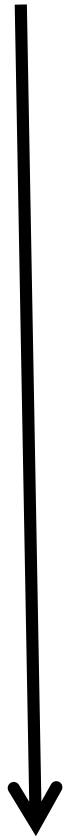
Stratégies de prise en charge des neutropénies fébriles

Etienne CANOUÏ
Equipe mobile d'infectiologie

Hôpital Cochin

PLAN:

- Les recommandations actuelles
- Définitions
- Epidémiologie
- Facteurs de risque/ pronostic
- Prise en charge initiale
- Prise en charge secondaire
- Proposition thérapeutique
- Prophylaxies



Cas clinique

Les recommandations actuelles

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]

GUIDELINE ARTICLE

European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia

Diana Averbuch,[1] Christina Orasch,[2] Catherine Cordonnier,[3] David M. Livermore,[4] Malgorzata Mikulska,[5] Claudio Viscoli,[5] Inge C. Gyssens,[6,7,8] Winfried V. Kern,[9] Galina Klyasova,[10] Oscar Marchetti,[2] Dan Engelhard,[1] and Murat Akova;[11] on behalf of ECIL4, a joint venture of EBMT, EORTC, ICHS, ESGICH/ESCMID and ELN

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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

Enferm Infecc Microbiol Clin. 2019;xxx(xx):xxx-xxx
Enfermedades Infecciosas y Microbiología Clínica
www.elsevier.es/eimc

Consensus statement

Executive summary of the consensus document of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Network for Research in Infectious Diseases (REIPI) and the Spanish Society of Haematology and Haemotherapy (SEHH) on the management of febrile neutropenia in patients with hematological malignancies☆

Carlota Gudiol[a,*], Manuela Aguilar-Guisado[b], José Ramón Azanza[c], Francisco Javier Candel[d], Rafael Cantón[e], Jordi Carratalà[a], Carolina Garcia-Vidal[f], Isidro Jarque[g], Manuel Lizasoain[h], José Molina Gil-Bermejo[h], Isabel Ruiz-Camps[i], Isabel Sánchez-Ortega[j], Carlos Solano[k], María Suárez-Lledó[i], Lourdes Vázquez[m], Rafael de la Cámara[n]

Infect Dis Ther (2022) 11:2063–2098
https://doi.org/10.1007/s40121-022-00700-1

GUIDELINES

The Dutch Working Party on Antibiotic Policy (SWAB) Recommendations for the Diagnosis and Management of Febrile Neutropenia in Patients with Cancer

J. R. de la Court · A. H. W. Bruns · A. H. E. Roukens · I. O. Baas · K. van Steeg · M. L. Toren-Wielema · M. Tersmette · N. M. A. Blijlevens · R. A. G. Huis in 't Veld · T. F. W. Wolfs · W. J. E. Tissing · Y. Kyuchukova · J. Heijmans

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Les recommandations locales

Ann Hematol (2014) 93:1083–1095
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

clinical practice guidelines

Annals of Oncology 21 (Supplement 5): v252–v256, 2010
doi:10.1093/annonc/mdq196

Management of febrile neutropenia: ESMO Clinical Practice Guidelines

J. de Naurois[1], I. Novitzky-Basso[2], M. J. Gill[3], F. Marti Marti[1], M. H. Cullen[1] & F. Roila[4]
On behalf of the ESMO Guidelines Working Group*

[1]Department of Medical Oncology; [2]Department of Haematology; [3]Department of Clinical Microbiology, University Hospital Birmingham NHS Foundation Trust, Birmingham, UK; [4]Department of Medical Oncology, S. Maria Hospital, Terni, Italy

Schnell et al. Ann. Intensive Care (2016) 6:90
DOI 10.1186/s13613-016-0189-6
Annals of Intensive Care

REVIEW Open Access

Management of neutropenic patients in the intensive care unit (NEWBORNS EXCLUDED) recommendations from an expert panel from the French Intensive Care Society (SRLF) with the French Group for Pediatric Intensive Care Emergencies (GFRUP), the French Society of Anesthesia and Intensive Care (SFAR), the French Society of Hematology (SFH), the French Society for Hospital Hygiene (SF2H), and the French Infectious Diseases Society (SPILF)

David Schnell[1], Elie Azoulay[2], Dominique Benoit[3], Benjamin Clouzeau[4], Pierre Demaret[5], Stéphane Ducassou[6], Pierre Frange[7], Matthieu Lafaurie[8], Matthieu Legrand[9], Anne-Pascale Meert[10], Djamel Mokart[11], Jérôme Naudin[12], Frédéric Pene[13], Antoine Rabbat[14], Emmanuel Raffoux[15], Patricia Ribaud[16], Jean-Christophe Richard[17], François Vincent[18], Jean-Ralph Zahar[19] and Michael Darmon[20,21*]

M.D, 50 ans

- Origine algérienne
- Pas d'antécédent notable, pas d'intoxication éthylo-tabagique.
- Avocat, marié, 2 enfants
- Diagnostic il y a 1 mois d'une LAM sur syndrome hémorragique associé à une neutropénie (PNN=0,4G/L)
- Hospitalisé en France pour chimiothérapie d'induction (Daunorubicine+ Cytarabine)
- A J8 de l'induction, aplasie fébrile.

Définition?
Fréquence?
Gravité?

Définitions

- **Fièvre**: T°c buccale ≥ 38,3°c une fois ou ≥ 38°c pendant 1h
- Pas de T°c Rectale chez le neutropénique

- **Neutropénie**: PNN< 500/ mm3 ou PNN< 1000/ mm3 avec une évolution prédite < 500/ mm3.

- Neutropénie profonde: <100/ mm3

- « Neutropénie fonctionnelle »

- **Haut vs bas risque**:
  - Nadir: 500/ mm3
  - Durée: 7jours
  - Anomalie fonctionnelle des PNN/ Déficit immunitaire associé

Averbuch et al, ECIL-4, Haematologica 2013
Freifeld et al, CID 2011

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COMMISSION DES ANTI-INFECTIEUX – COMAI

Version 3 – mai 2022
Groupe de travail : A. Contejean / C. Charlier / E. Canouï / D. Bouscary / J. Decroocq
Relecteurs : Laurent Chouchana/ Jeremie Zerbit/ Hélène Poupet

Conduite à tenir devant une neutropénie fébrile (NF)

<500 polynucléaires neutrophiles/mm3
Ou <1000 leucocytes/mm3 et baisse attendue < 500 polynucléaires neutrophiles/mm3 dans les 48 heures
ET
Température ≥ 38,3°C une fois ou ≥ 38°C à deux reprises à une heure d'intervalle
Ou température < 36°C

Épidémiologie

- 10-50% de NF dans le cadre de tumeur solide
- > 80% de NF dans le cadre d'hémopathies
- 20-30% des NF sont des infections documentées
- 20-30% des patients avec PNN< 100 (LAM/ Greffe de moelle) auront une bactériémie (5-7% en cas de tumeur solide).

=> Fréquent/ Répété/ Rarement documenté

Cullen et al NEJM 2005
Bucaneve et al NEJM 2005;353:977-87
Akova et al CID 2005

Définitions - 4 situations clinique

Fièvre d'origine indéterminée

Fièvre avec documentation microbiologique

Fièvre avec documentation clinique

Origine non infectieuse certaine

Médicament, pathologie, PSL…

Diapo empruntée à A. Contejean

Modèles expérimentaux

- Animal neutropénique:
  - Infection plus fréquente
  - Infection plus rapide
  - Inoculums plus faibles
  - Point de départ digestif (translocation)
  - Peu de signes inflammatoires
  - Décès plus fréquent

Diapo empruntée à S.Alfandari

Facteurs de risque épisode fébrile

- **Compétence immunologique de l'hôte**
  - Neutropénie: profondeur et durée
  - Immunosuppresseurs
    - Cytotoxiques
    - Anticorps monoclonaux
    - Corticoïdes
    - Immunosuppresseurs (allogreffe)
  - GVH
  - Irradiation corporelle totale
  - Comorbidités
- **Altération des barrières**
  - Muqueuses :
    - agents cytotoxiques: Mucite
    - irradiation
    - altération de la flore
  - Dispositifs invasifs : cathéter

Diapo empruntée à S.Alfandari

Mortalité des infections bactériennes

- Neutropénies fébriles
  - Enfant (n=759): 1%
  - Adulte (n=2321): 4%
- Bactériémies (Etudes EORTC)
  - 21% en 1978
  - 7% en 1994
  - 10% si BGN, 6% si Gram+
- Mortalité variant en fonction du type de NF (Haut vs Bas risque)

Cannas et al. Leuk Lymphoma 2012
Hann, Br J Haematol 1997

Neutropénie: sepsis sévère, choc et survie

Variable, N (%) or Median (25th–75th)	Alive (n = 215)	Dead (n = 213)	Odds Ratio (95% Confidence Interval)	*p*
Age, yrs	47 (35–57)	54 (43–65)	1.036 (1.02–1.05)	<.0001
Intensive care unit admission during the second period (between 2004 and 2008)	139 (64.6)	105 (49.3)	0.56 (0.36–0.89)	.01
Shock	123 (57.2)	181 (85.0)	2.69 (1.65–4.38)	<.0001
Acute respiratory failure	61 (28.4)	171 (80.3)	1.98 (1.14–3.44)	.015
Neurologic failure	7 (3.2)	37 (17.4)	4.03 (1.03–15.8)	.04
Hepatic failure	7 (3.2)	20 (9.4)	1.49 (1.16–1.91)	.002
Early acute noninfectious conditions	77 (35.8)	98 (46.0)	1.69 (1.06–2.68)	.02
Initial combination antibiotic therapy	210 (97.7)	181 (85.0)	0.164 (0.05–0.51)	.002
Indwelling catheter removal	68 (31.6)	39 (18.3)	0.50 (0.30–0.85)	.01

Mortalité
- Réa: 40,1%
- Hôpital: 49,8%
- 6 mois: 63,3%

Legrand, CCM 2012

Shock and Early Death in Hematologic Patients with Febrile Neutropenia

Mariana Guarana,[1] Marcio Nucci,[2]# and Simone A. Nouér[3] AAC 2019

1305 NF en hématologie, hemoc + dans 30%, mortalité à J30=8,3%

Table 4: Multivariate analysis of factors associated with shock and early death among 1,305 episodes of febrile neutropenia

