Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

La neutropenia febbrile: nuovi paradigmi di prevenzione e terapia

Livio Pagano

UOC di Ematologia Geriatrica ed Emopatie Rare

Roma

EUROPEAN HEMATOLOGY ASSOCIATION

EORTC
The future of cancer therapy

Invited Speaker – Consultant – Research grants

Stemline acquired by Menarini group

Jazz Pharmaceuticals

Celgene Committed to improving the lives of patients worldwide©

Pfizer

Gilead

Cidara Therapeutics

Novartis

Scynexis®

Janssen Pharmaceutical Companies of Johnson & Johnson

AstraZeneca

F2G The Rare Fungal Disease Company

moderna®

Neutropenic Fever Syndromes

International Immunocompromised Host Society 1990

- **Microbiologically documented infection**
  - Neutropenic fever with a clinical focus of infection
  - An associated pathogen
- **Clinically documented infection**
  - Neutropenic fever with a clinical focus (eg, cellulitis, pneumonia)
  - Without the isolation of an associated pathogen
- **Unexplained fever**
  - Neutropenic fever with no clinical focus of infection
  - No identified pathogen

Febrile Neutropenia

- **Risk in HM patients:**

  Fever may be the only sign of infection

  - Receiving cytotoxic therapy sufficient to adversely affect
    - Myelopoiesis
    - Developmental integrity of the gastrointestinal mucosa
- **Lower or absent effect of the neutrophil-mediated component of the inflammatory response**

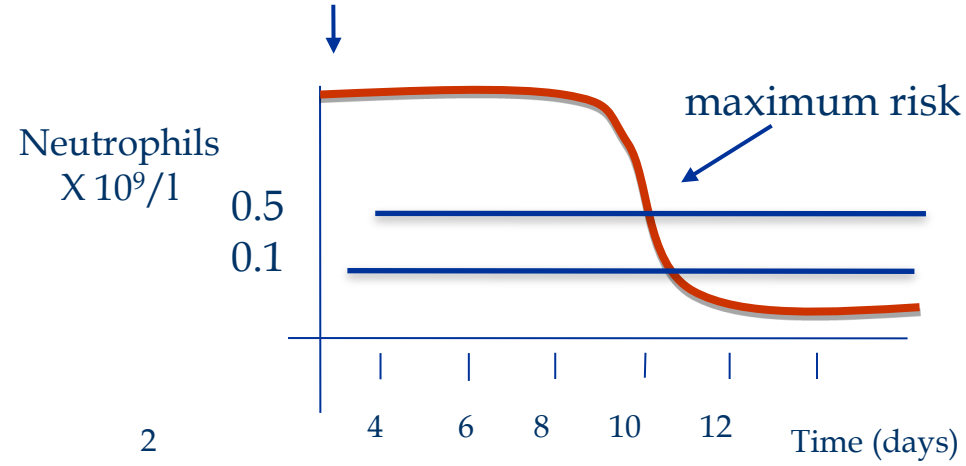
  Sickles EA et al Arch Intern Med 1975
- **Critical importance:**
  - Early recognition and prompt treatment

Pathogenesis

- **Direct effects of chemotherapy**
  - On mucosal barriers and the immune system
- **Chemotherapy-induced mucositis throughout the GI tract**
  - Seeding of the bloodstream from GI endogenous flora
- **Immune defects**
- **Neutrophils:**
  - Decreased number, chemotactic and phagocytic defects

Neutropenia: a common risk factor for Infections

Dopo oltre 60 anni il concetto di neutropenia profonda e prolungata non è cambiato

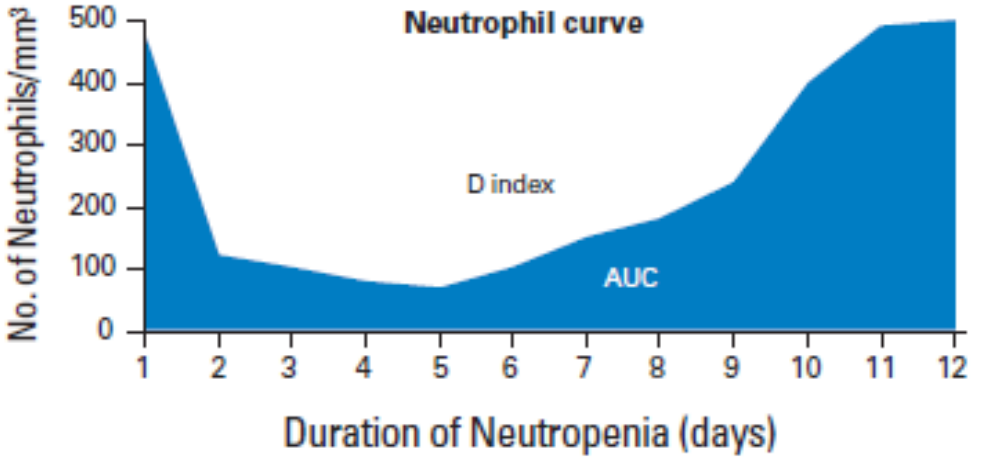


- <0.5 x 10^9/l: risk of infection
- <0.1 x 10^9/l: high risk of infection

Modified from Bodey et al, Ann intern Med 1966

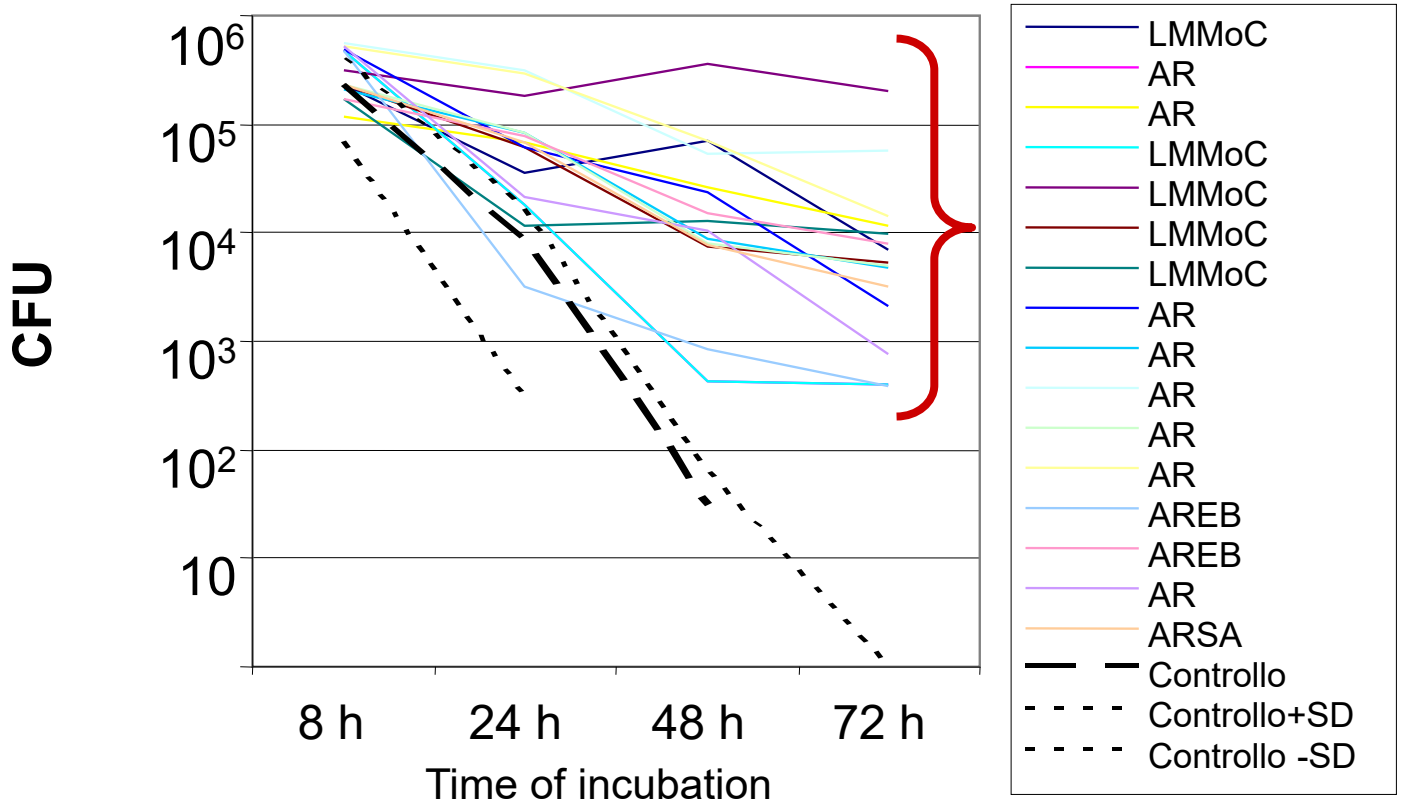
Index to Predict Invasive Mold Infection in High-Risk Neutropenic Patients Based on the Area Over the Neutrophil Curve

Rodrigo D. Portugal, Marcia Garnica, and Marcio Nucci — *J Clin Oncol 27:3849-3854.*



Impaired bactericidal and fungicidal activities of neutrophils in patients with myelodysplastic syndrome

