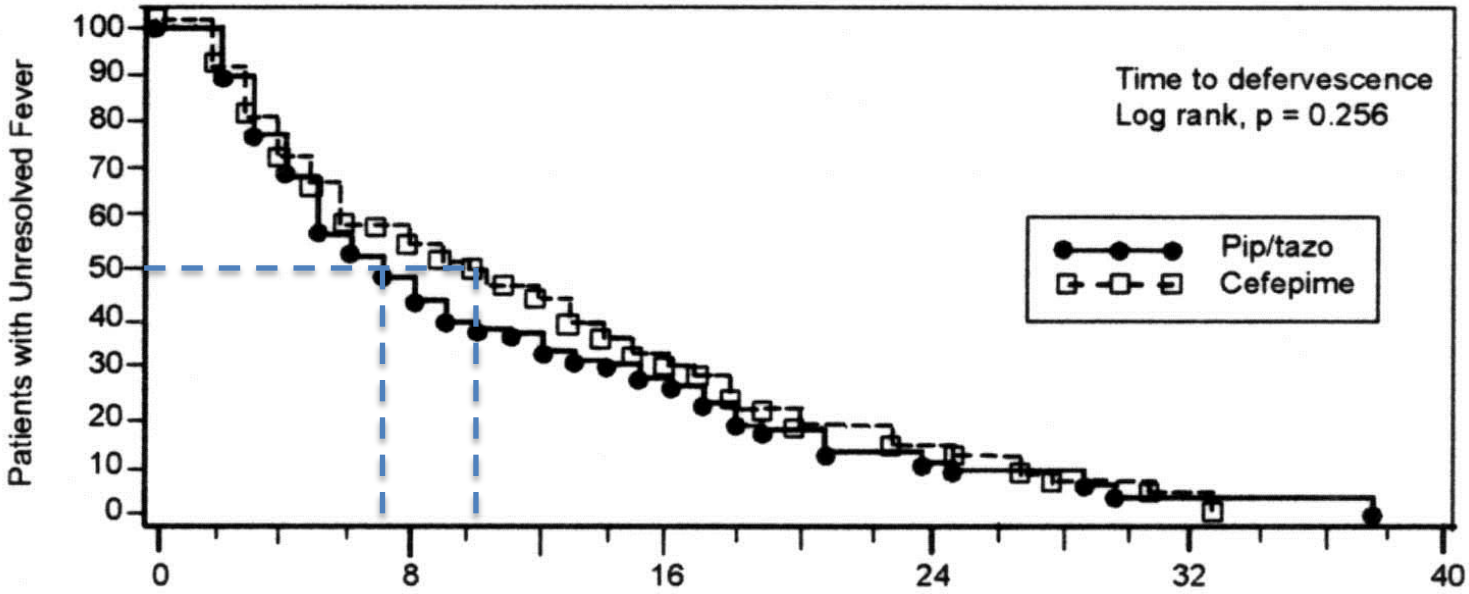
- **No difference in duration of fever**
- **No patient with gram-positive bacteremia died during the first 3 days of study**
- Drug-related nephrotoxicity: 2 *vs* 6% (p = 0.02)

- „These results do not support the empirical addition of vancomycin.“

EORTC-IATG + NCI-Canada, J Infect Dis 1991;163:951-8

Piperacillin/Tazobactam *vs* Cefepime for Initial Empirical Therapy for Febrile Neutropenia

- Time to defervescence:



Bow EJ et al (multicenter), Clin Infect Dis 2006;43:447-59

Empirical Vancomycin *vs* Placebo 2nd-Line for Fever Persisting after 48-60 Hours of Pip-Tazo

- Double-blind, placebo-controlled: P/T + vanco (n = 86) *vs* P/T + placebo (n = 79)
- Median duration of neutropenia < 500/µl: 14 days

	P/T + V	**P/T + Plc**
Defervescence under treatment	45%	44%
Days to defervescence (median)	3.5 ± 0.8	4.3 ± 0.8
Infection-related death (day)	1 (14)	1 (35)