	OR	95% CI	p
Shoch			
Bacteremia due to *Escherichia coli*	8.47	4.08 – 17.55	<0.001
Bacteremia due to *Enterobacter* sp.	7.53	1.60 – 35.33	0.01
Bacteremia due to *Acinetobacter* sp.	6.95	1.49 – 32.36	0.01
Early death			
Non-Hodgkin's lymphoma	3.57	1.18 – 10.73	0.02
Pneumonia	21.36	5.72 – 79.72	<0.001
Shock	11.64	2.77 – 48.86	0.01
Bacteremia due to *Klebsiella pneumoniae*	5.91	1.11 – 31.47	0.03
Adequate empiric antibiotic therapy	0.23	0.07 – 0.81	0.02

OR = odds ratio; 95% CI = 95% confidence interval

Contejean *et al. Ann. Intensive Care (2016) 6:102*
DOI 10.1186/s13613-016-0202-0

Annals of Intensive Care

RESEARCH Open Access

Increased mortality in hematological malignancy patients with acute respiratory failure from undetermined etiology: a *Groupe de Recherche en Réanimation Respiratoire en Onco-Hématologie* (Grrr-OH) study

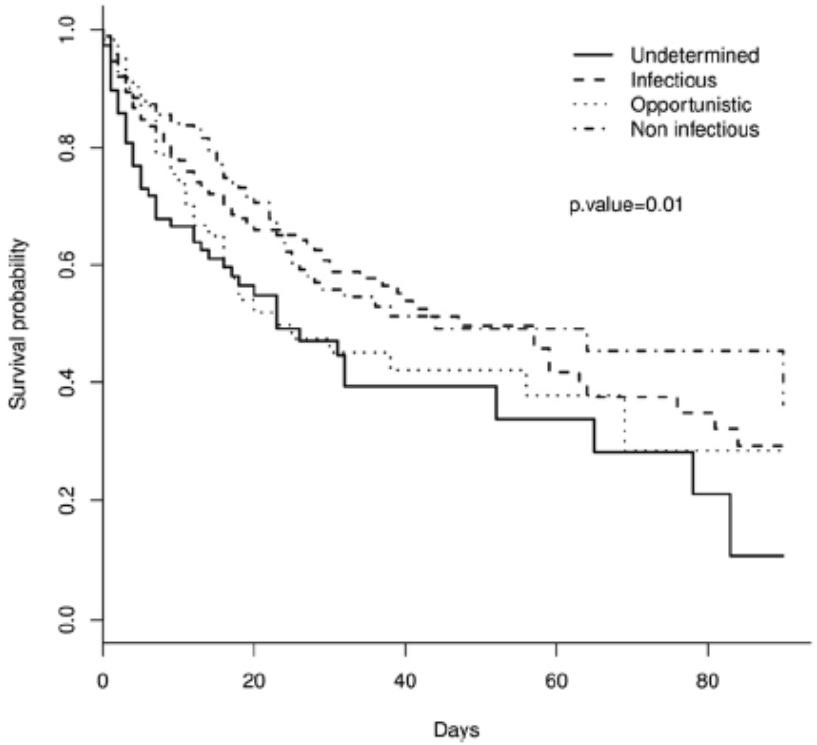


Fig. 3 Hospital mortality according to diagnostic category. Survival

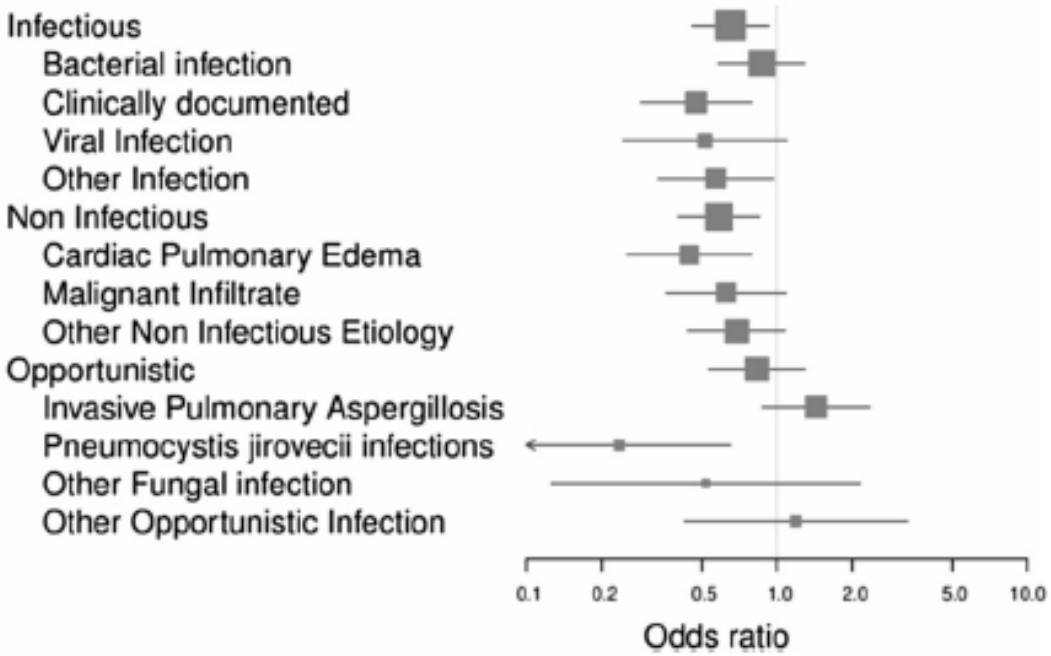


Fig. 2 Hospital mortality according to ARF etiology (univariate analysis). Undetermined ARF etiology has been used as a reference

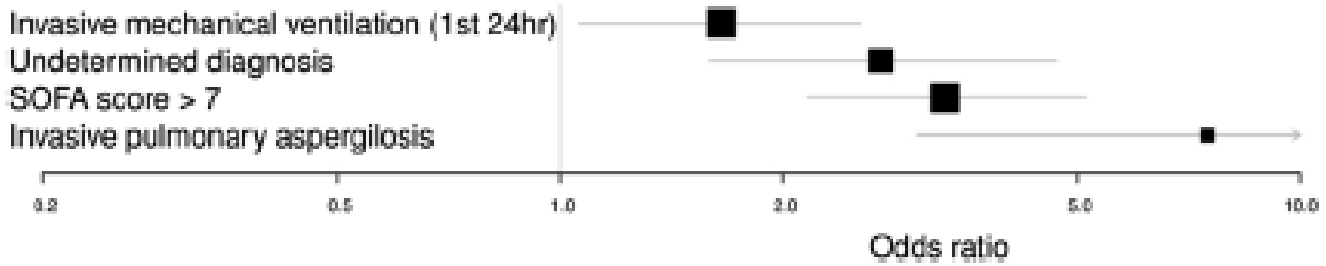


Fig. 4 Multivariable analysis of risk factors for hospital mortality. *Box*

M.D 50 ans, suite

- Vous pensez qu'il faut débuter un traitement Antibiotique rapidement.
- Quels germes ciblez-vous?
- De quelles informations microbiologiques avez-vous besoin?

Épidémiologie

Table 2. Bacterial causes of febrile episodes in neutropenic patients.

Gram-positive cocci and bacilli	*Chryseobacterium meningosepticum*
Staphylococcus species[a]	*Burkholderia cepacia*
Coagulase-positive (*Staphylococcus aureus*)	*Fusobacterium nucleatum*
Coagulase negative (*Staphylococcus epidermidis* and others)	*Leptotrichia buccalis*
Streptococcus species[a]	*Methylobacterium* species
Streptococcus pneumoniae	Anaerobic cocci and bacilli
Streptococcus pyogenes	*Bacteroides* species
Viridans group	*Clostridium* species
Enterococcus faecalis/faecium[a]	*Fusobacterium* species
Corynebacterium species[a]	*Propionibacterium* species
Bacillus species	*Peptococcus* species
Listeria monocytogenes	*Veillonella* species
Stomatococcus mucilaginosus	*Peptostreptococcus* species
Lactobacillus rhamnesus	
Leuconostoc species	
Gram-negative bacilli and cocci	
Escherichia coli[a]	
Klebsiella species[a]	
Pseudomonas aeruginosa[a]	
Enterobacter species	
Proteus species	
Salmonella species	
Haemophilus influenzae	
Acinetobacter species	
Stenotrophomonas maltophilia	
Citrobacter species	
Flavobacterium species	
Chromobacterium species	
Pseudomonas species (other than *P. aeruginosa*)	
Legionella species	
Neisseria species	
Moraxella species	
Eikenella species	
Kingella species	
Gardnerella species	
Shigella species	
Erwinia species	
Serratia marcescens	
Hafnia species	
Flavimonas oryzihabitan	
Achromobacter xylosoxidans	
Edwardsiella species	
Providencia species	
Morganella species	
Yersinia enterocolitica	
Capnocytophaga species	
Alcaligenes xylosoxidans	
Vibrio parahaemolyticus	

[a] The most common causes of bacteremia.

Table 1. Common Bacterial Pathogens in Neutropenic Patients

Common gram-positive pathogens
Coagulase-negative staphylococci
Staphylococcus aureus, including methicillin-resistant strains
Enterococcus species, including vancomycin-resistant strains
Viridans group streptococci
Streptococcus pneumoniae
Streptococcus pyogenes
Common gram-negative pathogens
Escherichia coli
Klebsiella species
Enterobacter species
Pseudomonas aeruginosa
Citrobacter species
Acinetobacter species
Stenotrophomonas maltophilia