Fianchi et al, Leuk Res 2012



<u>Dysplastic vs normal PMN:</u>

↓ fungicidal activity against yeasts

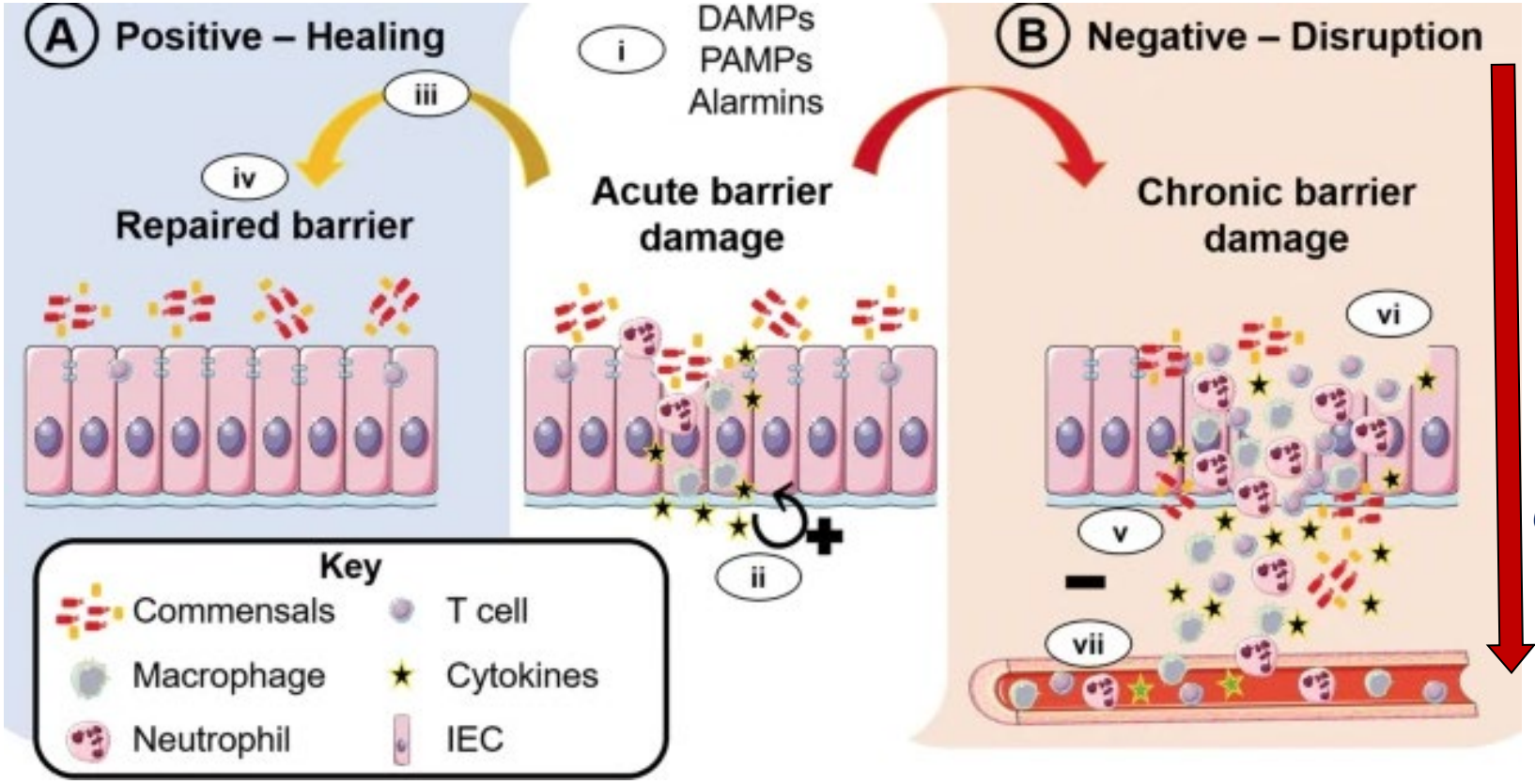
↑ susceptibility to infections in myelodysplasia

Pathogenesis of neutropenic enterocolitis

Intensive Chemotherapy Mainly Dauno

Neutropenia

Bowel wall damage



Clostridium difficile

P. aeruginosa

St.aureus

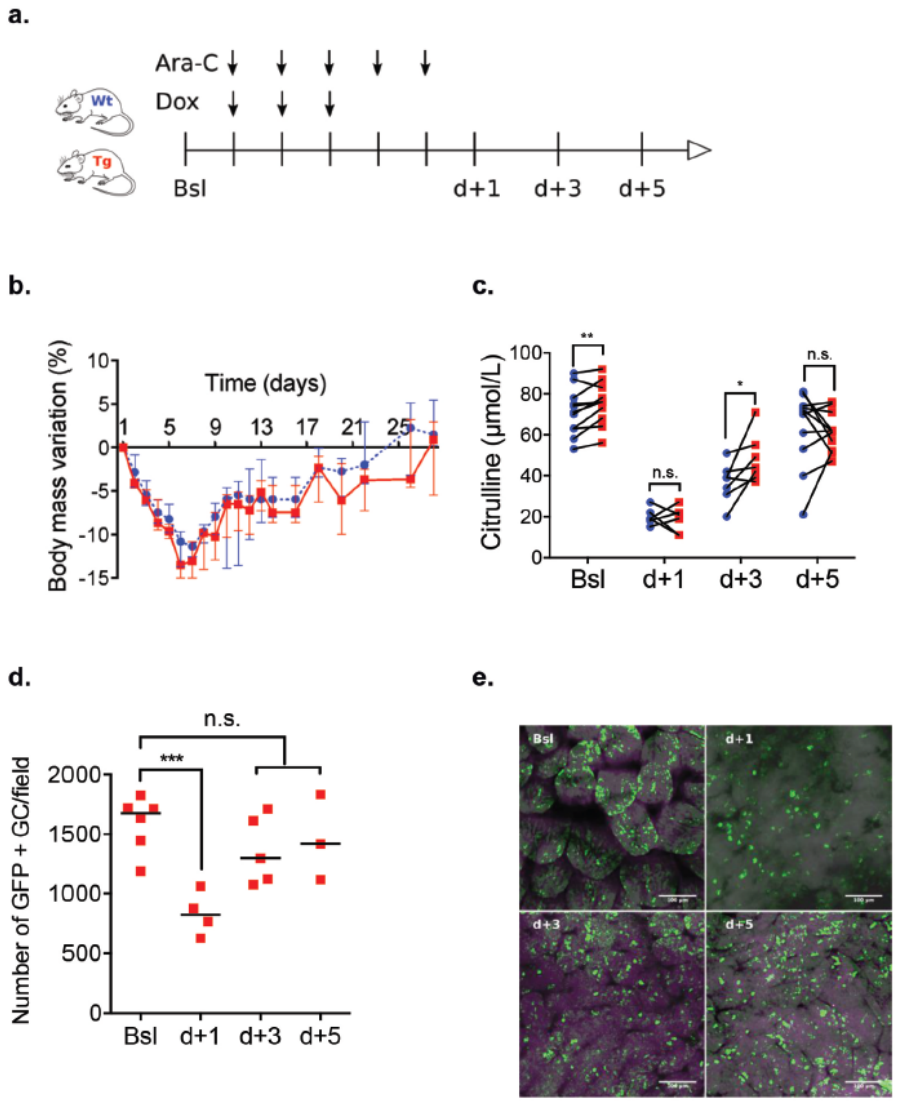
Enterobacteriaceae

Clostridium septicum

Candida

Micozzi et al. Supp Care Cancer 1996

Impact and consequences of intensive chemotherapy on intestinal barrier and microbiota in acute myeloid leukemia: the role of mucosal strengthening



- ✓ 15 AML patients treated with 3+7
- ✓ This human study revealed the deep impairment of the intestinal barrier with a transient epithelium damage associated with a prolonged loss of load, diversity, and function of the microbiota
- ✓ The murine model determined more precisely the specific impact of chemotherapy, which is characterized by a qualitative dysbiosis and physical barrier impairment that facilitates bacterial translocation
- ✓ These data support the concept that maintaining intestinal integrity in patients receiving an AML induction regimen and further chemotherapies could limit microbiota dysbiosis responsible for infectious disease and further complications such as GvHD after allo-SCT

Hueso et al, Gut Microbes 2020

A prospective survey of febrile events in hematological malignancies

- 19 EVALUABLE CENTERS for Epidemiological Analysis
- 3197 NEWLY DIAGNOSED PATIENTS

Underlying Malignancy	
Acute Lymphoblastic Leukemia	205
Acute Myeloid Leukemia	861
Chronic Myeloid Leukemia	64
Chronic Lymphocytic Leukemia	172
Lymphoma	953
Hodgkin's Lymphoma	138
Myelodysplastic Syndromes	190
Multiple Myeloma	410
Chronic Myeloprolipherative Diseases	204
Total	3197

	EVT	%
Bacterial	301	34.6
Fungal	95	10.9
Viral	7	0.8
DTRF	48	5.5
FUO	**386**	**44.4**
Mixed infections	32	3.6
Fungi/Bacteria	23	
Bacteria/Virus	6	
Fungi/Virus	2	
Bacteria/Fungi/Virus	1	
TOTAL	869	

869 FEBRILE EVENTS = 27.1%

Pagano et al. Ann Hematol 2011

Diagnostic Work-up

Microbiology

- **Blood Culture: positive in < 30% of febrile neutropenic episodes**
- **Urine, stool culture**

Biomarkers

- **C-Reactive protein (CRP)**
- **Pro-inflammatory cytokines:**TNF-α, IL-1, IL-6, IL-8, IFN-ɣ **(?)**
- **Procalcitonin (PCT)**

Diagnostic work-up

- ✓ A new standard lung X-ray
- ✓ Chest HRCT-scan (also in case of X-ray negative)
- ✓ CNS CT-scan (if clinically indicated)
- ✓ Bronchoalveolar lavage (if HRCT positive)
- ✓ Blood cultures for fungal infection
- ✓ Serum galactomannan
- ✓ (1–3)-β-D-Glucan Assay
- ✓ PCR for *Candida* and *Aspergillus*

CNS, central nervous system; CT, computed tomography; PCR, polymerase chain reaction; HRCT, high resolution computed tomography.