Cometta A et al (EORTC), Clin Infect Dis 2003;37:382-9

Linezolid *vs* Vancomycin in Neutropenic Patients with Refractory Fever (n = 605)

No significant difference with respect to:

- Time to defervescence
- Mortality rate day 16 post treatment
- Overall success
  - **No benefit** in subgroups: leukemia, lymphoma, myeloma or other malignancy
- Microbiological outcome: no significant difference

Jaksic B et al, Clin Infect Dis 2006;42:597-607

Empiric Antifungals in Neutropenic Patients with Refractory FUO (Day 4-6):

Prospective Randomized Study

Response to first-line and to second-line therapy (assessable febrile episodes).

Treatment	n	Responder			Non- responder	Death
First-line (n = 717)						
A: Pip/AMG	373	192 (51.5%)	p = 0.94		173 (46.4%)	8 (2.0%)
B: Ceph/AMG	344	176 (51.2%)			160 (46.5%)	8 (2.1%)
Second-line (n = 155)						
C: Imi/GLP	54	30 (55.6%)	p = 0.03*	p = 0.56	24 (44.4%)	0
D: Imi/GLP + AmB/5-FC	45	35 (77.8%)			9 (20.0%)	1 (2.2%)
E: Imi/GLP + Fluco	56	35 (62.5%)			20 (35.7%)	1 (1.8%)

- Fluconazole not significantly superior to no antifungal

Schiel X et al (PEG-Studie II), Infection 2006;34:118-26

Infections Post High-Dose Chemotherapy and Autologous Stem-Cell Transplantation

	n	*% of 178 cycles of high-dose chemotherapy*	*% of 112 febrile episodes*
Fever	112	63	100
Fever of unknown origin (FUO)	63	35.4	56.3
Pneumonia	6	3.4	5.4
Bacteremia	38	21.3	33.9
Coagulase negative staphylococci	15	15	13.4
Streptococci	14	14	12.5
Staphylococcus aureus	2	2	1.8
Gram-negative bacilli	7	7	6.3
Skin infection	2	1.1	1.8
Invasive fungal infection	3	1.7	2.7
Severe enterocolitis	1	0.6	0.9

G-pos cocci by far predominant!

Reich G et al, Bone Marrow Transplant 2001;27:525-9

Clinically Documented Infections: When Primary „Pre-Emptive“ Therapy is Indicated

- Lung Infiltrates
  - CT typical for *Pneumocystis* pneumonia
  - CT typical for / consistent with aspergillosis
- Sinus or cerebral scan compatible with aspergillosis or mucormycosis
- Abdominal or perianal infection
- CVC-related infection