Augmentation de la proportion des infections à BLSE, Pyo cefta-R

SARM: en diminution en France

ERV: rare

Mycologie: seconde cause surtout si pression ATB, NF prolongée

Hughes et al, CID 2002
Freifeld et al, CID 2011

infections et allogreffe de moelle

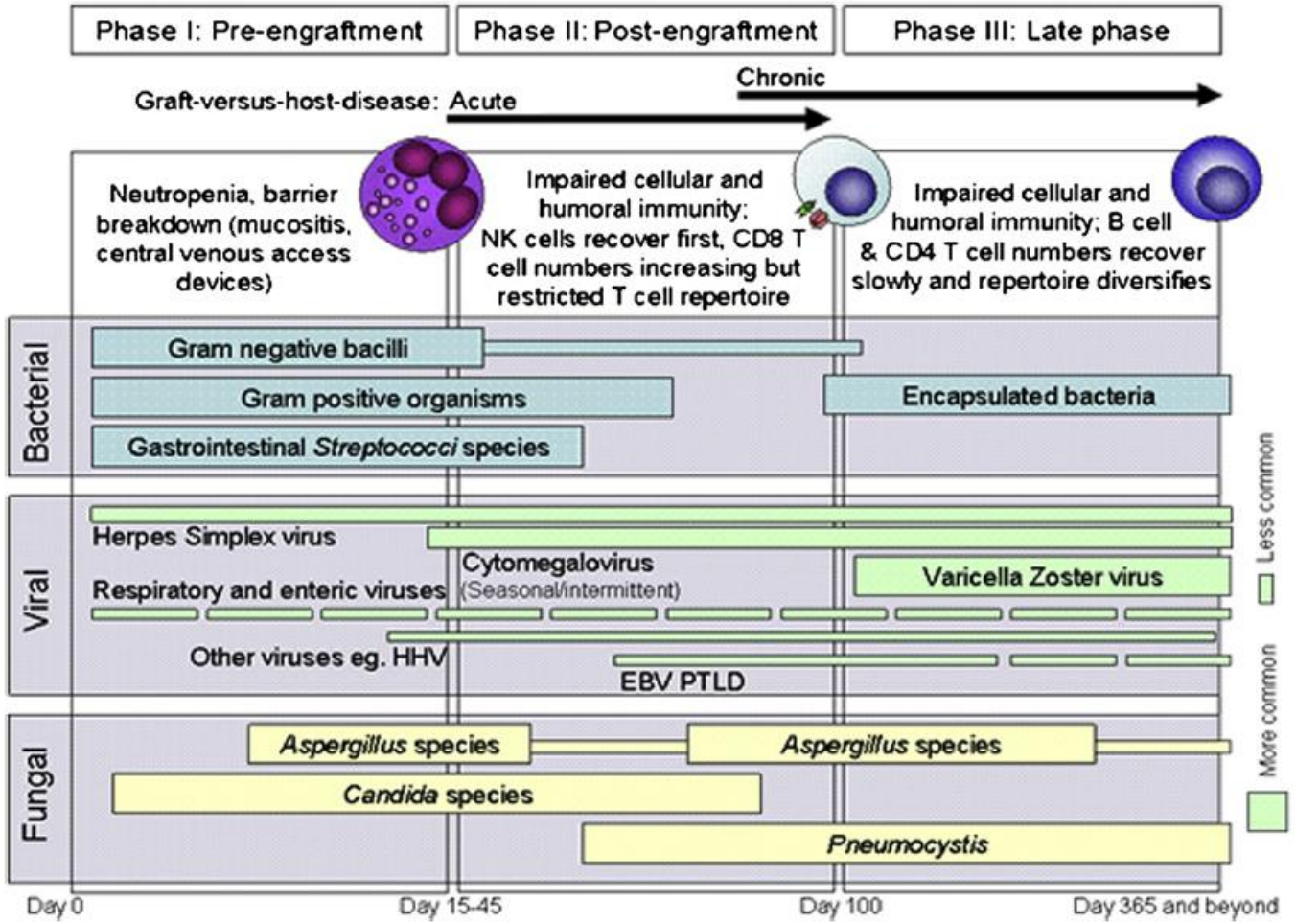


Figure 2. Phases of opportunist[illegible]fections among allogeneic HCT recipients Abbreviations: EBV, Epstein-Barr virus; HHV6, human herpesvirus 6; PTLD, posttransplant lymphop[illegible]e disease.

Marcie Tomblyn et al, Biol Blood Marrow Transplant 2009

Neutropénie fébrile: Epidémiologie

- Etude multicentrique française < 2003 (n=513)
  - Fièvre d'origine inconnue: 59%
  - Fièvre cliniquement documentée: 8%
  - Fièvre microbiologiquement documentée: 33% (dont 88% de bactériémies)

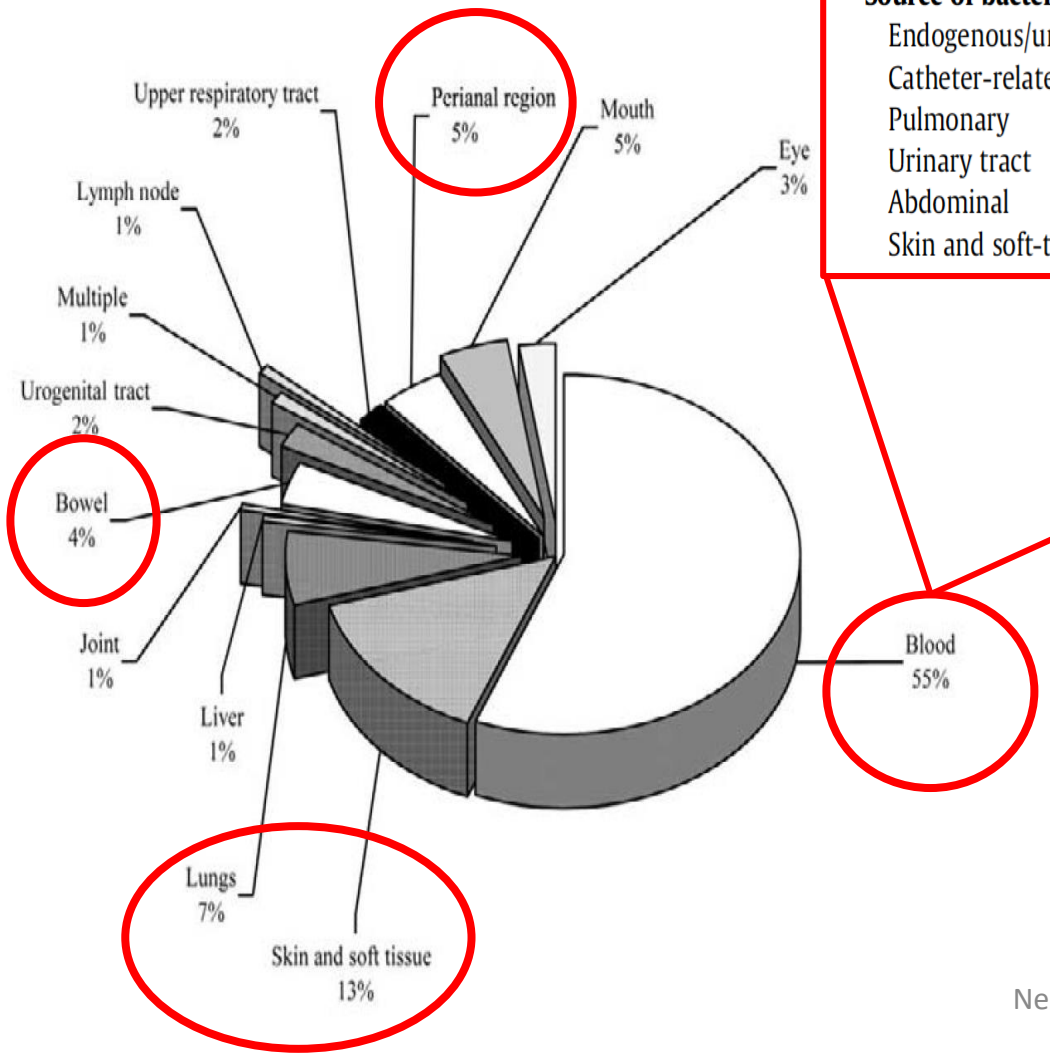
❖**CG+: 63.9%**
- SCN: 30.8%
- Strepto: 23.7%
- *S. aureus*: 8.3%

❖**BGN: 33.1%**
- *E. coli*: 17.7%
- *Pseudomonas*: 7.7%

Cordonnier et al, Haematologica 2005.

Particularités du patient neutropénique

Portes d'entrées multiples…



Source of bacteraemia	
Endogenous/unknown	485 (57.1)
Catheter-related	182 (21.4)
Pulmonary	71 (8.4)
Urinary tract	44 (5.2)
Abdominal	33 (3.9)
Skin and soft-tissue infection	27 (3.2)

… parfois difficiles à identifier !

Diagnoses, no. (%) of primary febrile episodes	
FUO	483/614 (79)
MDI with bacteremia	59/614 (10)
MDI without bacteremia	19/614 (3)
CDI	40/614 (6)
Invasive mycosis	13/614 (2)

Castagnola, CID, 2007
Puerta-Alcalde, CMI, 2018

Epidémiologie: un switch en hémato?

TABLE 2. Causal pathogens responsible for bacterial bloodstream infections in patients with hematologic malignancies according to neutropenic status

Microorganism	Total (*n* = 668)	Neutropenic (*n* = 616)	Nonneutropenic (*n* = 52)	p
Gram negative, total	353 (52.8)	335 (54.4)	18 (34.6)	0.006
Escherichia coli	187 (27.9)	181 (29.4)	6 (11.5)	0.006
Klebsiella pneumoniae	43 (6.4)	39 (6.3)	4 (7.7)	0.70
Enterobacter cloacae	26 (3.4)	24 (3.9)	2 (3.8)	0.98
Pseudomonas aeruginosa	66 (9.9)	63 (10.2)	3 (5.8)	0.30
Acinetobacter baumannii	3 (0.4)	3 (0.5)	0	0.61
Stenotrophomonas maltophilia	9 (1.3)	8 (1.3)	1 (1.9)	0.71
Gram positive, total	311 (46.6)	277 (44.9)	34 (65.4)	0.004
Coagulase-negative staphylococci	166 (24.8)	148 (24.0)	18 (34.6)	0.09
Staphylococcus aureus	11 (1.6)	7 (1.1)	4 (7.7)	<0.001
Viridans group streptococci	36 (5.4)	35 (5.7)	1 (1.9)	0.25
Streptococcus pneumoniae	2 (0.3)	0	2 (3.8)	<0.001
Enterococcus spp.	67 (10.1)	63 (10.2)	4 (7.7)	0.56
Enterococcus faecalis	27 (4.1)	24 (3.9)	3 (5.8)	0.51
Enterococcus faecium	37 (5.5)	36 (5.8)	1 (1.9)	0.23
Anaerobes	4 (0.6)	4 (0.6)	0	0.56

TABLE 3. Antimicrobial susceptibility profiles of all Gram-negative bacteria and of most frequently isolated bacterial species

Gram negative microorganism	Total	Susceptible, *n* (%) Ceftazidime	Ciprofloxacin	Meropenem	Amikacin	Gentamicin	Piperacillin/tazobactam
Total[a]	344	203 (59.1)	69 (20.1)	272 (79.1)	293 (85.2)	238 (69.2)	240 (69.8)
Escherichia coli	187	131 (70.0)	18 (9.6)	184 (98.4)	183 (97.9)	155 (82.9)	156 (83.4)
Klebsiella pneumoniae	43	18 (41.9)	13 (30.2)	28 (65.1)	25 (58.1)	29 (67.4)	19 (44.2)
Enterobacter doacae	26	12 (46.1)	13 (50.0)	24 (92.3)	23 (88.5)	23 (88.5)	12 (46.1)
Pseudomonas aeruginosa	66	30 (45.4)	13 (19.7)	19 (28.8)	43 (65.1)	15 (22.7)	38 (57.6)

[a]Total of Gram-negative bacteria was 344; nine *Stenotrophomonas maltophilia* isolates were excluded.