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)†

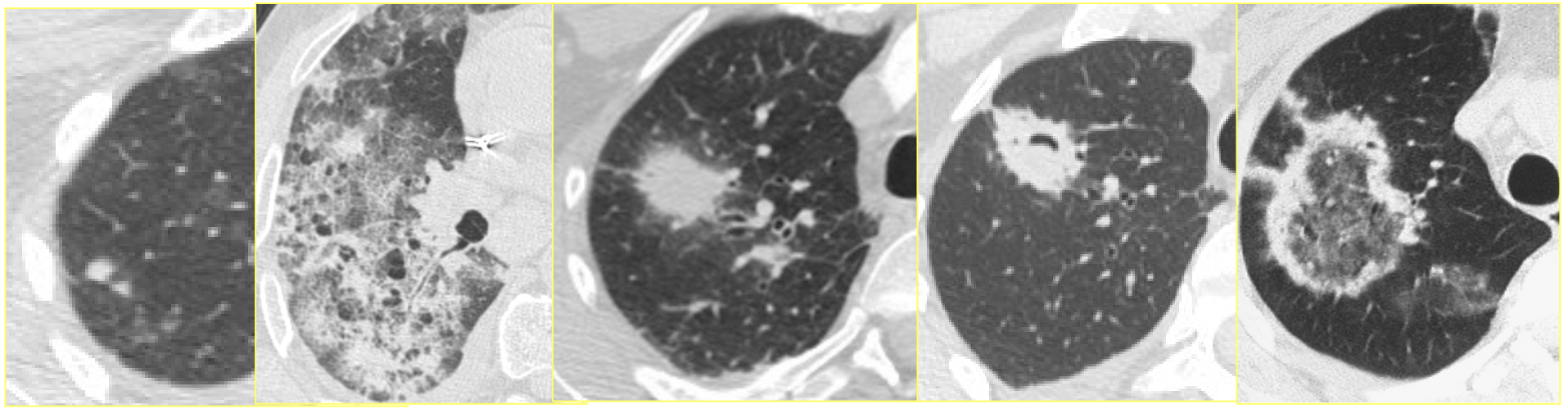
Recommendation	Strength
Patients with FUO not responding to an appropriate first-line therapy after 72-96 h should undergo multislice or HR-CT scan of the lungs and a CT scan of paranasal sinuses if symptoms or signs of sinusitis are present	A-II
CT scan must be available at a maximum of 24 h after clinical indication has been established	A-II
In most cases, thoracic CT scan can be done without contrast media *(CT angiography may increase diagnostic specificity in patients with mold infection)*	B-II

Maschmmeyer G et al. Ann Oncol 2015

HRCT – findings for IFI

nodule
mass / consolidation / GGO
“halo sign”
“air crescent sign”
“reversed halo sign”

} imaging findings can overlap



nodule | consolidation/ GG opacities | “halo sign” | “air crescent sign” | “reversed halo sign”

GGO, ground glass opacity, HRCT, high-resolution computed tomography; IFI, invasive fungal infection.
Courtesy of Larici, Institute of Radiology, Catholic University, Roma.

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)†

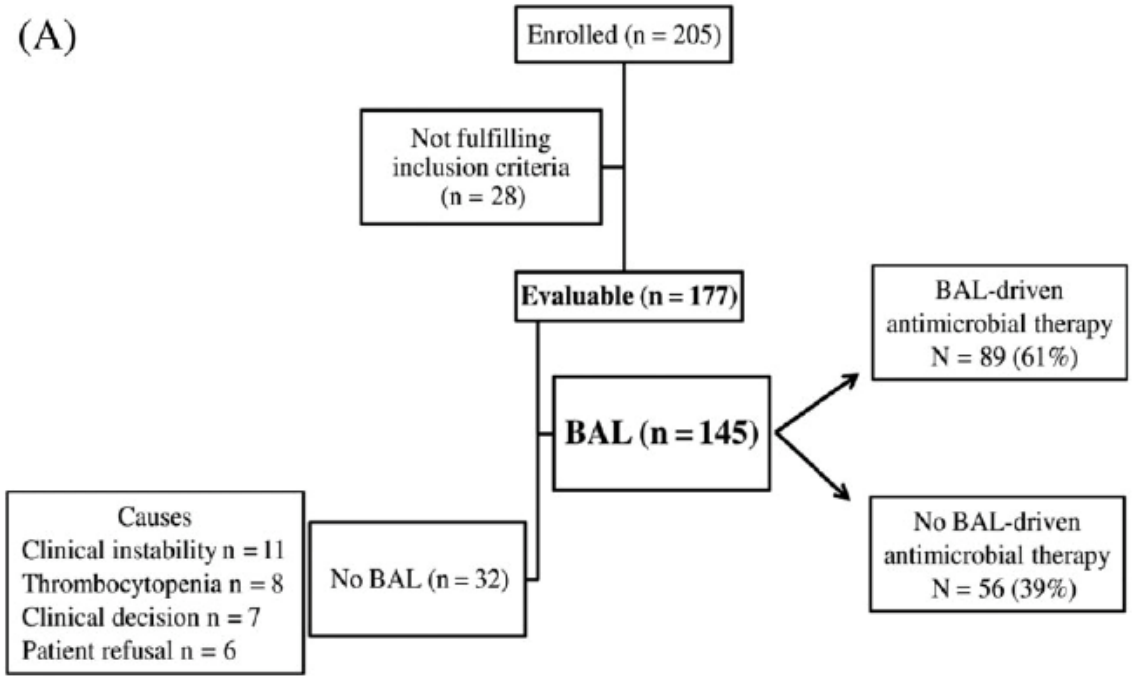
The detection rate of potential pathogens from BAL samples has been described to be 25%-50% or even higher

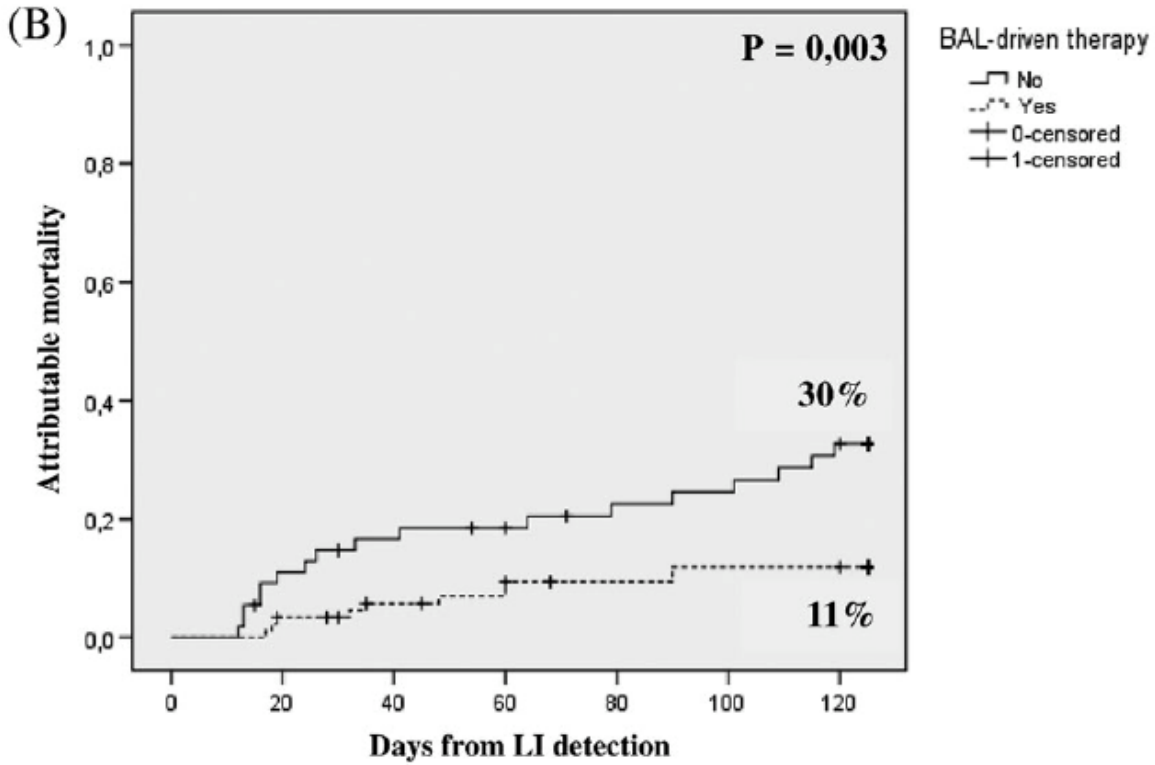
Recommendation	Strength
Bronchoscopy and BAL should be available within 24 h after clinical indication has been established	B-III
Urgent need to start or modify antimicrobial therapy should not be postponed by bronchoscopy and BAL	A-II
Bronchoscopy and BAL should only be carried out in patients without critical hypoxemia	B-II

Maschmmeyer G et al. Ann Oncol 2015

SEIFEM

A bronchoalveolar lavage-driven antimicrobial treatment improves survival in hematologic malignancy patients with detected lung infiltrates: A prospective multicenter study of the SEIFEM group



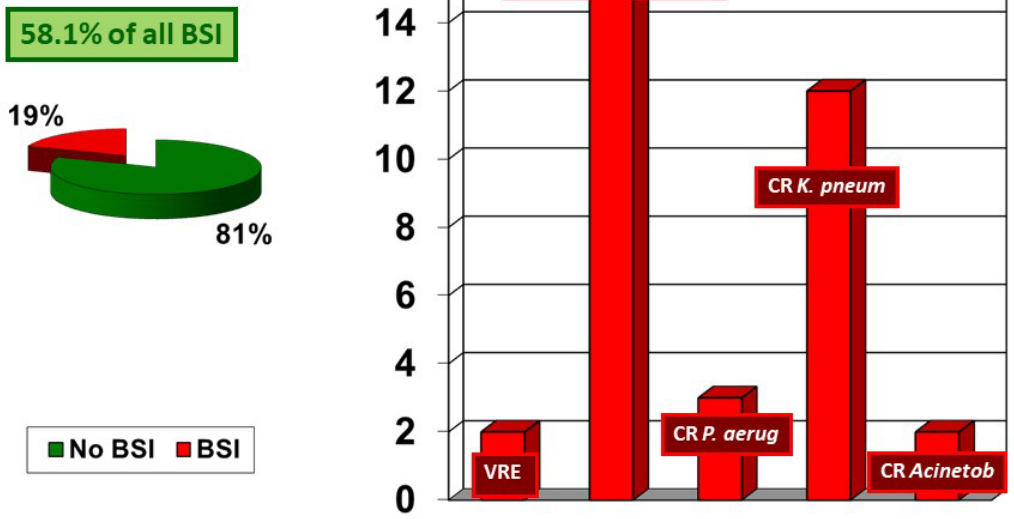


- BAL allows to identify a causal microbiological agent in 75% of cases
- BAL is a safe procedure even in this "difficult" population
- BAL-driven antimicrobial therapy is feasible in 61% of cases and allows to improve the clinical outcome in terms of survival

Marchesi et al. Am Hematol 2019

Surveillance swab

MDR-related BSI (n=36)



C. Cattaneo et al. *"Bloodstream infections in ss cancer patients colonized by multidrug-resistant bacteria" Annals of Hematology (2018) 97:1717–1726*

Predictors of a greater likelihood of developing sepsis

Positive surveillance swab	
perianal site	**5 (9,8%)**
Isolated species	**4 (80%)**
Klebsiella pneumoniae carbapenemasi-produttrice	2 (33%)
Acinetobacter baumannii	1 (16%)
Klebsiella oxytoca	1 (16%)
Pseudomonas aeruginosa	1 (16%)

All patients developed widespread infection caused by the pathogen identified by the swab

The identification of any bacterial colonizations present can allow for the best selection of the empirical antibiotic treatment, in such a way as to set up an adequate therapy that leads to a better therapeutic response.