Patients with Fever and Lung Infiltrates Benefit from First-Line Amphotericin B

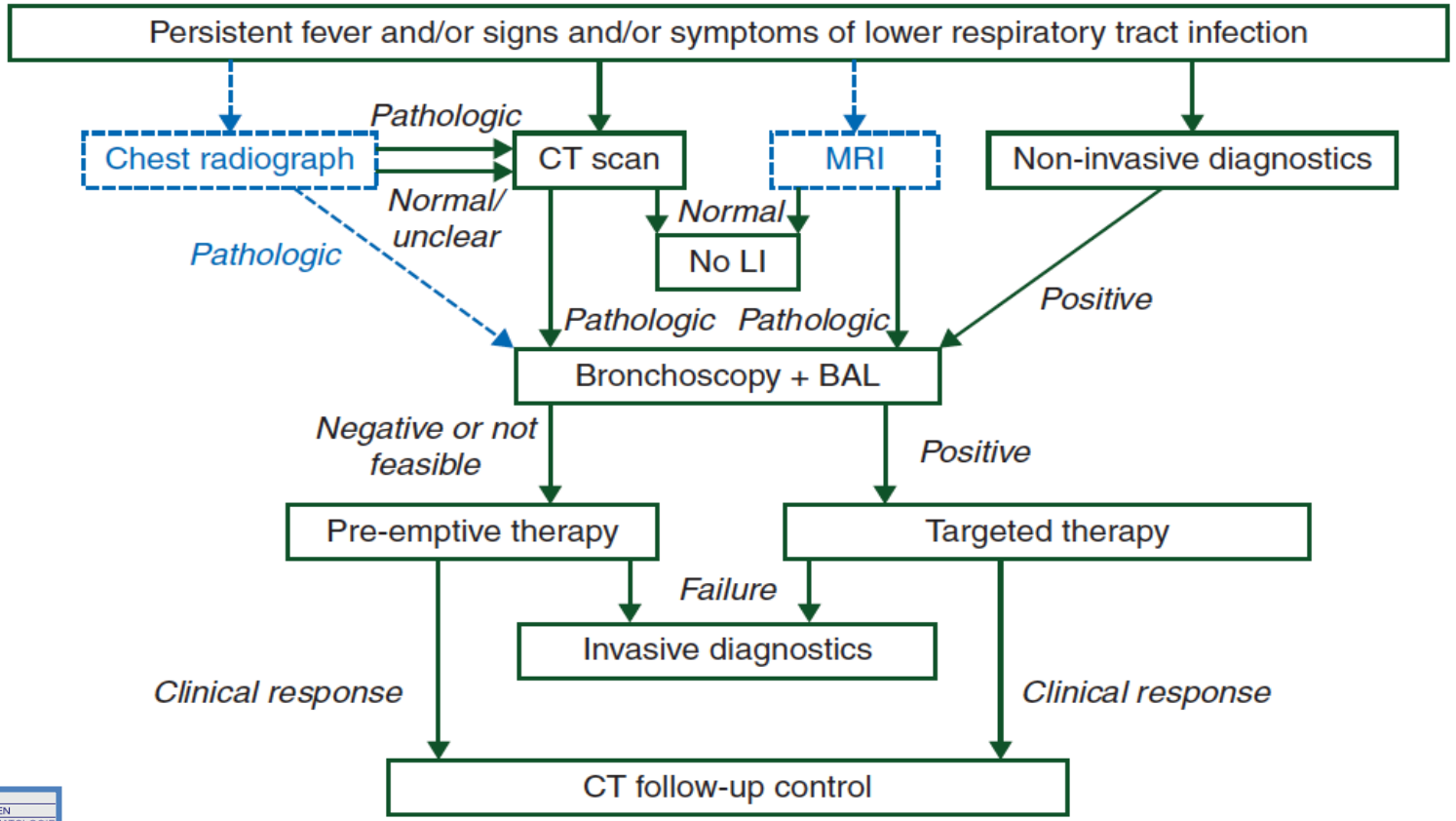
	n	*CR (%)*	*NR (%)*	*ED (%)*
• Supplementation of AmB only in non-responders	269	61.3*	17.1	21.6
• Antibacterials plus AmB from the start	157	78.2*	4.2	17.6

*) $p < 0.01$ (Fisher's exact test, two-tailed)