1991-1996 **2006-2010**

TABLE 2. Causative organisms of all episodes of bacteremia compared by study periods

Causative organisms	First period *n* = 272 (%)	Second period *n* = 283 (%)	p
Gram-positive bacteria	174 (64)	116 (41)	<0.001
Staphylococcus aureus	10 (6)	14 (12)	–
Methicillin-resistant *S. aureus*	1 (17)[a]	4 (28.6)[a]	–
Coagulase-negative staphylococci	81 (46.5)	50 (43)	–
Corynebacterium spp.	8 (5)	4 (3)	–
Viridans group streptococci	71 (42)	22 (23)	–
Streptococcus pneumoniae	6 (3)	7 (6)	–
Enterococcus spp.	10 (6)	26 (23)	–
E. faecalis	3 (30)[b]	10 (38.5)[b]	–
E. faecium	6 (60)[b]	13 (50)[b]	–
E. gallinarum	1 (10)[b]	3 (11.5)[b]	–
Gram-negative bacteria	75 (28)	138 (49)	<0.001
Escherichia coli	50 (67)	71 (51)	–
Pseudomonas aeruginosa	20 (27)	32 (23)	–
Klebsiella pneumoniae	5 (7)	31 (22)	–
Klebsiella oxytoca	0	1 (1)	–
Proteus mirabilis	0	3 (2)	–
Enterobacter cloacae	6 (7)	12 (9)	–
Acinetobacter baumannii	1 (1)	2 (1)	–
Stenotrophomonas maltophilia	0	2 (1)	–
Multi-drug resistant gram-negative bacilli[c]	2 (3)	16 (11)	0.04
Anaerobes	5 (2)	8 (3)	0.57
Prevotella spp.	3	0	–
Fusobacterium spp.	2 (40)	4 (50)	–
Bacteroides spp.	0	2	–
Clostridium spp.	1	2	
Fungi	4 (1.5)	12 (4)	0.074
Candida tropicalis	3	7	–
Candida glabrata	0	4	–
Candida krusei	2	0	–
Candida parapsilosis	1	0	–
Fusarium solani	0	1	–
Polymicrobial bacteraemia[d]	35 (13)	26 (9)	0.17

[a]Percentage of methicillin-resistant *S. aureus* among all *S. aureus* isolates.
[b]Percentage of different *Enterococcus* spp. among all enterococcal isolates.
[c]Multidrug-resistant gram-negative bacilli: extended spectrum β-lactamase-producing *Enterobacteriaceae*, AmpC cephalosporinase hyperproducing *Enterobacteriaceae*, multi-drug resistant *P. aeruginosa*, *S. maltophilia*, and *A. baumannii*.
[d]Polymicrobial bacteraemia was defined as a bloodstream infection caused by at least two different microorganisms.

Trecarichi et al, CMI 2015
Gudiol et al, CMI 2012

Aetiology and resistance in bacteraemias among adult and paediatric haematology and cancer patients

Małgorzata Mikulska [a,*], Claudio Viscoli [a], Christina Orasch [b], David M. Livermore [c], Diana Averbuch [d], Catherine Cordonnier [e], Murat Akova [f], on behalf of the Fourth European Conference on Infections in Leukemia Group (ECIL-4), a joint venture of EBMT, EORTC, ICHS, ELN and ESGICH/ESCMID

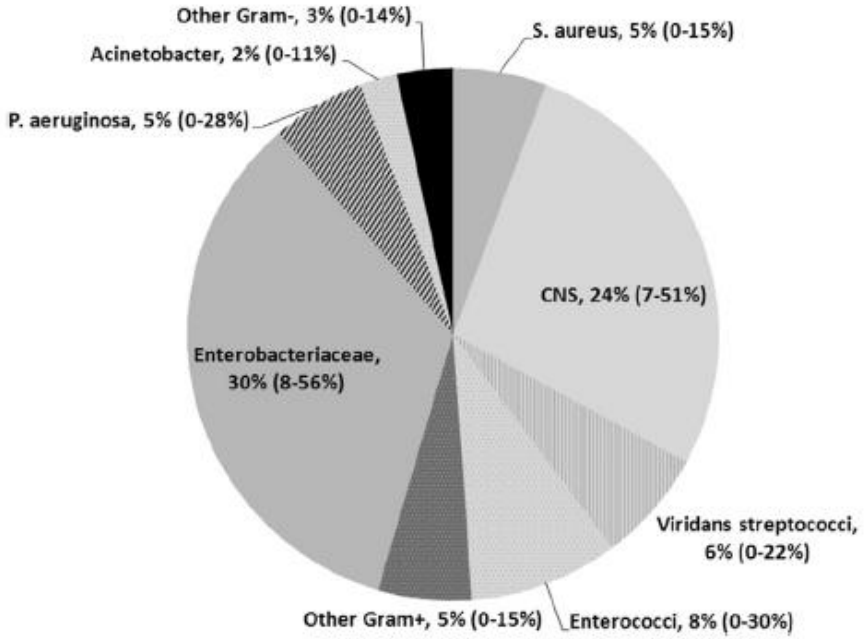


Table 2 Causative agents of all episodes of bloodstream infection in patients with haematological malignancies and solid tumours.

Causative organisms	Haematological malignancies	Solid tumours	*p*
Gram-positive bacteria	206 (41.8)	27 (31.4)	0.075
Coagulase-negative staphylococci	94 (45.6)	6 (22.2)	0.005
Viridans group streptococci	39 (18.9)	6 (22.2)	1.0
Enterococcus spp	44 (21.3)	2 (7.4)	0.032
Streptococcus pneumoniae	12 (5.8)	3 (11.11)	0.476
Staphylococcus aureus	24 (11.6)	5 (18.5)	0.788
Methicillin resistant S. aureus	7 (29.1)	1 (20)	1.00
Gram-negative bacilli	234 (47.5)	52 (60.5)	0.027
Escherichia coli	121 (51.7)	19 (36.5)	0.684
Klebsiella pneumoniae	54 (23)	12 (23)	0.461
Pseudomonas aeruginosa	52 (22.2)	22 (42.3)	<0.001
Enterobacter cloacae	20 (8.5)	1 (1.92)	0.343
MDR gram-negative bacilli[a]	36 (15.4)	2 (3.84)	0.1
ESBL-producing Enterobacteriaceae[b]	21 (58.3)	2 (2.4)	0.556
Stenotrophomonas maltophilia	9 (25)	0 (0)	0.369
AmpC-producing Enterobacteriaceae	3 (8.3)	0 (0)	1.000
MDR *Pseudomonas aeruginosa*[a]	2 (3.33)	0 (0)	1.000
Acinetobacter baumannii	1 (2.7)	0 (0)	1.0
Anaerobes	11 (2.2)	3 (3.5)	0.448
Polymicrobial	51 (10.3)	8 (9.3)	1.0
Fungi[c]	11 (2.2)	0 (0)	0.369

[a] MDR: Multidrug-resistant.
[b] ESBL: Extended-spectrum β-lactamase.
[c] Fungi BSI: Candida spp 10, *Fusarium solani* 1.

Bloodstream infections in neutropenic patients with cancer: Differences between patients with haematological malignancies and solid tumours

Mar Marin [a,*], Carlota Gudiol [b,c], Carmen Ardanuy [d,g], Carol Garcia-Vidal [b,c], Mariona Calvo [a], Montserrat Arnan [e,f], Jordi Carratalà [b,c]

Clinical Infectious Diseases

SUPPLEMENT ARTICLE

Bacterial Pathogens Differed Between Neutropenic and Non-neutropenic Patients in the Same Hematological Ward: An 8-Year Survey

Jun Zhu,[a] Kun Zhou,[a] Ying Jiang, Huixia Liu, Haitao Bai, Jieling Jiang, Yanrong Gao, Qi Cai, Yin Tong, Xianmin Song, Chun Wang, and Liping Wan

Department of Hematology, Shanghai Jiao Tong University-affiliated Shanghai General Hospital, China

Table 3. Comparison of Antibiotic Resistance Rates of Enterobacteriaceae and Non-fermentative Gram-negative Bacilli Isolated From Neutropenic and Non-neutropenic Patients

	Enterobacteriaceae			Non-fermentative Gram-negative Bacilli		
Antibiotics	Neutropenic Patients (n = 108)	Non-neutropenic Patients (n = 243)	*P* Value	Neutropenic Patients (n = 133)	Non-neutropenic Patients (n = 139)	*P* Value
Piperacillin	61.0	55.7	>.05	29.6	23.9	>.05
Ampicillin	93.9	91.5	>.05			
Gentamycin	40.4	37.2	>.05	19.6	23.9	>.05
Amikacin	14	9.3	>.05	20.8	14.7	>.05
Cefazolin	70.6	65.3	>.05			
Cefaclor	58.0	62.1	>.05			
Cefuroxime	52.6	50.4	>.05			
Ceftazidime	19.3	15.0	>.05	21.4	23.2	>.05
Cefotaxime	41.9	35.9	>.05			
Cefepime	31.6	18.4	<.01	11.3	20.6	<.05
Cefprozil	58.8	54.3	>.05			
Ciprofloxacin	45.6	47.3	>.05	3.8	19.7	<.01
Trimethoprim-Sulfamethoxazole	54.7	48.9	>.05	9.7	40.4	<.01
Imipenem	1.8	0.8	>.05	42.1	20	<.01
Meropenem	1.6	0.7	>.05	31.6	20.3	<.05
Cefoperazone sulbactam	12.9	9.9	>.05	9.1	7.9	>.05
Piperacillin tazobactam	12.3	14.3	>.05	18.6	15.1	>.05
Minocycline				23.8	31.8	>.05
Total	91 (100)			116 (100)		

Particularités du patient neutropénique

Etude bicentrique espagnole
Hémocs + 2010-2019
N=1563

Cocci Gram +	42%
SCN	19%
S aureus	5%
MRSA	17%
Enterocoque	14%
faecalis	30%
faecium	67%
ERV	5%
Streptocoque	6%
Pneumocoque	17%

Bacilles Gram -	56%
E coli	24%
BLSE	21%
Carbapénémase	1%
K pneumonae	9%
BLSE	23%
Carpabénépase	2%
P aeruginosa	15%
MDR	25%
XDR	16%
Enterobacter spp.	4%
HCASE	16%
S. maltophilia	2%
BGN MDR	13%

Candidémie	3%
albicans	22%
Non *albicans*	78%

Polymicrobien	12%

→ Niveaux élevés de résistances → **EPIDEMIO LOCALE!!!!**

Chumbita, AAC, 2021

M.D 50 ans, suite

- Avant de débuter le traitement, quelle évaluation clinico-radio-biologique réalisez vous?
- Est-ce que cette évaluation va impacter votre choix thérapeutique?