Bloodstream infections due to Gram-negative bacteria in patients with hematologic malignancies: updated epidemiology and risk factors for multidrug-resistant strains in an Italian perspective survey

Microorganisms	Total							MDR isolates
		Ceftazidime	Ciprofloxacin	Meropenem	Amikacin	Gentamicin	Piperacillin/ tazobactam	
Total[a]	**834**	517 (61.9)	335 (40.2)	675 (80.9)	663 (79.5)	606 (72.6)	555 (66.5)	**256 (30.7)**
Escherichia coli	440	315 (71.6)	147 (33.4)	436 (99.1)	394 (89.6)	355 (80.7)	360 (81.8)	75 (17.1)
Klebsiella pneumoniae	160	57 (35.6)	48 (30.0)	78 (48.7)	100 (62.5)	86 (53.7)	55 (34.4)	101 (63.1)
Pseudomonas aeruginosa	122	81 (66.4)	73 (59.8)	80 (65.6)	89 (72.9)	86 (70.5)	74 (60.6)	45 (36.9)
Enterobacter cloacae	31	23 (74.2)	24 (77.4)	29 (93.5)	31 (100)	28 (90.3)	23 (74.2)	4 (12.9)
Acinetobacter baumannii	14	1 (7.1)	5 (35.7)	5 (35.7)	5 (35.7)	6 (42.8)	3 (21.4)	9 (64.3)
Others	53	39 (73.6)	38 (71.7)	47 (88.7)	44 (83.2)	45 (84.9)	40 (75.5)	8 (15.1)
MDR isolates	256	20 (7.8)	7 (2.7)	99 (38.7)	106 (41.4)	72 (28.1)	36 (14.1)	-

Antimicrobial susceptibility profiles of all Gram-negative bacteria and of the most frequently isolated and MDR bacterial isolates.

[a] *Stenotrophomonas maltophilia* isolates (n=14) were not reported (all isolates except one were susceptible to trimethoprim/sulfamethoxazole) and were considered MDR.

Trecarichi et al, Int J Antimicrob Ag 2023

Fluoroquinolone Prophylaxis: How And Why (Not)

HOW:

Select the right patients

Consider the risk of adverse reactions

Preserve the host microbior

WHY:

Reduce the risk of febrile neutropenia

Reduce viral riactivation

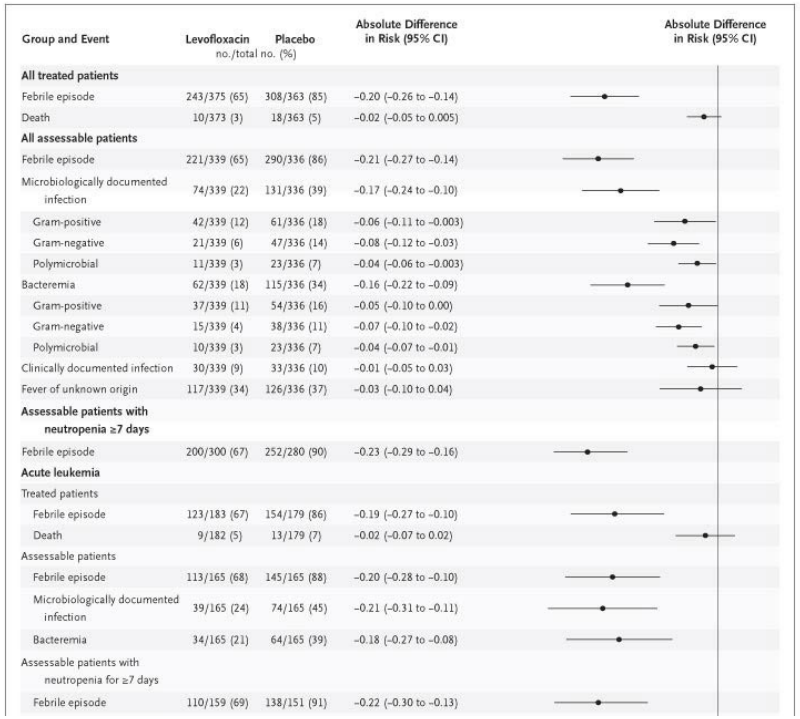
Microbiologic decontamination

Fluoroquinolone prophylaxis: the beginning

Meta-analysis of 52 trials evaluating FQ prophylaxis among 1973-2004:

- reduced risk for all-cause mortality (RR 0.52 [CI, 0.35 to 0.77])

- increased risk for strains resistant to the specific drug, **not statistically** significant (RR 1.69 [CI, 0.73 to 3.92])



Group and Event	Levofloxacin no./total no. (%)	Placebo no. (%)	Absolute Difference in Risk (95% CI)	Absolute Difference in Risk (95% CI)
All treated patients				
Febrile episode	243/375 (65)	308/363 (85)	−0.20 (−0.26 to −0.14)	
Death	10/373 (3)	18/363 (5)	−0.02 (−0.05 to 0.005)	
All assessable patients				
Febrile episode	221/339 (65)	290/336 (86)	−0.21 (−0.27 to −0.14)	
Microbiologically documented infection	74/339 (22)	131/336 (39)	−0.17 (−0.24 to −0.10)	
Gram-positive	42/339 (12)	61/336 (18)	−0.06 (−0.11 to −0.003)	
Gram-negative	21/339 (6)	47/336 (14)	−0.08 (−0.12 to −0.03)	
Polymicrobial	11/339 (3)	23/336 (7)	−0.04 (−0.06 to −0.003)	
Bacteremia	62/339 (18)	115/336 (34)	−0.16 (−0.22 to −0.09)	
Gram-positive	37/339 (11)	54/336 (16)	−0.05 (−0.10 to 0.00)	
Gram-negative	15/339 (4)	38/336 (11)	−0.07 (−0.10 to −0.02)	
Polymicrobial	10/339 (3)	23/336 (7)	−0.04 (−0.07 to −0.01)	
Clinically documented infection	30/339 (9)	33/336 (10)	−0.01 (−0.05 to 0.03)	
Fever of unknown origin	117/339 (34)	126/336 (37)	−0.03 (−0.10 to 0.04)	
Assessable patients with neutropenia ≥7 days				
Febrile episode	200/300 (67)	252/280 (90)	−0.23 (−0.29 to −0.16)	
Acute leukemia				
Treated patients				
Febrile episode	123/183 (67)	154/179 (86)	−0.19 (−0.27 to −0.10)	
Death	9/182 (5)	13/179 (7)	−0.02 (−0.07 to 0.02)	
Assessable patients				
Febrile episode	113/165 (68)	145/165 (88)	−0.20 (−0.28 to −0.10)	
Microbiologically documented infection	39/165 (24)	74/165 (45)	−0.21 (−0.31 to −0.11)	
Bacteremia	34/165 (21)	64/165 (39)	−0.18 (−0.27 to −0.08)	
Assessable patients with neutropenia for ≥7 days				
Febrile episode	110/159 (69)	138/151 (91)	−0.22 (−0.30 to −0.13)	

Gafter-Gvili et al. Ann Intern Med 2005

Double-blind, placebo-controlled trial in high risk neutropenic patients:

- reduction of patients with fever requiring empirical antibiotic therapy

- prevalence of Gram- FQ resistant bacteremia did not differ significantly

- no significant effect of levofloxacin in the reduction of mortality

Table 2. Characteristics of Bacterial Isolates and Number with Resistance to Levofloxacin.

Characteristic	Levofloxacin (N=339)	Placebo (N=336)
Microbiologically documented infection	74	131
No. with bacteremia	62	115
Single gram-positive isolate	37	54
S. aureus	0	10
Coagulase-negative staphylococcus	31	32
Streptococcus species	5	9
Other gram-positive organisms	1	3
Single gram-negative isolate	15	38
Pseudomonas species	6	8
E. coli	7	22
Other gram-negative organisms	2	8
Polymicrobial isolate	10	23
Gram-positive organisms only	5	5
Gram-positive and gram-negative organisms	5	18
No. without bacteremia	12	16
Single gram-positive isolate	5	7
Single gram-negative isolate	6	9
Polymicrobial isolate	1	0
Levofloxacin resistance in single-agent bacteremias — no. resistant/total no. available for analysis	41/47	32/68

Table 3. Mortality Rates in the Treated Population.

Variable	Levofloxacin (N=373)*	Placebo (N=363)	P Value
	no. of patients		
Death	10	18	0.15
Death due to infection	9	14	0.36
Microbiologically documented infection	4	7	0.25
Microbiologically documented infection with bacteremia	3	5	0.34

Bucaneve et al. NEJM 2005

Bloodstream infections caused by *Escherichia coli* in onco-haematological patients: Risk factors and mortality in an Italian prospective survey

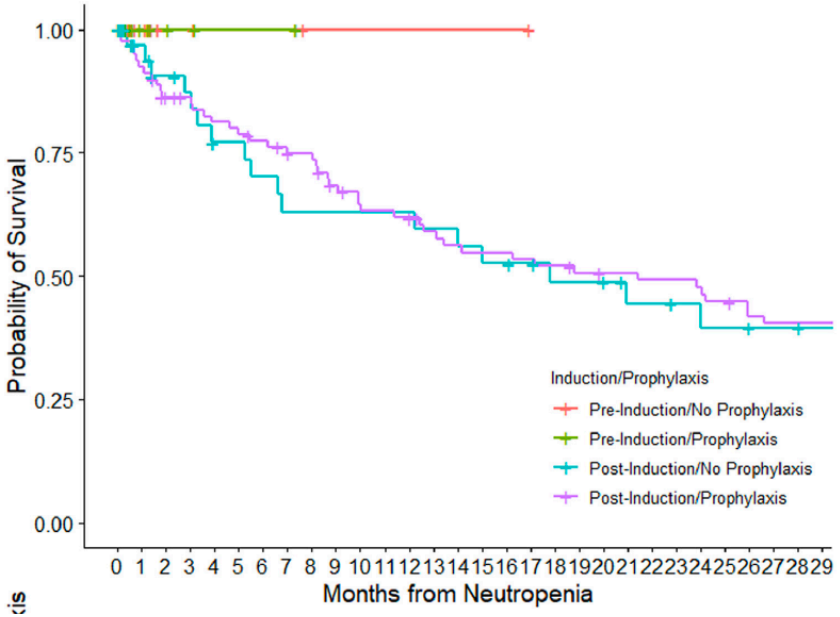
- A total of 342 cases of monomicrobial EC BSI were included between January 2016-December 2017
- The rate of resistance to third generation cephalosporin among *E. coli* isolates was **25.7%** (88/342).
- 30-day mortality rate: **7.1%** (24/342)
- 30-day mortality rate: **13.6%** (12/88) among E. coli resistant BSI patients vs. **4.7%** (12/254) among no-resistant BSI patients (P=0.004).