Link H et al (PEG-Studie I), Ann Hematol 1994;69:231-43

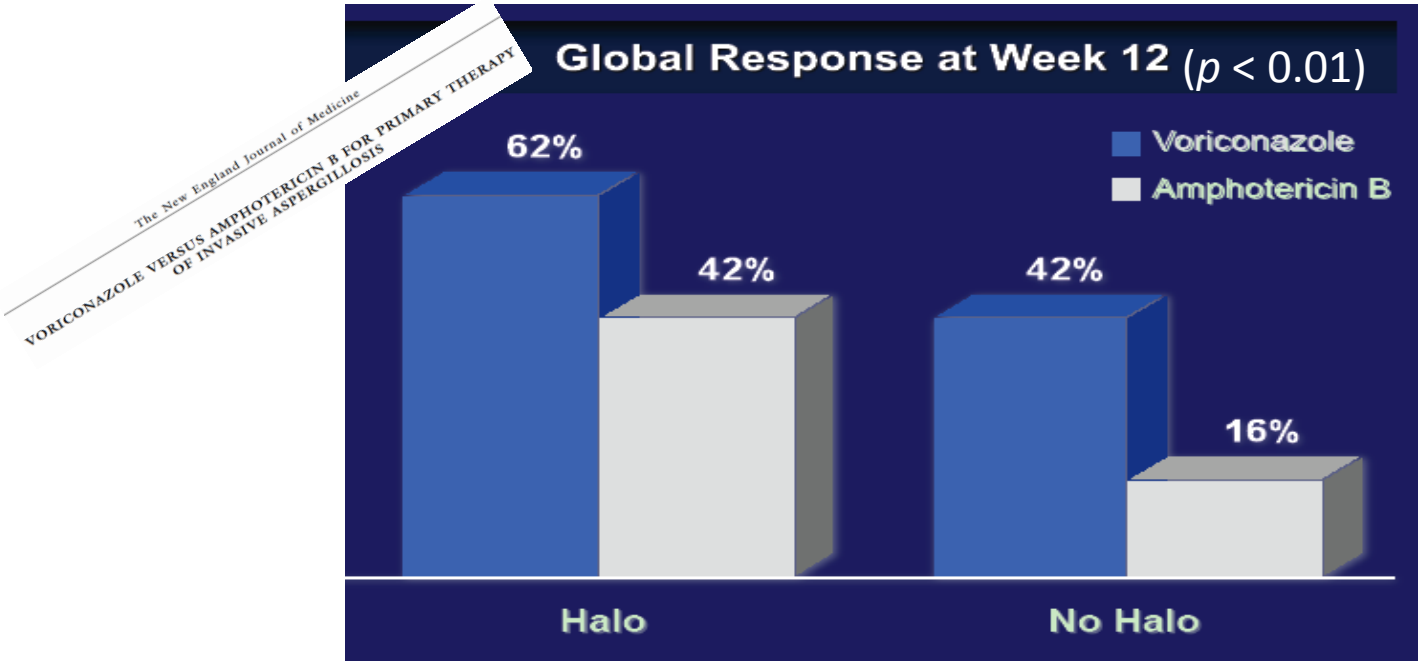
Schiel X et al (PEG-Studie II), Infection 2006;34:118-26

Management of FN Pts with Lung Infiltrates



Maschmeyer G et al (AGIHO), Ann Oncol 2015;26:21-33

Improved Survival with Pre-Emptive Treatment Based on "Halo Sign"