Evaluation initiale

- **<u>Bilan systématique du patient en aplasie fébrile : avant le début de l'antibiothérapie</u>**
- NFS, Ionogramme sanguin, urée et créatinine plasmatiques.
- Bilan hépatique complet : ASAT, ALAT, gamma-GT, phosphatases alcalines, bilirubinémie totale et conjuguée.
- Hémocultures : deux paires (aérobie + anaérobie) sur deux sites différents
  - Si voie veineuse centrale (PAC, Picc-Line, KT central) : hémocultures différentielles
    - Hémocultures prélevées au même moment sur tous les sites
    - Avec une quantité suffisante d'au moins 8- 10ml de sang par flacon
    - Et la même quantité de sang dans tous les flacons
    - Débuter par le flacon aérobie
- Radiographie de thorax au lit
- Écouvillon naso-pharyngé PCR grippe et SARS-CoV-2 en période épidémique

- **<u>Bilan orienté selon la clinique : ne doit pas retarder le début de l'antibiothérapie</u>**
- Si signe de gravité : Gaz du sang artériels + lactates, TP, TCA, fibrinogène
- Si signes fonctionnels urinaires : ECBU
- Si signes fonctionnels respiratoires : ECBC avec kinésithérapeute (crachat induit), antigénuries Légionnelle et Pneumocoque, discuter TDM thoracique sans injection.
  - Discuter la réalisation précoce d'un prélèvement respiratoire invasif.
- Si diarrhée : coproculture standard et recherche de toxine de *Clostridium difficile*.
- Si douleur abdominale de novo : TDM abdomino-pelvienne avec injection.
- Pas de dépistage BMR / BHRe systématique SAUF :
  - Si NF à haut risque prévue (induction/ consolidation de leucémie aigüe ; Autogreffe) : Dépistage BMR + BHRe
  - Si voyage en zone d'endémie (Asie du Sud-Est, Inde, Maghreb et Afrique sub-saharienne) < 6 mois, résidence en long séjour, hospitalisation en réanimation : dépistage BMR
  - Si hospitalisation hors métropole < 1 an : dépistage BMR + BHRe.
- Si agranulocytose isolée : recherche de médicament récemment introduit pouvant être incriminé

Averbuch et al, ECIL-4, Haematologica 2013
Freifeld et al, CID 2011
Schnell et al, ann intensiv care 2016

INFECTIOUS DISEASES,
2017; VOL. 0,
NO. 0, 1–10

https://doi.org/10.1080/23744235.2017.1340665

ORIGINAL ARTICLE

Check for updates

Clinical significance of repeat blood cultures during febrile neutropenia in adult acute myeloid leukaemia patients undergoing intensive chemotherapy

Shun-ichi Kimura, Ayumi Gomyo, Jin Hayakawa, Masaharu Tamaki, Yu Akahoshi, Naonori Harada, Tomotaka Ugai, Machiko Kusuda, Kazuaki Kameda, Hidenori Wada, Yuko Ishihara, Koji Kawamura, Kana Sakamoto, Miki Sato, Kiriko Terasako-Saito, Misato Kikuchi, Hideki Nakasone, Shinichi Kako, Aki Tanihara and Yoshinobu Kanda

Division of Hematology, Saitama Medical Center, Jichi Medical University, Saitama, Japan

Les reco de l'IDSA:

- Hémoc primordiale au debut de la NF
- Pas d'interêt au hémoc répété si NF persistante sous ATB
- Faire hémoc en cas de modification clinique et notamment recurrence de la fièvre

⇒Etude rétrospective de 2007 à 2015

⇒Faible rentabilité des hemocs dans les NF persistante sous ATB (5%)

⇒Documentation dans les nouveau épisodes de NF (9%)

⇒Frisson+ hyperthermie élevée 39,9: associés à une hémoc +

Evaluation du risque:

- En pratique:
  - Durée prolongée > 7jours et Nadir PNN < 100/mm3
  - et/ ou Comorbidité et/ ou Signes cliniques

    (HypoTA, trouble digestif, mucite sévère, trouble neurologique aigu, Infection de KT, trouble respiratoire, I.rénale aigue ou cytolyse hépatique)

    => Hospitalisation et ATB IV

  - Durée < 7jours et peu de comorbidités et pas d'isolement

    => candidat pour domicile et ATB IV/ PO

NeutropénieS fébrileS

	Risque élevé	Risque faible
Durée d'aplasie +++	> 7 jours	< 7 jours
Type d'infection	Pulmonaire Cellulite Bactériémie Digestive	Fièvre d'origine indéterminée
Contexte clinique	Induction de LAM Allogreffe Maladie non contrôlée	Maladie en rémission
Clinique	Signes de gravité	Bonne tolérance

Diapo empruntée à A. Contejean

European Journal of Internal Medicine xxx (2017) xxx–xxx

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European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

History and outcome of febrile neutropenia related to non-chemotherapy drugs: A retrospective study of the Strasbourg's agranulocytosis cohorte

30 ans, 76 patients, NF non chimio-induite

- 8 NF nosocomiale
- 1 médicament responsable dans 64 cas
- 2 à 4 médicaments responsables dans 12 cas
- ATB (Beta-lactamines, SXT), ATS, Neuroleptiques, Antiepileptique
- 130 PNN en moyenne

- Traitement par ATB large spectre
- 59% GCSF
- Durée de neutropénie: 7,5 jours
- 8 décès, 10%

Table 1
Clinical manifestations during hospitalization for the 76 patients.

	n (%)
Isolated fever (unknown origin)	23 (30%)
Sore throat, acute tonsillitis and maxillar infection	14 (18.4%)
Documented pneumonia	14 (18.4%)
Septicaemia	11 (14.5%)
Septic shock	5 (6.5%)
Deep abdominal or pelvic abscess	3 (39%)
Cutaneous infection	2 (2.6%)
Meningitides	2 (2.6%)
Cholecytitis	1 (1.3%)
Infectious arthritis or osteonecrosis	1 (1.3%)

Orientation des patients:

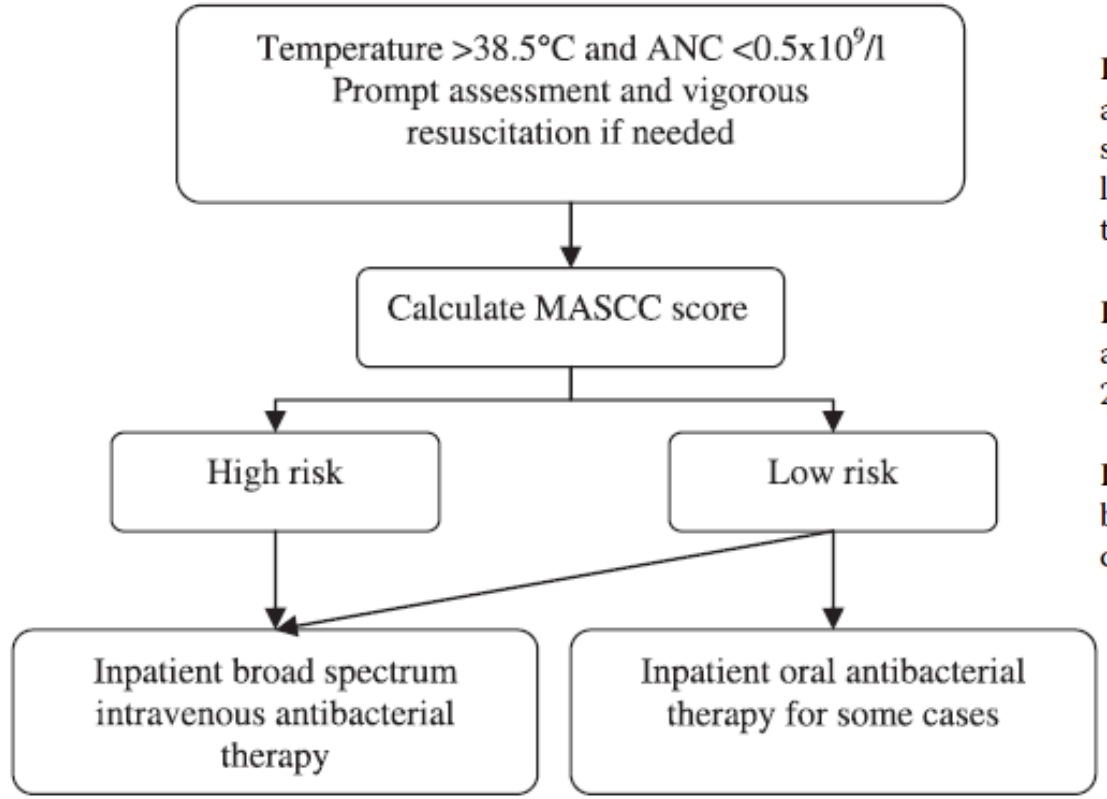


Figure 1. Initial management of febrile neutropenia.

ICU admission and prognosis

RI-1 Neutropenia should probably not be used as triage criteria in cancer patients considered for ICU admission. Performance status, comorbidities, and potentially life-prolonging treatment available are more relevant in this regard (Grade 2−, strong agreement).