Variables	OR	(95% IC)	P values
Recent endoscopic procedures	3.68	(1.23–11.04)	0.02
MDR bacteria culture-positive surveillance rectal swabs	2.81	(1.59–4.95)	<0.001
Antibiotic prophylaxis with fluoroquinolones	1.95	(1.16–3.28)	0.01
PMN < 500/mmc for at least 10 days	1.82	(1.08–3.06)	0.02

Trecarichi et al. PlosOne 2019

Impact of Fluoroquinolone Prophylaxis on Neutropenic Fever, Infections, and Antimicrobial Resistance in Newly Diagnosed AML Patients

Outcomes	No Prophylaxis N = 34	Prophylaxis N = 87	*P*-value
Neutropenic Fever, N (%)	28 (82.4%)	56 (64.4%)	
Crude Time-Varying HR [95% CI] – Post Induction	*Reference*	0.73 [0.45-1.18]	.193
Multivariable[a] Time-Varying HR [95% CI] – Post Induction	*Reference*	0.59 [0.36-0.97]	.039
Mortality, N (%)	17 (50.0%)	48 (55.2%)	
Crude Time-Varying HR [95% CI] – Post Induction	*Reference*	0.98 [0.56-1.71]	.939
Multivariable* Time-Varying HR [95% CI] – Post Induction	*Reference*	0.95 [0.54-1.68]	.860

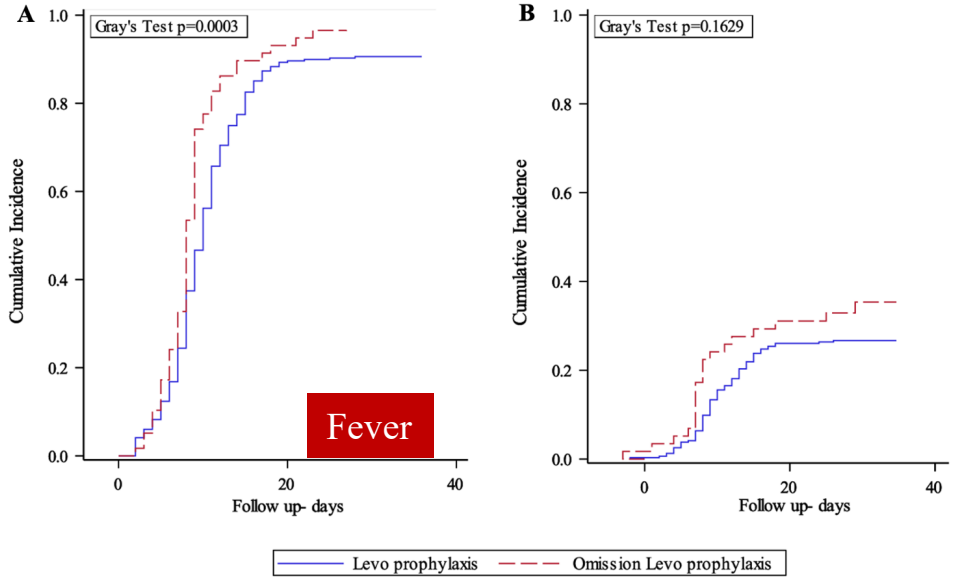


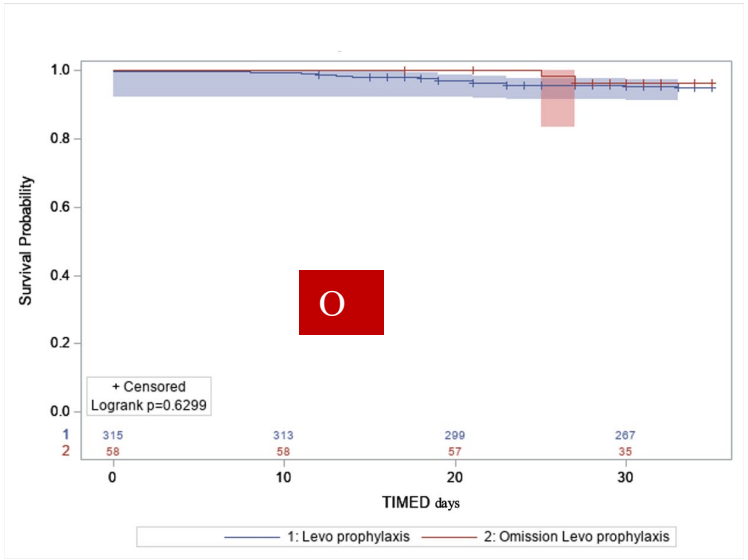
Primary fluoroquinolone prophylaxis in newly diagnosed AML patients reduced the risk of neutropenic fever and systemic bacterial infections without increased antimicrobial resistance.

Caro et al. Clin Lymph, Myeloma & Leuk 2022

Levofloxacin prophylaxis versus no prophylaxis in acute myeloid leukemia during post induction aplasia: a single center study

N° (%)	Levofloxacin prophylaxis (Group A)	No levofloxacin prophylaxis (Group B)	OR (IC95%), p value
PATIENTS	315	58	
Induction death	16 (5)	2 (3)	1.50 (0.34 – 6.70), p=0.284
Neutropenic fever	286 (91)	56 (97)	0.35 (0.08-1.52), p=0.162
Bloodstream infection (BSI)	84 (27)	20 (34)	0.69 (0.38 – 1.25), p=0.222
1 BSI	76	14	
2 BSI	8	6	
Septic shock	15 (5)	4 (7)	0.68 (0.22-2.11), p=0.499
TOTAL EPISODES OF BSI	92	26	
Gram-positive	63 (68)	15 (58)	
Gram-negative	28 (30)	10 (38)	0.66 (0.27 – 1.60), p=0.355
Polymicrobial	1 (2)	1 (4)	
FQ Resistant bacteria	55 (59)	6 (22)	5.07 (1.87 – 13.73), p=0.001
Gram-negative MDR	9 (31)	4 (36)	0.75 (0.15 – 3.70), p=0.727





This study showed that avoiding levofloxacin prophylaxis was not associated with an increased risk of induction death. Cumulative incidence of neutropenic fever was higher in non-prophylaxis group, while no difference was observed for BSIs. In the prophylaxis group we observed a higher incidence of FQ resistant organisms.

Urbino et al. MJHID 2023

IDSA guidelines In 2018

Taplitz et al. JCO 2018

RECOMMENDATIONS

Table 1 provides a summary of antimicrobial prophylaxis recommendations.

CLINICAL QUESTION 1

Antibacterial Prophylaxis. Does antibacterial prophylaxis with a fluoroquinolone, compared with placebo, no intervention, or another class of antibiotic, reduce the incidence of and mortality as a result of febrile episodes in patients with cancer?

Recommendation 1.2. Antibiotic prophylaxis with a fluoroquinolone is recommended for patients who are at high risk for FN or profound, protracted neutropenia—for example, patients with acute myeloid leukemia/myelodysplastic syndromes (AML/MDS) or HSCT treated with myeloablative conditioning regimens. Antibiotic prophylaxis is not routinely recommended for patients with solid tumors. (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate.)

Qualifying Statements.

- Antibacterial prophylaxis is recommended during the expected period of neutropenia in patients who meet the proposed criteria for use.
- Antibacterial prophylaxis is not recommended for patients who are at low risk of profound, protracted neutropenia.
- Antibacterial and antifungal prophylaxis would generally not be indicated when CSF prophylaxis effectively reduces the depth and duration of neutropenia.[6]
- Fluoroquinolone-based antibacterial prophylaxis may have limited utility among matched-related HSCT on the basis of reduced-intensity conditioning regimens.[40]
- Fluoroquinolone resistance rates among community-acquired Enterobacteriaceae isolates in the United States have risen from < 1% to as high as 30% during the decade from the late 1990s to 2009.[41] GI colonization by fluoroquinolone-resistant—and extended-spectrum β-lactamase–positive—gram-negative bacilli has been a risk factor for bacteremic events in the setting of GI mucositis, and fluoroquinolone resistance may result in inappropriate initial empirical antibacterial therapy and increased all-cause mortality.[42,43] A threshold prevalence of fluoroquinolone resistance among *Escherichia coli* isolates above which the protective efficacy of fluoroquinolone prophylaxis may be limited has not been defined.[44]