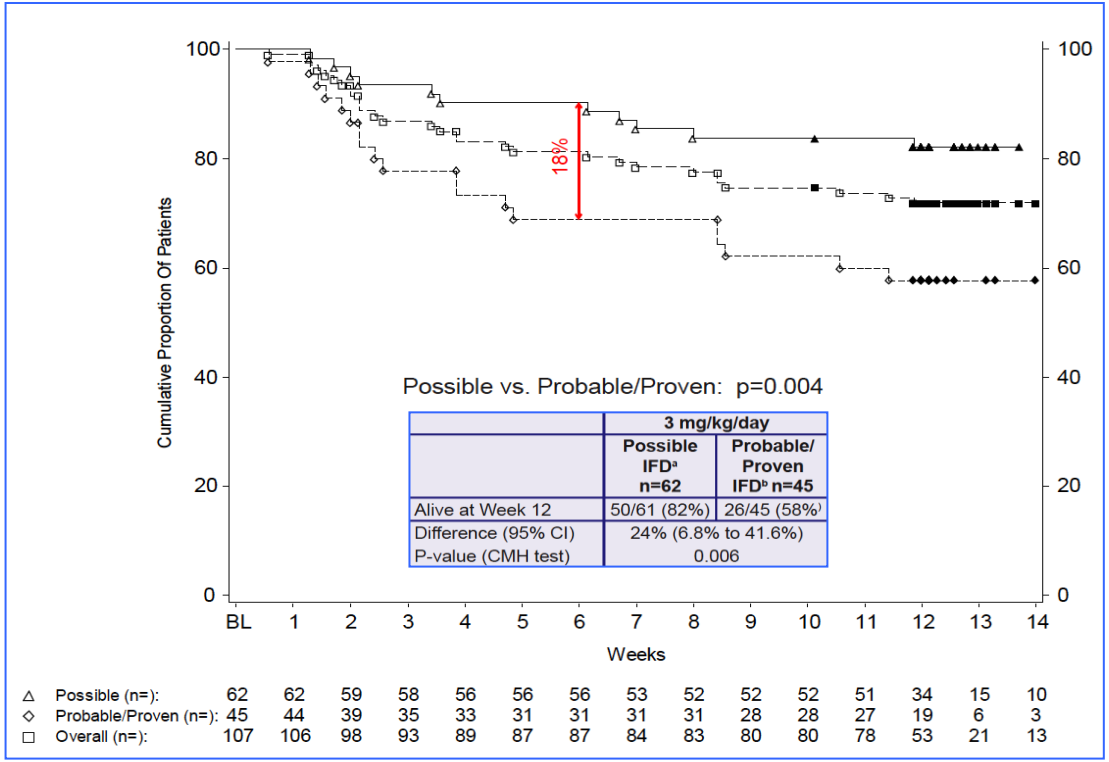


3 mo. survival = 71% *vs* 53%; $p < 0.01$

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

L-AmB (3 mg/kg/d) in Immunocompromised Patients with Invasive Filamentous FI:

Survival in Patients with Possible *vs* Proven/Probable IPA



Cornely OA et al (AmBiLoad Study), Mycoses 2011;54:e449-55

Outcome Depends on Neutrophil Recovery

- PEG Study I (n = 1,573) -

	Recovery	No Recovery	*p*
FUO			
- Response	97.8%	86.5%	*< 0.001*
- Death	1.5%	8.5%	*< 0.001*
Documented Infection			
- Response	86.9%	62.3%	*< 0.001*
- Death	7.0%	20.5%	*< 0.001*

Link H et al (PEG-Studie I), Ann Hematol 1994;69:231-43

Identifiying Low-Risk Patients:
MASCC Score

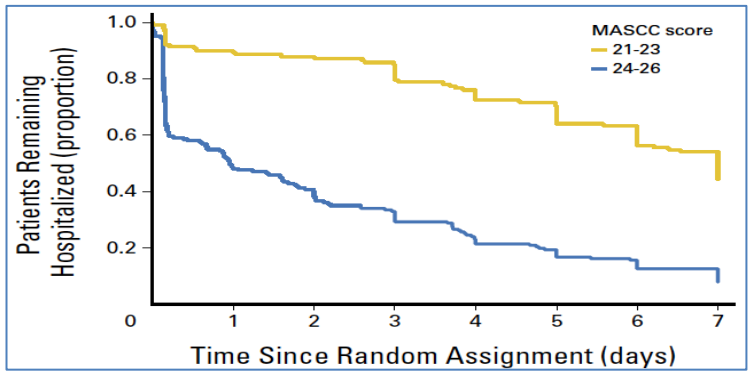
Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms*	5
No hypotension (systolic blood pressure > 90 mmHg)	5
No chronic obstructive pulmonary disease†	4
Solid tumor or hematologic malignancy with no previous fungal infection‡	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms*	3
Outpatient status	3
Age < 60 years	2

≥ 21 = Low-Risk

Klastersky J et al (MASCC), J Clin Oncol 2000;18:3038-51

Oral Moxifloxacin is Equivalent to Cipro + AmoxiClav in Febrile „Low-Risk“-Patients

Outcome	Moxifloxacin		Ciprofloxacin Plus Amoxicillin/ Clavulanic Acid	
	No.	%	No.	%
Success				
ITT population	136 of 169	80	134 of 164	82
Evaluable patients	131 of 156	84	132 of 156	85



<= MASCC Score clearly predictive!