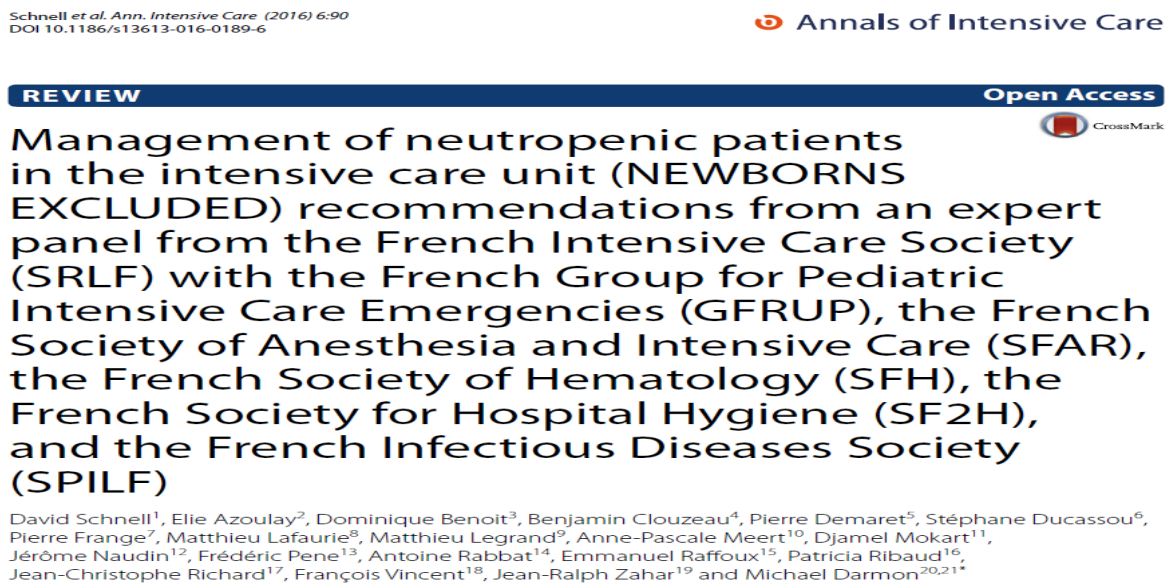
RI-2 Neutropenia should probably not be considered as a prognostic factor in critically ill cancer patients (Grade 2−, weak agreement).

RI-3 Intensive care unit admission should probably not be delayed if ICU admission is deemed necessary in critically ill cancer patients (Grade 2−, strong agreement).

Avis **précoce** USI/ réa:
- atteinte respiratoire
- Enterocolite

De Naurois, An. Of oncology, 2010
Schnell, An. Intens. Care 2016

NF avec critère de gravité:



Schnell et al. Ann. Intensive Care (2016) 6:90
DOI 10.1186/s13613-016-0189-6

Annals of Intensive Care

REVIEW Open Access

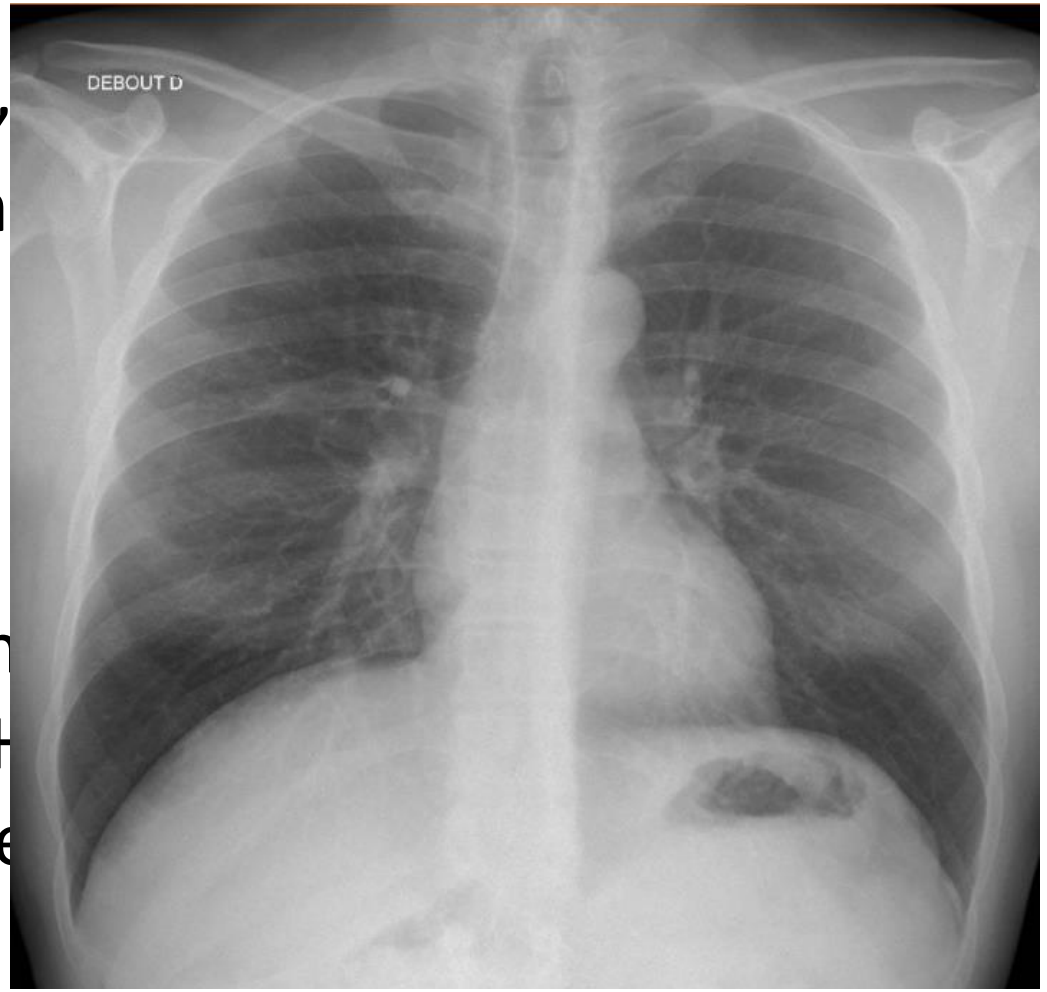
Management of neutropenic patients in the intensive care unit (NEWBORNS EXCLUDED) recommendations from an expert panel from the French Intensive Care Society (SRLF) with the French Group for Pediatric Intensive Care Emergencies (GFRUP), the French Society of Anesthesia and Intensive Care (SFAR), the French Society of Hematology (SFH), the French Society for Hospital Hygiene (SF2H), and the French Infectious Diseases Society (SPILF)

David Schnell[1], Elie Azoulay[2], Dominique Benoit[3], Benjamin Clouzeau[4], Pierre Demaret[5], Stéphane Ducassou[6], Pierre Frange[7], Matthieu Lafaurie[8], Matthieu Legrand[9], Anne-Pascale Meert[10], Djamel Mokart[11], Jérôme Naudin[12], Frédéric Pene[13], Antoine Rabbat[14], Emmanuel Raffoux[15], Patricia Ribaud[16], Jean-Christophe Richard[17], François Vincent[18], Jean-Ralph Zahar[19] and Michael Darmon[20,21*]

- Modalité de ventilation
- Modalité de dialyse
- Prise en charge de l'entérocolite: coloscopie, chirurgie
- Modalité des transfusion et G-CSF
- Antibiothérapie… et prophylaxies

M.D 50 ans, suite

- T°c=39 avec frissons, PA=120/65 mmHg,
- KTC en place propre, pas de plaintes fon
  dermato, pneumo).
- Pas de mucite
- Quelques diarrhées
- CRP=150, Clostri negatif, radiographie th
  hémocultures en cours, ECBU négatif, BH
  Ag asp et B-d-glucanes négatifs, Colonise
- Quelle antibiothérapie choisissez vous?



Choix ATB: la vraie vie de la neutropénie fébrile

- On ne sait pas ce que l'on traite…et le plus souvent on ne le saura jamais…mais il faut traiter vite !
  - Urgence thérapeutique <2h
  - Doit couvrir les BGN (dont le *Pseudomonas*) et les CGP

- Contraintes
  - Examen clinique peu contributif
  - Imagerie standard peu contributive
  - Traitement le plus souvent probabiliste

- Réévaluation indispensable à 72 heures
  - Aggravation précoce = échec
  - Amélioration même imparfaite = succès
  - Prise en compte des résultats microbiologiques et paracliniques

Antibiothérapie probabiliste: les principes et les questions

- Antibiothérapie à large spectre:
  - Doit être Bactéricide et peu toxique
  - Critère de gravité?
  - Colonisation à BMR?
  - Facteur de risque de colonisation à BMR?
  - Mono ou multithérapie?
  - Anti-Gram +? Aminoside? Carbapénème?
  - Existe-t-il une porte d'entrée/ orientation clinique?

Les grands principes:

Table 1. **Principles of antimicrobial stewardship for hematology patients.**

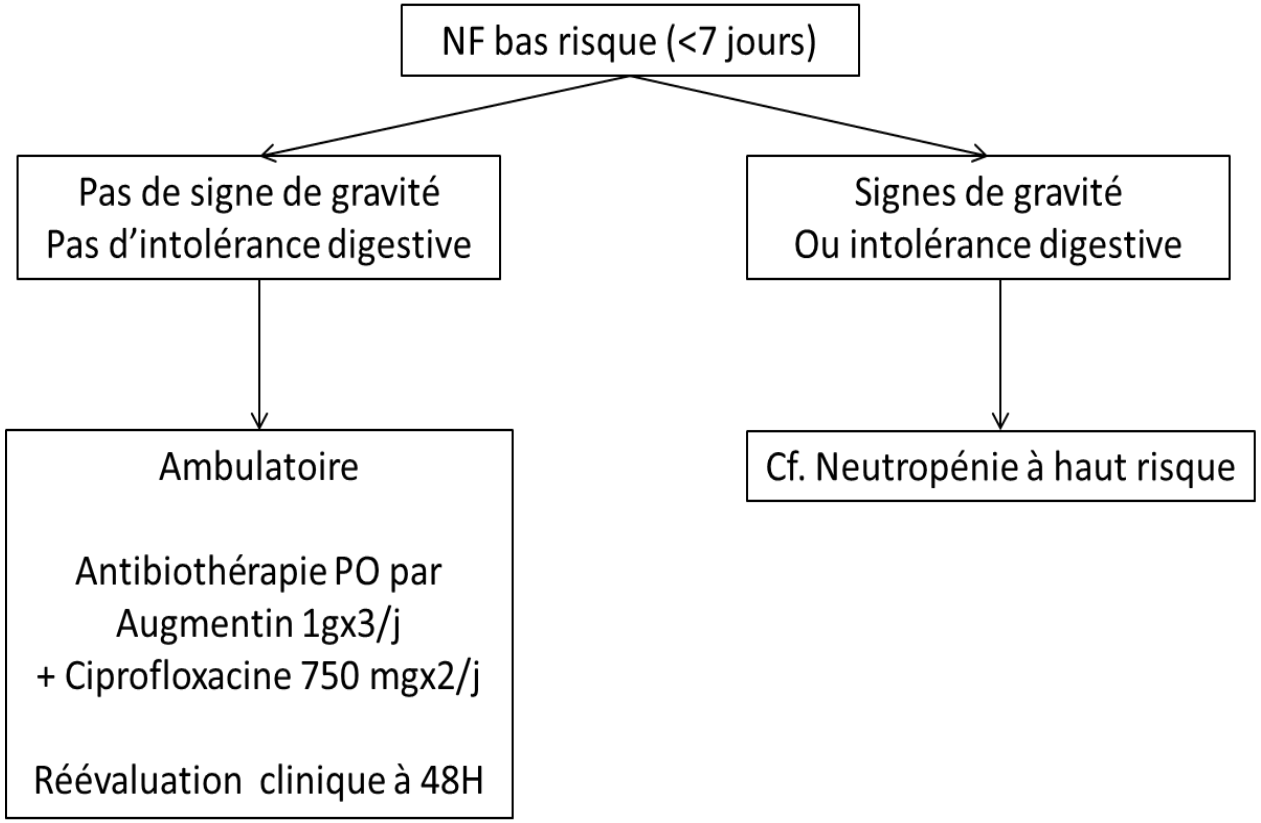
– The initiation of empirical antibiotic treatment should be prompted by fever and clinical signs, and not by C-reactive protein or other biomarkers, as studies of these have shown inconsistent results;[10] antibiotics should not be initiated on the basis of colonization by resistant organisms.
– Empirical antibiotic treatment should never be started or changed before taking at least two blood cultures, along with relevant specimens from the clinically-suspected sites of infection
– Risk stratification (low/high risk) for infection should be undertaken according to the Multinational Association for Supportive Care in Cancer (MASCC) score,[14] and should be considered in the empirical therapy algorithm[10]
– The spectrum of initial empirical therapy should, at the very least, cover common virulent Enterobacteriaceae (*Escherichia coli* and *Klebsiella pneumoniae*), also *Pseudomonas aeruginosa*, and, depending on the setting, and/or prophylaxis strategies, *S. aureus* including MRSA, but not coagulase-negative staphylococci.
– Individualized risk assessment for multi-resistant pathogens should guide the development of the management algorithms.[2]
– Strategies to reassess empirical antibiotic therapy after 2-3 days (i.e. once microbiology results are available) should be implemented, with de-escalation if possible.
– The algorithms should guide treatment duration, as outlined in point 2.
– Individualized risk assessments for infection can be undertaken, e.g. identifying clinical parameters that have been associated in the literature with a risk for secondary infection after a first episode of fever and neutropenia.[15]