NCCN guidelines In 2021

ANTIMICROBIAL PROPHYLAXIS BASED ON OVERALL INFECTION RISK IN PATIENTS WITH CANCER

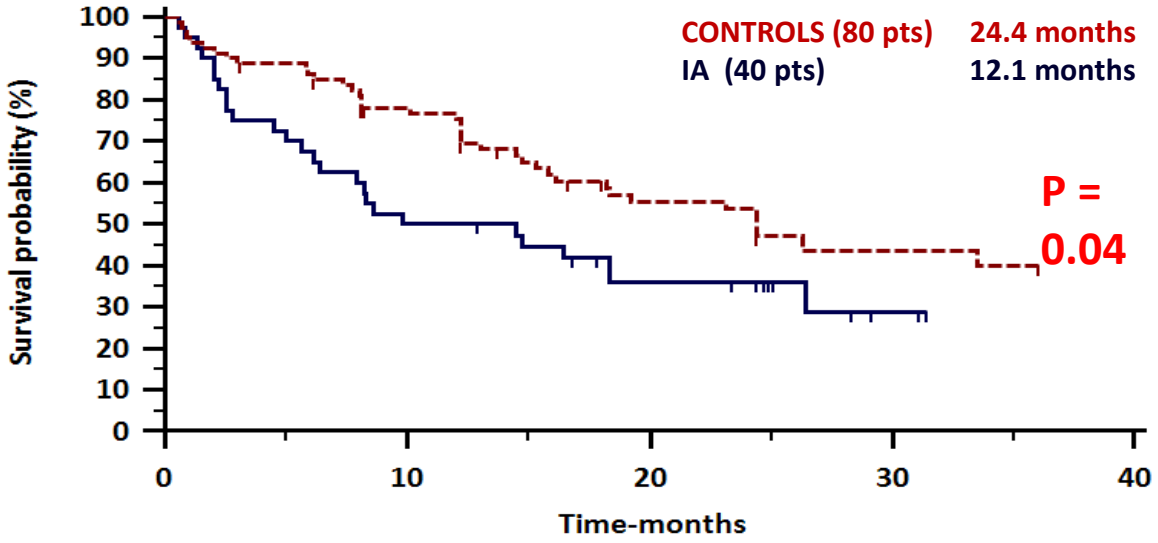
Overall Infection Risk in Patients with Cancer[a]	Disease/Therapy Examples	Antimicrobial Prophylaxis[d]
Low	• Standard chemotherapy regimens for most solid tumors • Anticipated neutropenia less than 7 days	• Bacterial - None • Fungal - None • Viral - None unless prior HSV episode
Intermediate	• Autologous HCT • Lymphoma[c] • Multiple myeloma[c] • CLL[c] • Purine analog therapy (ie, fludarabine, clofarabine, nelarabine, cladribine) • Anticipated neutropenia 7–10 days	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia[e] • Fungal - Consider prophylaxis during neutropenia and for anticipated mucositis (See INF-2); consider PJP prophylaxis (See INF-6) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)
High[b]	• Allogeneic HCT including cord blood • Acute leukemia ▸ Induction ▸ Consolidation/maintenance • Alemtuzumab therapy • Moderate to severe GVHD • Anticipated neutropenia greater than 10 days	• Bacterial - Consider fluoroquinolone prophylaxis during neutropenia[e] • Fungal - Consider prophylaxis during neutropenia (See INF-2); consider PJP prophylaxis (See INF-6) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)

Antibacterial prophylaxis is not recommended for patients with a low risk of overall infection.
In patients deemed at intermediate or high risk, the NCCN Guidelines Panel advises that fluoroquinolone prophylaxis be considered in patients with an expected duration of neutropenia (absolute neutrophil count <1000/mcL) for more than 7 days.

https://www.nccn.org/guidelines/category_3

SEIFEM 2012-A Prospective Follow-up of Acute Myeloid Leukemia with and without Invasive Aspergillosis in first Induction

Candoni et al, Mycoses 2020



Secondary endpoint: The better outcome in a 4-years follow-up was observed in those patients of both groups that obtained a CR

Changes in the incidence and mortality of candidemia in patients with hematological malignancies in the last ten years. SEIFEM 2015-B report

Pagano et al, Haematologica 2017

	Historical cohorts (1999-2003)				Present survey (2011-2015)				
	Patients	Candidemia	Attributable mortality	Case Fatality Rate	Patients	Candidemia	Attributable mortality	Case Fatality Rate	p-value
AML		124 (4.1%)				70 (1.5%)			<0.001
	3012		44 (1.5%)		4581		14 (0.3%)		<0.001
				44/124 (35%)				14/70 (20%)	0.02
ALL		22 (1.9%)				15 (1.6%)			0.60
	1173		8 (0.7%)		954		0 (0%)		0.01
				8/22 (36%)				0/15	0.008
NHL		21(0.6%)				42 (0.5%)			0.45
	3457		4 (0.1%)		8452		10 (0.1%)		0.97
				4/21 (19%)				10/42 (24%)	0.66
MM		3 (0.2%)				8 (0.3%)			0.43
	1616		1 (0.06%)		2542		6 (0.2%)		0.18
				1/3 (33%)				6/8 (75%)	0.20
TOTAL		170 (1.8%)				135 (0.8%)			<0.001
	9258		57 (0.6%)		16529		30 (0.18%)		<0.001
				57/170 (34%)				30/135 (22%)	0.03

ECIL 5 update/ IDSA 2017/ECCMID 2017

Antifungal drugs for Prophylaxis in AML

Antifungal	ECIL 2015	IDSA 2017	ECCMID 2018
Posaconazole	A I	Strong recommendation; high-quality evidence	AI
Itraconazole	B I	Strong recommendation; moderate-quality evidence	D II
Fluconazole	B I	Not recommended	/
Voriconazole	B II	Strong recommendation; moderate-quality evidence	C II
L-AmB	C II	Not recommended	C II (all doses)
ABCD	C II	Not recommended	C III
Echinocandins	C II	Weak recommendation; low-quality evidence	C II (only Micafungin)
Aerosol L-AmB	B I	Not recommended	/
Aerosol AmB	A I against	Not recommended	B I (associated to Fluconazole)
AmB deoxycholate	A II against	Not recommended	/

Maertens et al, ECIL 5, 2013; Patterson et al, CID 2016; Ullmann et al, CMI 2018

Interactions of mould-active azoles with co-administered chemotherapeutic agents and targeted therapies

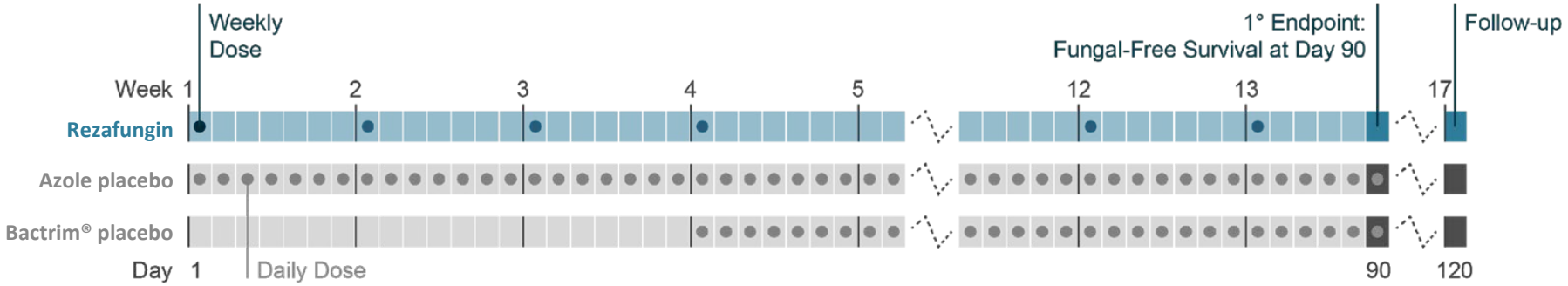
	Co-administered agent	Interaction mechanism	Effect	Recommendations and actions
ALL	**Vincristine**	Inhibition CYP3A4	Increased neurotoxicity	**Avoid combo**
	Cyclophosphamide	Inhibition CYP3A4/2C9	↑ Hepatotoxicity ↓ Activation to hydroxy-CTX	Monitor **Avoid combo**
	Imatinib	Inhibition CYP3A4	↑ Imatinib exposure	**Avoid combo**
	Dasatinib	Inhibition CYP3A4	↑ D. exposure, **↑ QT interval**	**Avoid combo, monitor ECG**
	Nilotinib	Inhibition CYP3A4	↑ N. exposure, **↑ QT interval**	**Avoid combo, monitor ECG**
	Ponatinib	Substrate CYP3A4	↓ TKI dosage	**Avoid combo**
AML	**Sorafenib**	Inhibition CYP3A4	No effect	**Monitor QTc**
	Midostaurin	Inhibition CYP3A4	↑ Adverse reaction	**Avoid combo, monitor QTc**
	Quizartinib	Inhibition CYP3A4	↑ Quizartinib exposure	**↓ Dose (40 mg → 20 mg)**
	Venetoclax	Inhibition CYP3A4	↑ Venetoclax exposure	**↓ Dose** 50% if moderate; 75% if potent

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CYP3A4, cytochrome P450 3A4; D., dastinib; ECG, electrocardiogram; N., nilotinib; TKI, tyrosine kinase inhibitor; QTc, corrected QT interval.
Adapted from Busca & Pagano. Exp Rev Anti-Infect Ther. 2018;16:531–542.

The ReSPECT Trial

Prophylaxis in HSCT

REZAFUNGIN
(N≅300)
400/200 mg once weekly

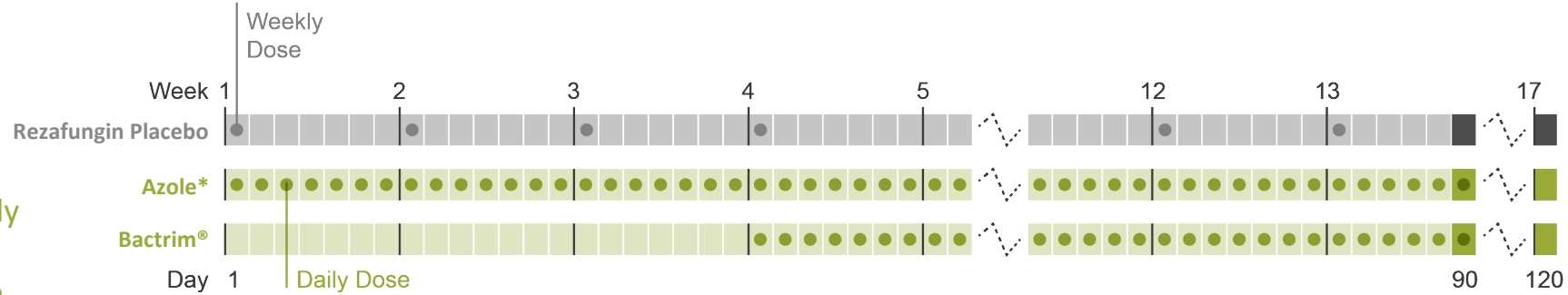


COMPARATOR
(N≅150)