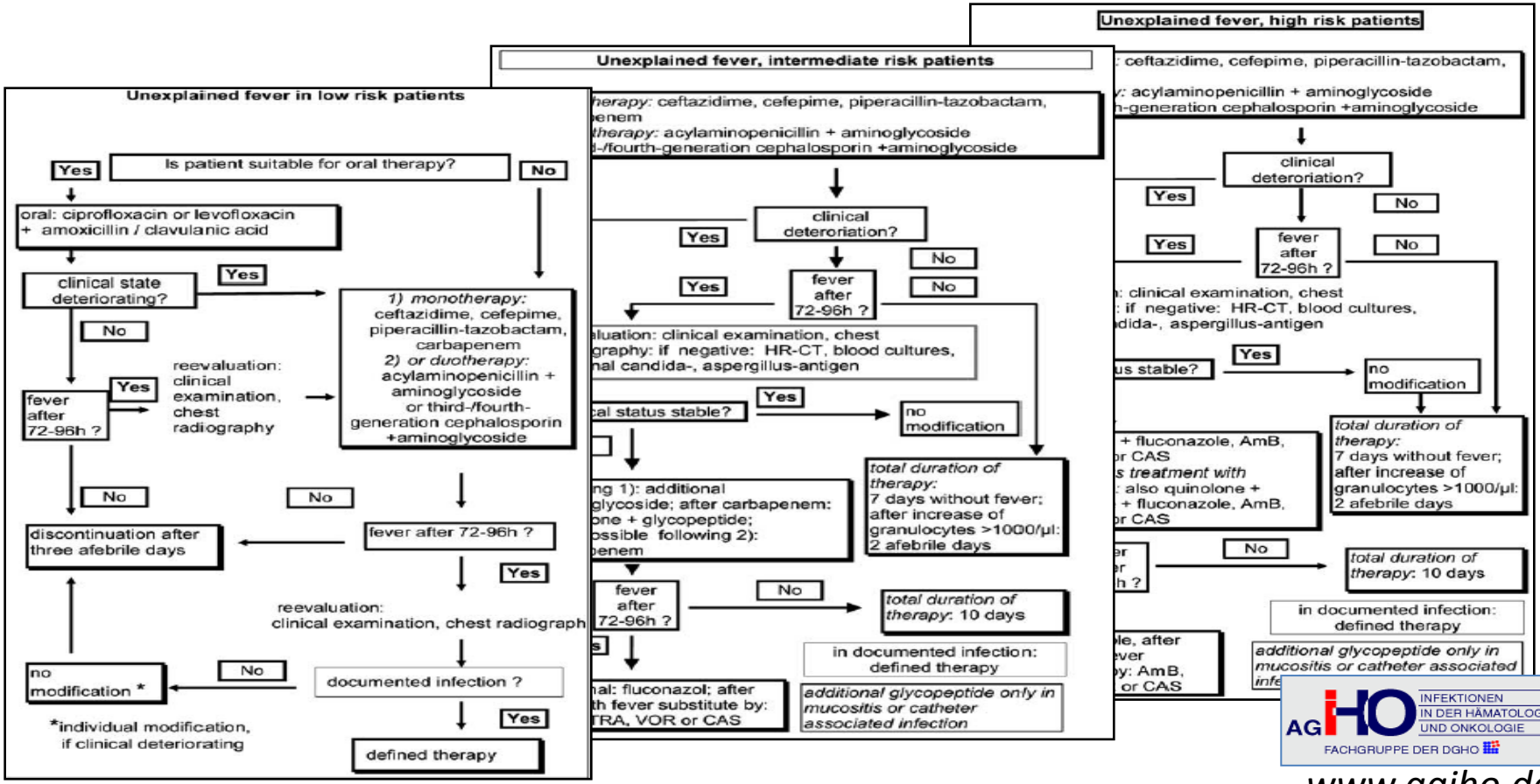
Kern WV et al (EORTC), J Clin Oncol 2013;31:1149-56