Gyssens I., Haematologica 2013

Antibiothérapie probabiliste: NF à bas risque

- Amoxicilline-acide clavulanique 1gx3/j + Ciprofloxacine 750 mg x2/j
  - En cas d'allergie: clindamycine/ cefixime à la place de l'augmentin
  - Si ciprofloxacine au long cours, Augmentin seul
  - Jamais de Ciprofloxacine en monothérapie du fait du manque de couverture anti Gram+/ levofloxacine forte dose permettrait une bonne couverture anti-pyo et gram+
- REEVALUATION à 48h+++

Freifeld A, NEJM 1999
Freifeld A, CID 2011



Si prophylaxie au long cours par ciprofloxacine : Augmentin seul

Si allergie à la pénicilline :

Type I : Clindamycine 600mgx3 + Ciprofloxacine 750mgx2

Non de type I : Oroken 200mgx2 + Ciprofloxacine 750mgx2

Chemtouh R, Bernard S, Kernéis S; Procédure Hôpital Cochin 2019

Antibiothérapie probabiliste: NF à haut risque

- β-lactamine à large spectre (anti-pseudomonas):
  - Piperacilline/ Tazobactam: 4g x4/j en perfusion prolongée avec une Dose de charge
  - Ceftazidime: 2g x3/j avec une dose de charge, idéalement IVSE
  - Cefepime: 2g x2-3/j en perfusion prolongée
  - Carbapeneme: Imipeneme 1g x3/j ou meropeneme 2g x3/j IVSE
- En cas d'allergie:
  - Aztreonam+ vancomycine
  - Céphalosporine si pas d'allergie de type I
  - Carbapénème
  - Fluoroquinolone+ clindamycine/ vancomycine

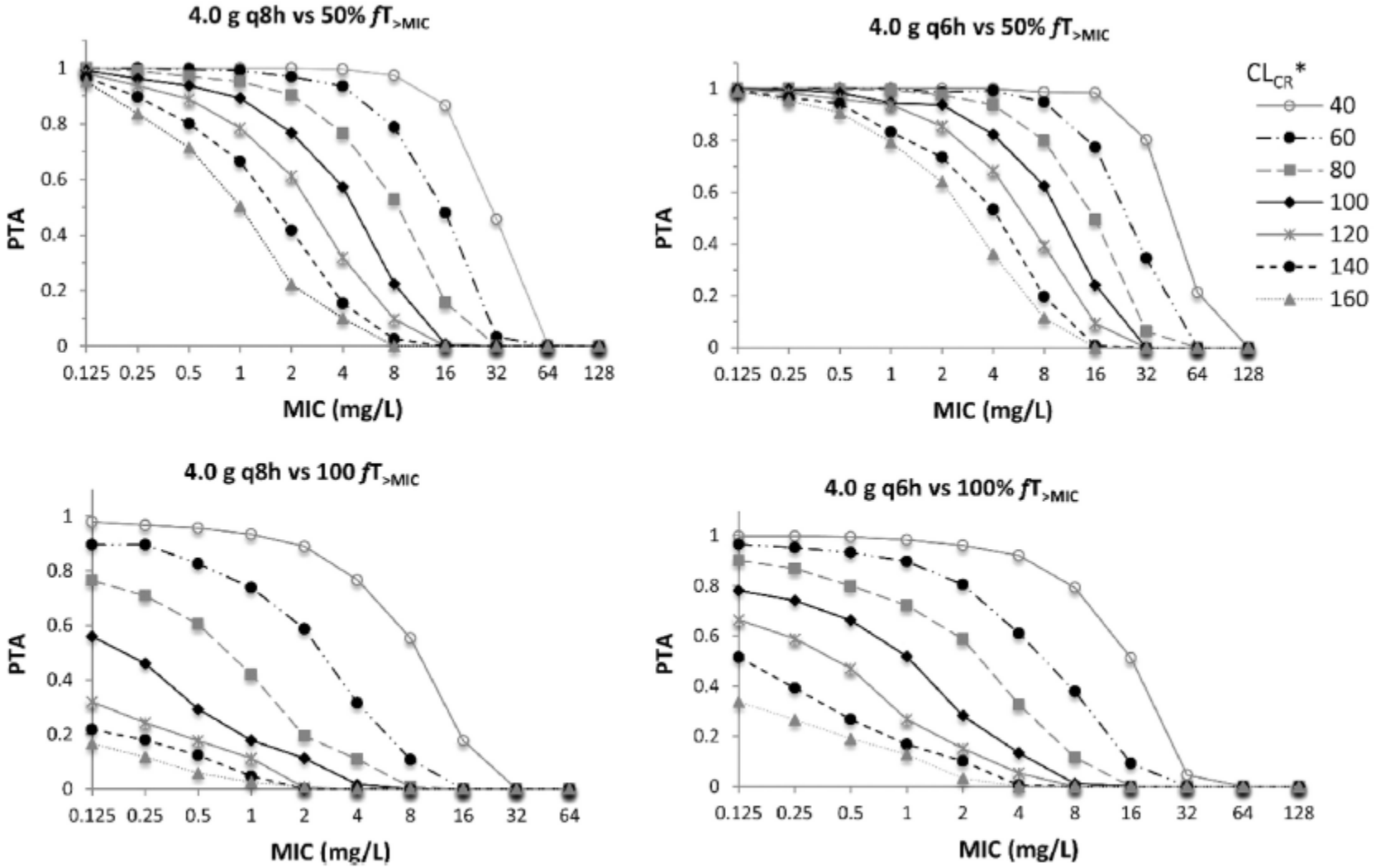


FIG 2 Probability of target attainment for conventional intermittent dosing regimens of piperacillin for PK/PD targets of 50% $fT_{>MIC}$ and 100% $fT_{>MIC}$. CL_{CR}, creatinine clearance in ml/min/1.73 m^2; PTA, probability of target attainment; q8h, every 8 h intermittent infusion; q6h, every 6 h intermittent infusion.

TABLE 3 PTA for alternative prolonged infusion dosing regimens during the first 24 h[a]

Dosing regimen and CL_{CR} (ml/min/1.73 m²)	PTA for 50% $fT_{>MIC}$ by MIC (mg/liter)								PTA for 100% $fT_{>MIC}$ by MIC (mg/liter)							
	0.125	0.25	0.5	1	2	4	8	16	0.125	0.25	0.5	1	2	4	8	16
4.0-g EI over 4 h q8h																
40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−
60	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−
80	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−
100	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
120	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
140	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
160	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
4.0-g EI over 3 h q6h																
40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
60	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−
80	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−
100	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−
120	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−
140	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−
160	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−
4.0-g LD + 8.0-g CI																
40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
60	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
80	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
100	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
120	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	−
140	+	+	+	+	+	+	−	−	+	+	+	+	+	+	−	−
160	+	+	+	+	+	+	−	−	+	+	+	+	+	+	−	−
4.0-g LD + 12.0-g CI																
40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
60	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
80	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
100	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
120	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
140	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
160	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
4.0-g LD + 16.0-g CI																
40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
60	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
80	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
100	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
120	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
140	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
160	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−

[a]+, PTA of ≥0.9; −, PTA of <0.9.