400 mg fluconazole once daily*

80 mg TMP/400 mg SMX once daily

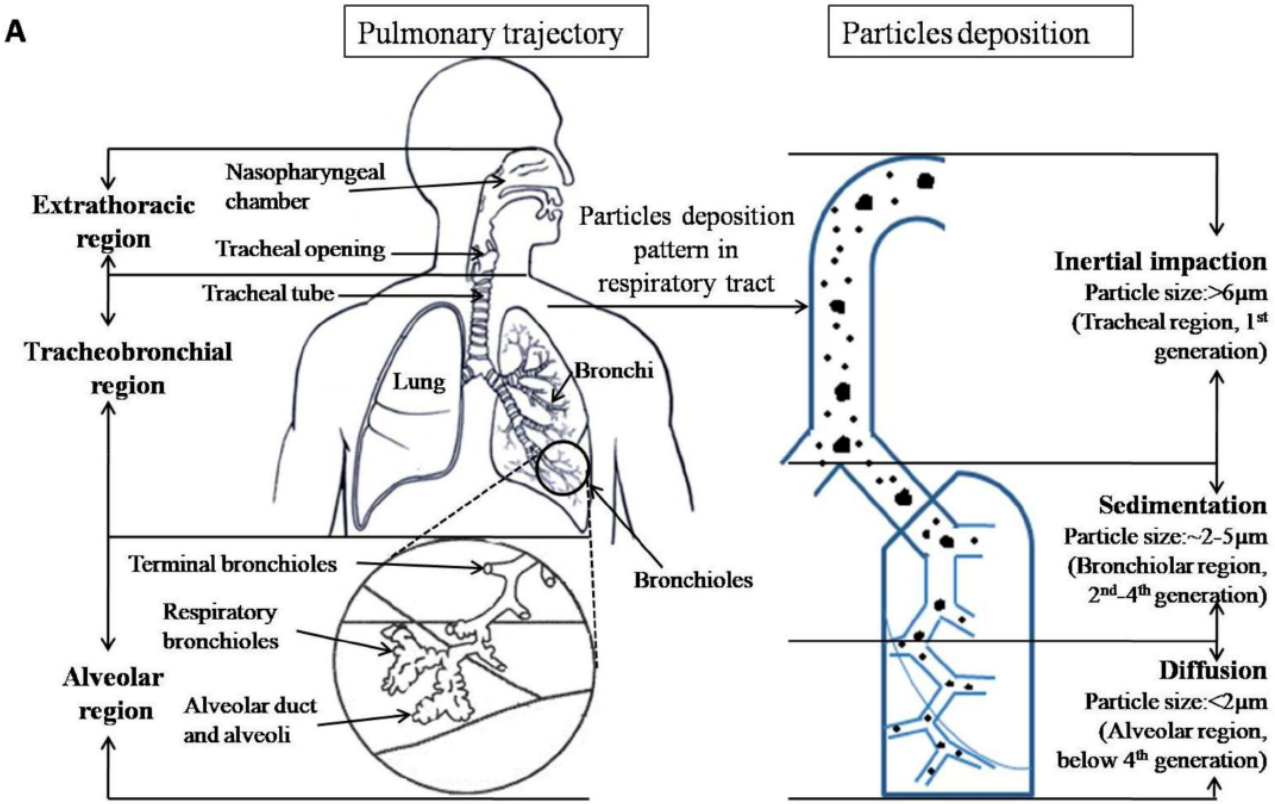
*Patients with acute GVHD can be switched to posaconazole

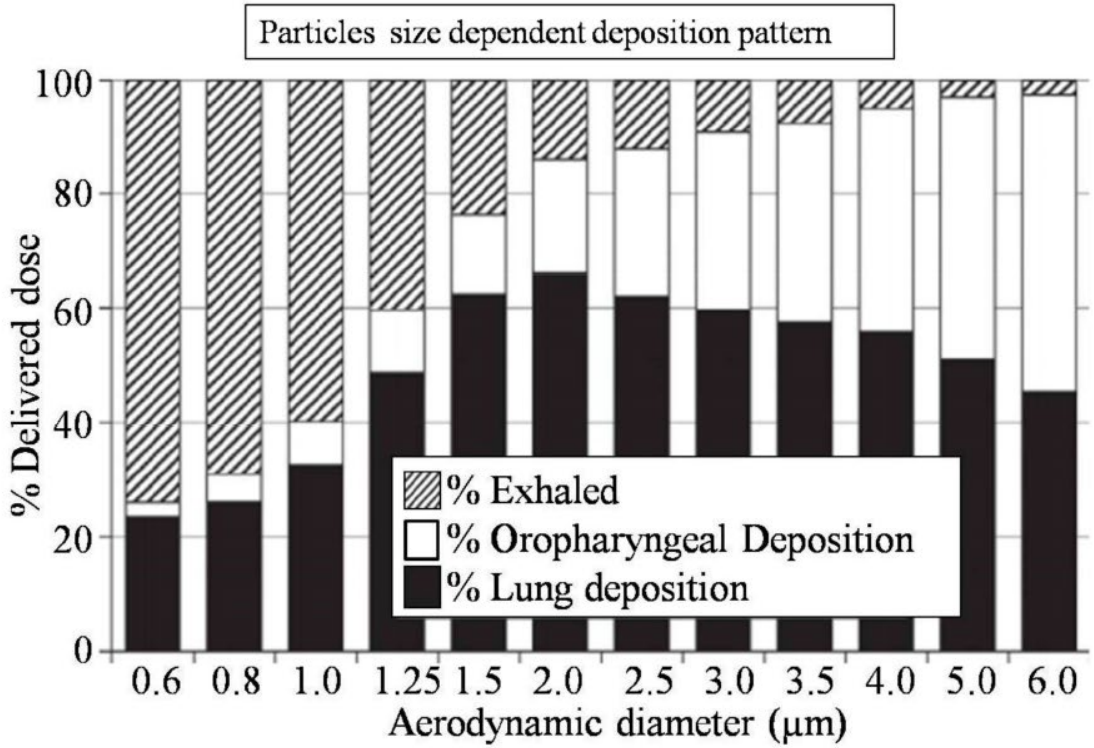


BMT, blood and marrow transplantation; GVHD, graft-versus-host disease; IFD, invasive fungal disease; SMX, sulfamethoxazole; TMP, trimethoprim.

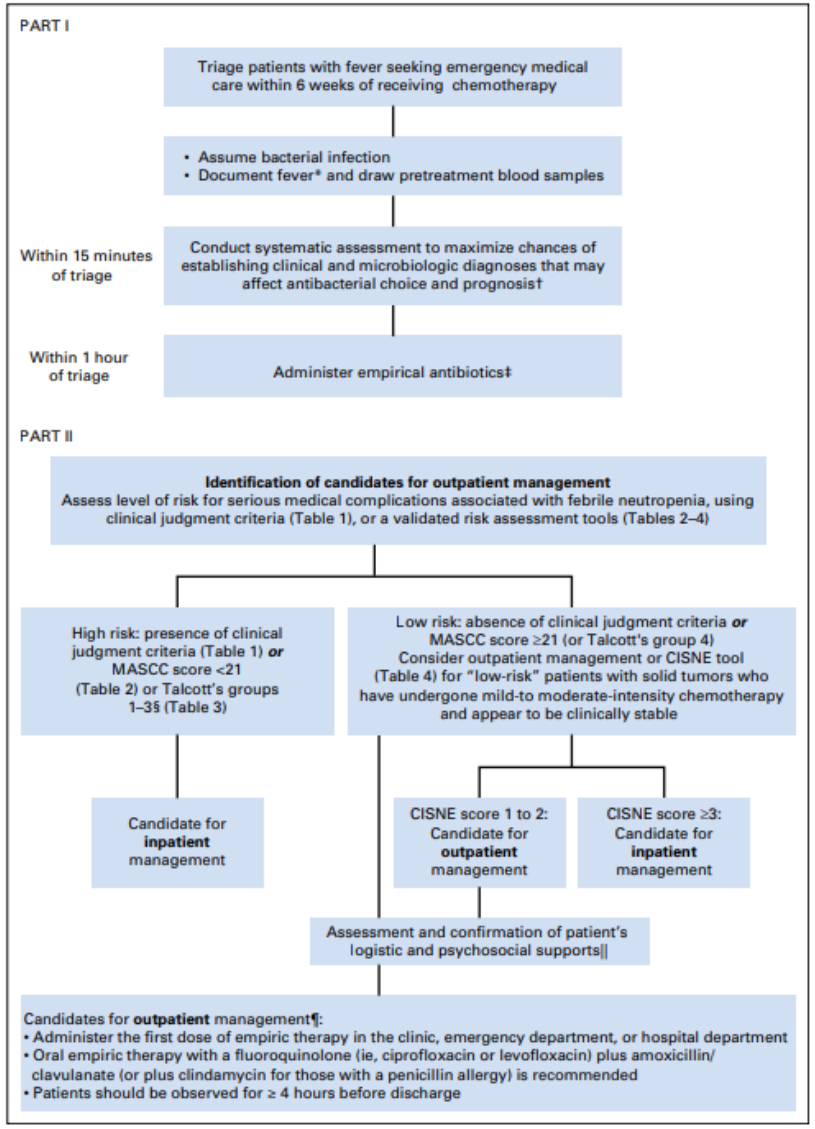
1. Clinicaltrials.gov NCT04368559 accessed 4 Feb 2021.

Dry Powder Inhaler





Empiric Therapy



Outpatient management

- Combination of ciprofloxacine and amoxicillin/clavulanate
- Persistence of fever for more than 2-3 days prompts re-evaluation of antibiotics therapy
- In case of signs and/or symptoms of infections, microbiological isolates, new onset of fever admission is mandatory
- Education of patients and care givers

ASCO/IDSA Taplitz et al JCO 2018

Empiric Therapy

Inpatient management

- Beta-lactam with anti pseudomonal activity, among which piperacilline/tazobactam is associated with lower mortality
- «Addition of aminoglycoside is generally non recommended except in case of septic shock» (??!!??)

Local epidemiology!