Why Oral Treatment in FN Low-Risk Patients Sometimes Fails

Clinical condition/reason	*Number of patients*
Infection with multi-resistant bacteria, verified microbiologically*	11
Invasive fungal infection, clinically suspected or proven#	8
Gastrointestinal complications and swallowing difficulties	4
Generally deteriorating condition	4
Central venous catheter infections	3
Deep abscess of soft tissue	2
Endocarditis	1
Previously included twice in the study	1
Psychiatric disease	1
Refusal to take oral antibiotics	1
Unspecified	2

Cherif H et al (Karolinska Inst), Haematologica 2006;91:215-22

Risikoadapted Intervention: AGIHO Charts



AGIHO INFEKTIONEN IN DER HÄMATOLOGIE UND ONKOLOGIE
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Newer Antibiotics: Useful for Febrile Neutropenic Pts?

- Daptomycin
- Tigecyclin
- Linezolid
- Telavancin
- Cefozopran
- Doripenem
- Fidaxomicin
- *Ceftolozan-Tazobactam (No Data in FNP)*

Daptomycin in Neutropenic Cancer Patients with G+ Bacteremia

- 186 pts, 86% evaluable, 62% with neutropenia < 0.1 Gpt/l)
- 78% bacteremia, mostly VRE, CNS and MRSA
- 84% pre-treated
- Response rate: 85%
- Response in pts with neutropenia <0.1 Gpt/l: 84%

Rolston KV et al (Registry data), Support Care Cancer 2014;22:7-14

Daptomycin in Neutropenic Cancer Patients with G+ Bacteremia

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- 78% bacteremia, mostly VRE, CNS and MRSA
- 84% pre-treated
- [illegible] rate: 85%
- Response in pts with neutropenia <0.1 Gpt/l: 84%

Alert: Daptomycin gets inactivated by surfactant

Rolston KV et al (Registry data), Support Care Cancer 2014;22:7-14

Results of a Multicenter, Controlled, Randomized Clinical Trial Evaluating the Combination of Piperacillin/Tazobactam and Tigecycline in High-Risk Hematologic Patients With Cancer With Febrile Neutropenia

- 390 pts., success rate 67.9% *vs* 44.3% ($p < 0.001$)
- Superior at multi-resistant pathogens (MRSA, coag.-neg. staph, ESBL)
- No overall survival difference
- "Combination regimen should be reserved to febrile neutropenic patients at high risk of developing infections because of MDR pathogens."

Bucaneve G et al, J Clin Oncol 2014;32:1463-71

Empiric use of linezolid in febrile hematology and hematopoietic stem cell transplantation patients colonized with vancomycin-resistant *Enterococcus spp*

Luiz F. Lisboa [a], Bianca G. Miranda [b], Marjorie B. Vieira [b], Frederico L. Dulley [c], Guilherme G. Fonseca [c], Thais Guimarães [d], Anna S. Levin [b], Maria A. Shikanai-Yasuda [b], Silvia F. Costa [b,*]

- n = 100 VRE-colonized patients, 35 of which empirically treated also with linezolid
- Mortality 54.3 *vs* 41.5% *(p = 0.29)*

Int J Infect Dis 2015;33:171-6

Linezolid-Associated Pancytopenia

- 2 patients post solid organ transplantation
- Multi-resistant gram-positive infection
- No obvious other cause than linezolid
- Hematopoitic recovery after discontinuation of linezolid

Faguer S et al (Toulouse), Infection 2007;35:275-7

Cefozopran, Meropenem, Imipenem or Cefepime in Febrile Neutropenic Adult Patients

- n = 376, initial empiric therapy for FN (prospective, randomized)
- Response rates
- Cefozopran: 54/90 (60%)
- Meropenem: 60/92 (65%)
- Imipenem: 63/88 (72%)
- Cefepime: 56/85 (66%)
- **=> no significant differences**

Nakane T et al (Japan), J Infect Chemother 2015;21:16-22

Case-Control Study of Telavancin as an Alternative Treatment for Gram-Positive Bloodstream Infections in Patients with Cancer

Anne-Marie Chaftari, Ray Hachem, Mary Jordan, Kumait Garoge, Zainab Al Hamal, Aline El Zakhem, George M. Viola, Bruno Granwehr, Victor Mulanovich, Andrew Gagel, Ruth Reitzel, Ammar Yousif, Ying Jiang, Issam Raad

Department of Infectious Diseases, Infection Control, and Employee Health, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA

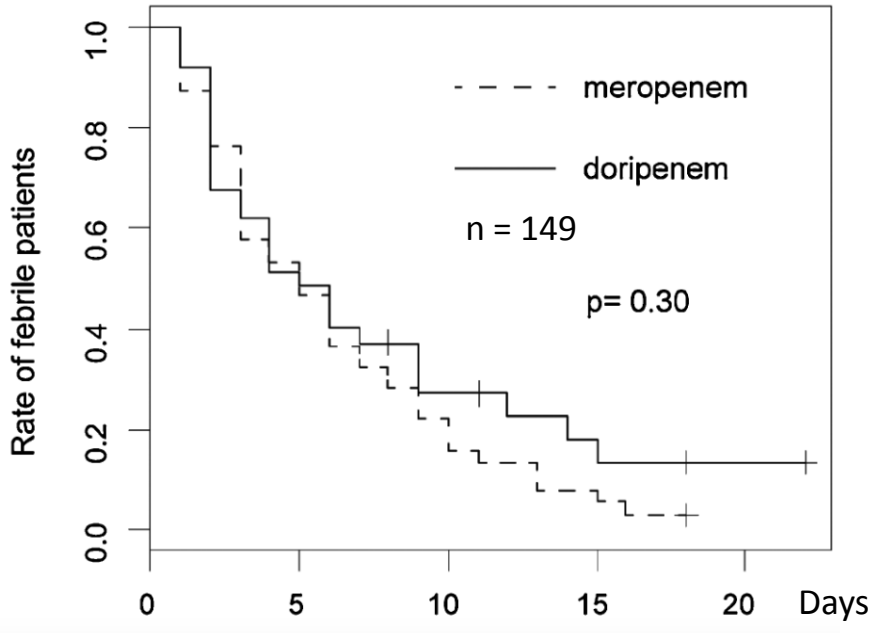
- N = 39 cancer patients with uncomplicated Gram-positive BSIs treated with IV telavancin
- **Matched** with 39 pts with Gram-positive BSIs treated with **vancomycin**
- *S. aureus* (51%), alpha-hemolytic streptococci (23%), *Enterococcus* spp. (15%), CNS (8%), beta-hemolytic streptococci (3%)
- 62% hematological malignancies, 38% solid tumors, 51% neutropenic
- **Overall response rate 86% *vs* 61% (*p* = 0.013)**
- Drug-related adverse events 31% *vs* 23% (*p* = 0.79)

Antimicrob Agents Chemother 2015;60:239-44

A Comparative Analysis of Meropenem and Doripenem in Febrile Patients with Hematologic Malignancies: a Single-Center Retrospective Study

Takashi Toya, Yasuhito Nannya, Kensuke Narukawa, Motoshi Ichikawa, and Mineo Kurokawa*

Department of Hematology & Oncology, The University of Tokyo, Tokyo 113-8655, Japan



Jpn J Infect Dis 2012;65:228-32

Clostridium difficile-associated Diarrhea

	Systemic antibiotics continued			No systemic AB	*p*
Cure rate	84.4%			92.6%	*<0.001*
Duration of diarrhea	97 h			54 h	*<0.001*
	Fidaxo-micin	**Vancomycin**	***p***		
Cure rate	90.0%	79.4%	*0.04*		
Re-infection	16.9%	29.2%	*<0.048*		

Mullane KM et al, Clin Infect Dis 2011;53:440-7

Subgroup of **tumor patients (n = 183)**:
Fidaxomicin significantly more active than vancomycin

Cornely OA et al, J Clin Oncol 2013;31:2493-9

Many Thanks for Your Attention