- Carbapenems are not recommended in absence of high suspicion of BSI caused by ESBL-producing Enterobacteriaceae
- Glycopepdides are not recommended yet in case of clinical manifestations, CVC insertion or high suspicion of MRSA

Paul et al Cochrane Database Syst Rev 2010

Freifeld et al Clin Infect Dis 2011

Mediterranean Journal of Hematology and Infectious Diseases

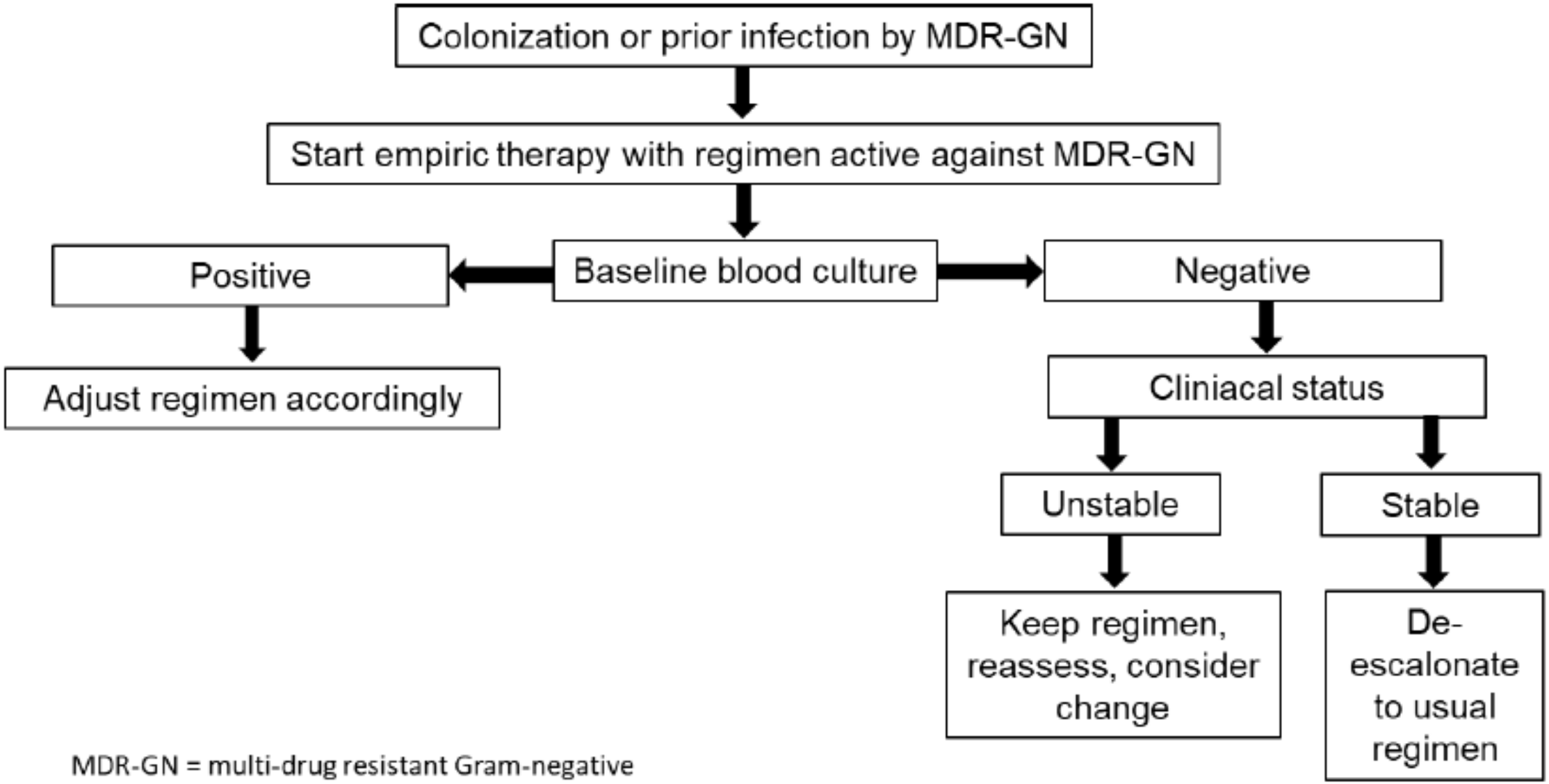
2021

Review Article

How I Treat Febrile Neutropenia

Marcio Nucci.

Action	My opinion	Comments
Antibacterial prophylaxis	Ciprofloxacin or levofloxacin	Autologous and allogeneic HCT, pre-engraftment Acute leukemia, induction Before deciding for quinolone prophylaxis, take into consideration local epidemiology and re-evaluate periodically in light of changes in the epidemiology
Antifungal prophylaxis	Fluconazole	AML induction, allogeneic HCT, pre-engraftment, low risk*
	Posaconazole or voriconazole	AML induction, allogeneic HCT, pre-engraftment, high risk*
Workup at first fever	Medical history, physical examination, blood cultures	Additional tests on a case per case basis
Monitor for MDR Gram-negative bacteria	Anal swab on admission	Consider weekly swabs if MDR in the unit
Empiric therapy	Cefepime	Empiric regimen should be active against colonizing MDR Gram-negative if the patient is colonized
Vancomycin in the initial regimen	No	Gram-positive infection is not associated with early death
Empiric vancomycin if persistently febrile	No	Add only if documented infection by MRSA
Empiric carbapenem if persistently febrile	No	Do not change the regimen if persistent fever only
Anal or abdominal pain	Metronidazole	If typhlitis is suspected, perform abdominal CT scan
Clinical deterioration	Carbapenem	Change to carbapenem even if afebrile
Empiric antifungal therapy	No	Perform serial serum galactomannan and images, and give preemptive therapy instead
Discontinuation of empiric therapy	With neutrophil recovery	Immediately if no documentation of infection
	No neutrophil recovery	If afebrile >3 days, provided that vital signs are normal



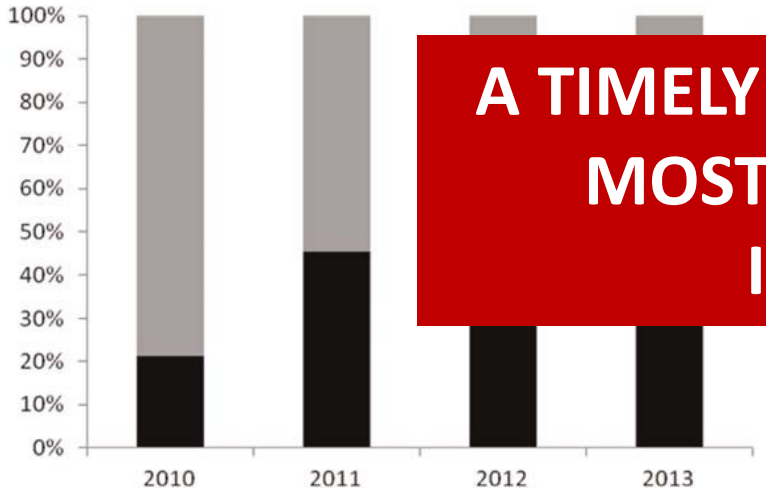
MDR-GN = multi-drug resistant Gram-negative

Nucci, MJHID 2021

Bloodstream infections caused by *Klebsiella pneumoniae* in onco-hematological patients: clinical impact of carbapenem resistance in a multicentre prospective survey

Predictors of mortality from *K. pneumoniae* BSI among patients with HM

Mortality 52.2%



A TIMELY AND TARGET TREATMENT IS THE MOST IMPORTANT PARAMETER TO IMPROVE MORTALITY !!!

Variables	HR	(95% IC)	*P* values
MODEL (A)			
Septic shock	3.86	(2.47–6.02)	<0.001
Acute respiratory failure	2.32	(1.45–3.70)	<0.001
Initial inadequate antimicrobial therapy	1.87	(1.08–2.22)	0.02
Carbapenem-resistance by KP isolate	1.85	(1.01–3.42)	0.04
MODEL (B)			
Septic shock	2.64	(1.57–4.45)	<0.001
Acute respiratory failure	2.83	(1.63–4.92)	<0.001
Combination therapy	0.32	(0.19–0.54)	<0.001

		vors (*n* = 177)	OR (95% IC)	*P* values
		104 (58.8)	2.13 (1.21–3.84)	0.005
		1 (0.6)	-	0.44
		17 (9.6)	0.92 (0.35–2.29)	0.84
		1 (0.6)	1.76 (0.02–138.92)	0.68
		35 (19.8)	0.35 (0.13–0.81)	0.008
		5 (2.8)	-	0.08
		3 (1.7)	1.78 (0.23–13.48)	0.48
		5 (2.8)	0.69 (0.06–4.34)	0.66
		43 (24.3)	2.13 (1.22–3.72)	0.004
Complete remission	6 (5.9)	51 (28.8)	0.16 (0.05–0.39)	<0.001
Refractory/Relapsed after 2 or more remissions	42 (41.6)	61 (34.5)	1.35 (0.79–2.31)	0.23
Hematopoietic stem cell transplantation	17 (16.8)	45 (25.4)	0.59 (0.30–1.14)	0.09
Autologous	3 (2.9)	15 (8.5)	0.33 (0.06–1.21)	0.07
Allogeneic-Matched Related	0	6 (3.4)	-	0.06
Allogeneic-Matched Unrelated	10 (9.9)	12 (6.8)	1.51 (0.56–3.98)	0.35
Allogeneic-Mismatched	4 (3.9)	12 (6.8)	0.57 (0.13–1.94)	0.33
Septic shock	58 (57.4)	13 (7.3)	17.02 (8.20–36.62)	<0.001
Altered state of consciousness	42 (41.6)	7 (4)	17.28 (7.10–47.56)	<0.001
Acute renal failure	29 (28.7)	7 (4)	9.78 (3.93–27.45)	<0.001
Acute respiratory failure	63 (62.4)	17 (9.7)	15.60 (7.87–31.44)	<0.001
Acute hepatic failure	18 (17.8)	2 (1.1)	18.97 (4.33–170.73)	<0.001
Inadequate initial antimicrobial therapy	79 (78.2)	73 (41.2)	5.11 (2.83–9.39)	<0.001
Carbapenem-resistance by KP isolate	84 (83.1)	77 (43.5)	6.41 (3.41–12.43)	<0.001

Trecarichi et al Am J Hematol 2016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