TABLE 5 FTA for various dosing regimens of piperacillin against the EUCAST MIC distributions of *E. coli*, *K. pneumoniae*, and *P. aeruginosa* during the first 24 h

Treatment type, PK/PD target (% $fT_{>MIC}$), and dosing regimen	FTA (%) by bacteria and CL_{CR} (ml/min/1.73 m^2)[a]																				
	E. coli							*K. pneumoniae*							*P. aeruginosa*						
	40	60	80	100	120	140	160	40	60	80	100	120	140	160	40	60	80	100	120	140	160
Empirical																					
50																					
4.0 g q8h	96	91	82	72	59	45	31	87	80	69	56	42	29	18	77	64	50	35	22	13	8
4.0 g q6h	97	95	92	86	80	69	61	89	86	81	73	64	53	44	82	75	65	54	43	32	24
4.0 g q8h, 4-h EI	97	96	96	95	94	94	93	90	88	87	86	84	84	83	83	79	77	70	71	68	67
4.0 g q6h, 3-h EI	97	97	96	96	96	95	95	90	90	88	88	87	87	85	84	82	79	78	77	76	73
4.0-g LD + 8.0-g CI	96	95	94	94	93	92	91	88	87	85	83	82	80	78	80	77	71	68	66	60	56
4.0-g LD + 12.0-g CI	97	96	96	95	94	94	93	90	88	88	86	85	84	83	83	80	77	75	71	69	67
4.0-g LD + 16.0-g CI	97	97	96	96	95	95	94	91	90	88	88	87	86	85	85	83	79	78	77	73	71
100																					
4.0 g q8h	82	56	26	12	5	2	2	69	40	16	7	2	1	1	50	22	8	3	1	0	0
4.0 g q6h	90	75	56	34	18	11	7	80	60	40	21	11	6	3	64	40	22	10	5	2	1
4.0 g q8h, 4-h EI	91	79	61	39	21	12	7	80	64	44	24	12	7	4	63	43	24	11	5	2	1
4.0 g q6h, 3-h EI	94	89	78	64	49	33	21	85	77	63	48	33	20	12	72	59	42	27	15	9	5
4.0-g LD + 8.0-g CI	96	95	94	93	93	91	91	88	87	84	83	82	79	77	78	76	70	67	64	58	55
4.0-g LD + 12.0-g CI	96	96	96	95	94	94	93	89	88	88	86	84	84	83	81	78	77	73	70	68	67
4.0-g LD + 16.0-g CI	96	96	96	96	95	94	94	89	89	88	88	87	85	84	81	80	78	77	76	72	70
Directed																					
50																					
4.0 g q8h	100	97	89	78	64	48	33	100	94	83	68	51	35	22	97	84	65	45	29	17	11
4.0 g q6h	100	99	97	92	85	74	66	100	99	95	88	77	64	54	99	95	85	71	57	42	31
4.0 g q8h, 4-h EI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	96	92	90	88
4.0 g q6h, 3-h EI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	99	95
4.0-g LD + 8.0-g CI	100	100	100	100	100	99	98	100	100	100	100	100	97	95	100	100	93	89	87	79	74
4.0-g LD + 12.0-g CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	97	93	90	88
4.0-g LD + 16.0-g CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	96	93
100																					
4.0 g q8h	88	61	28	13	5	3	2	83	49	20	9	2	1	1	66	28	10	4	1	0	0
4.0 g q6h	96	81	60	36	20	12	7	94	72	49	26	13	8	4	84	52	29	13	6	3	1
4.0 g q8h, 4-h EI	97	85	65	42	23	13	8	95	77	53	29	15	8	4	82	56	31	14	7	3	2
4.0 g q6h, 3-h EI	100	95	84	69	53	36	22	99	92	77	58	40	24	14	94	77	55	36	20	11	6
4.0-g LD + 8.0-g CI	100	100	100	100	100	98	98	100	100	100	100	99	96	94	100	99	92	88	84	75	72
4.0-g LD + 12.0-g CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	95	92	89	87
4.0-g LD + 16.0-g CI	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	99	94	92

[a]Shaded area indicates optimal FTA of greater than or equal to 85%.

Clinical Infectious Diseases

MAJOR ARTICLE

Extended vs Bolus Infusion of Broad-Spectrum β-Lactams for Febrile Neutropenia: An Unblinded, Randomized Trial

Ron Ram,[1,2] Yael Halavy,[2] Odelia Amit,[1,2] Yael Paran,[2,3] Eugene Katchman,[2,3] Bruria Yachini,[1] Svetlana Kor,[1] Irit Avivi,[1,2] and Ronen Ben-Ami[2,3]

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=>étude prospective randomisée: outcome des NF à haut risque traitée par IVSE ou IVL de Beta-lactamines

⇒unicentrique, ouverte, de superiorité: IVSE> IVL

⇒PTZ ou CAZ en IVSE ou IVL

- Inclusion:
  - Avant toute chimiothérapie
  - > 18 ans, HCST, LA (induction ou conso)
- Non-inclusion:
  - DFG<40 ml/min
  - Infection ou colonisation à germe ATB-R dans les 30j
- Soit PTZ 4g/8h soit CAZ 2g/8h si allergi péni
  - Sur 30 minutes
  - Dose de charge sur 30 minutes puis 6h apres 1ère dose sur plus de 4h
- +/- amika/ vanco/ levofloxacine puis switch carbapeneme

- Critère de jugement principal:
  - Réponse globale à J4 du début des symptomes:
    - Apyrexie en 24h
    - Réponse microbiologique à J3-4
    - Résolution des symptômes d'infection
    - Pas besoin d'adjonction d'ATB ou de switch

⇒**Succès si tous les critères sont remplis.**

- Critère secondaire:
  - Récidive de bactériémie > 5j
  - Recurrence de la fievre > 5j
  - ICD
  - DC dans les 30 jours
  - Irénale Aigue dans les 4 jours
  - Nécessité de NAD

Table 1. Characteristics of 123 Enrolled Patients

Characteristic	Bolus Infusion (n = 63)	Extended Infusion (n = 60)	*P* Value
Age, years; median (IQR)	60.1 (45.8–66.3)	60.4 (50.9–67.5)	.74
Sex, female	28 (44.4)	23 (38.3)	.58
Weight, kg; median (range)	75 (50.4–111.7)	81 (58–108)	.13
Primary diagnosis			.46
Acute leukemia/myelodysplastic syndrome	26 (41)	18 (30)	…
Lymphoma	17 (27)	17 (28)	…
Multiple myeloma	18 (29)	24 (40)	…
Other	2 (3)	1 (2)	
Reason for admission			.29
Allogeneic HCT	21 (33)	18 (30)	…
Autologous HCT	29 (46)	36 (60)	…
Induction for acute leukemia	7 (11)	4 (7)	…
Consolidation for acute leukemia	6 (10)	2 (3)	…
Myeloablative regimen[a]	12 (57)	8 (44)	.43
HCT-CI; median (IQR)[a]	2 (2–3)	2 (1–3)	.21
Karnofsky score; median (IQR)	100% (90–100)	100% (80–100)	.15
Neutropenia <500/μL, days; median (range)	7 (1–46)	7 (1–37)	.32
Neutropenia <100/μL, days; median (range)	6 (0–36)	6 (0–30)	.42
Fluoroquinolone prophylaxis	35 (56)	34 (57)	.98
Antibiotic use, days; median (range)[b]	1 (0–14)	2 (0–17)	.61
Febrile neutropenia	58 (92.0)	47 (78.3)	.041
Hospital days before febrile neutropenia; median (range)	12 (1–24)	12 (1–22)	.6
Clinically documented infection	29 (46.0)	20 (33.3)	.19
Pneumonia	8 (12.7)	6 (10.0)	.7
Colitis	4 (6.3)	2 (3.3)	.6
Exit site infection	5 (7.9)	4 (6.6)	1.0
Microbiologically documented infection	11 (7.4)	10 (6.6)	1.0
Bloodstream infection	10 (15.8)	7 (11.6)	.6
Estimated glomerular filtration rate (mL/min/1.73 m^2),[c] mean ± standard deviation	109.4 ± 17.7	109.8 ± 21.5	.9
Primary antibiotic treatment			.6
Piperacillin-tazobactam	52 (89.6)	44 (93.6)	…
Ceftazidime	4 (6.9)	3 (6.3)	…
Meropenem	2 (3.4)	0 (0)	…
Vancomycin co-treatment	22 (39.2)	19 (42.2)	.8

All numbers represent number of patients (percent of total in treatment arm), except where otherwise specified.

Abbreviations: CI, comorbidity index; HCT, hematopoietic cell transplantation; IQR, interquartile range.

[a]Allogeneic HCT only.

[b]Before onset of febrile neutropenia, excluding prophylactic ciprofloxacin.

[c]Calculated with the Chronic Kidney Disease Epidemiology Collaboration formula.

Table 3. Treatment Outcomes of Patients With Febrile Neutropenia

Outcome	Intention-to-Treat Population			Per-Protocol Population		
	Intermittent Bolus (n = 58)	Extended Infusion (n = 47)	*P* Value	Intermittent Bolus (n = 48)	Extended Infusion (n = 43)	*P* Value
Overall response	32 (55.1)	35 (74.4)	.044	30 (62.5)	35 (81.4)	.063
Clinically documented infection	10/28 (35.7)	13/19 (68.4)	.039	9 (42.8)	13 (81.2)	.041
Pneumonia	0/8 (0)	4/5 (80)	.007	0/7 (0)	4/4 (100)	.003
Microbiologically documented infection	2/11 (18.1)	4/9 (44.4)	.3	1/6 (16.6)	4/7 (57.1)	.26
Bloodstream infection	1/10 (10)	3/6 (50)	.1	1/6 (16.6)	3/5 (60)	.24
Components of overall response						
Persistent fever	17 (29.3)	13 (27.6)	1.0	14 (29.1)	10 (23.2)	.6
Clinical failure	11 (18.9)	3 (6.3)	.08	5 (10.4)	1 (2.3)	.2
Microbiological failure	2 (3.5)	0 (0)	.5	1 (2.0)	0 (0)	1.0
Premature antibiotic change	21 (36.2)	10 (21.2)	.13	13 (27.0)	6 (13.9)	.1
Switch to carbapenem	14 (24.1)	9 (19.1)	.6	7 (14.5)	5 (11.6)	.7
Aminoglycoside added	6 (10.3)	3 (6.3)	.7	3 (6.2)	3 (6.9)	1.0
Fluoroquinolone added	2 (3.4)	3 (6.3)	.6	2 (4.1)	2 (4.6)	1.0
Secondary outcomes						
Fever, days (median, range)	2 (1–17)	2 (1–9)	.9	2 (1–17)	2 (2–9)	.9
Use of noradrenaline due to hypotension	10 (17.2)	4 (8.5)	.2	4 (8.3)	2 (4.6)	.6
Acute kidney injury	6 (10.3)	3 (6.3)	.7	4 (8.3)	3 (6.9)	1.0
Clostridium difficile infection	2 (3.4)	0 (0)	.5	2 (4.2)	0 (0)	.5
Breakthrough bloodstream infection	7 (12.0)	2 (4.2)	.18	7 (14.5)	2 (4.6)	.1
Breakthrough fever after day 4	10 (17.2)	6 (12.7)	.5	9 (18.7)	5 (11.6)	.3
Length of stay, days (median, range)	24 (13–145)	23 (15–61)	.3	23 (15–145)	22 (15–61)	.3
Death, 30 days	2 (3.7)	1 (2.5)	1.0	1 (2.2)	1 (2.7)	1.0

Efficacy of extended infusion of β-lactam antibiotics for the treatment of febrile neutropenia in haematologic patients (BEATLE): a randomised, multicentre, open-label, superiority clinical trial

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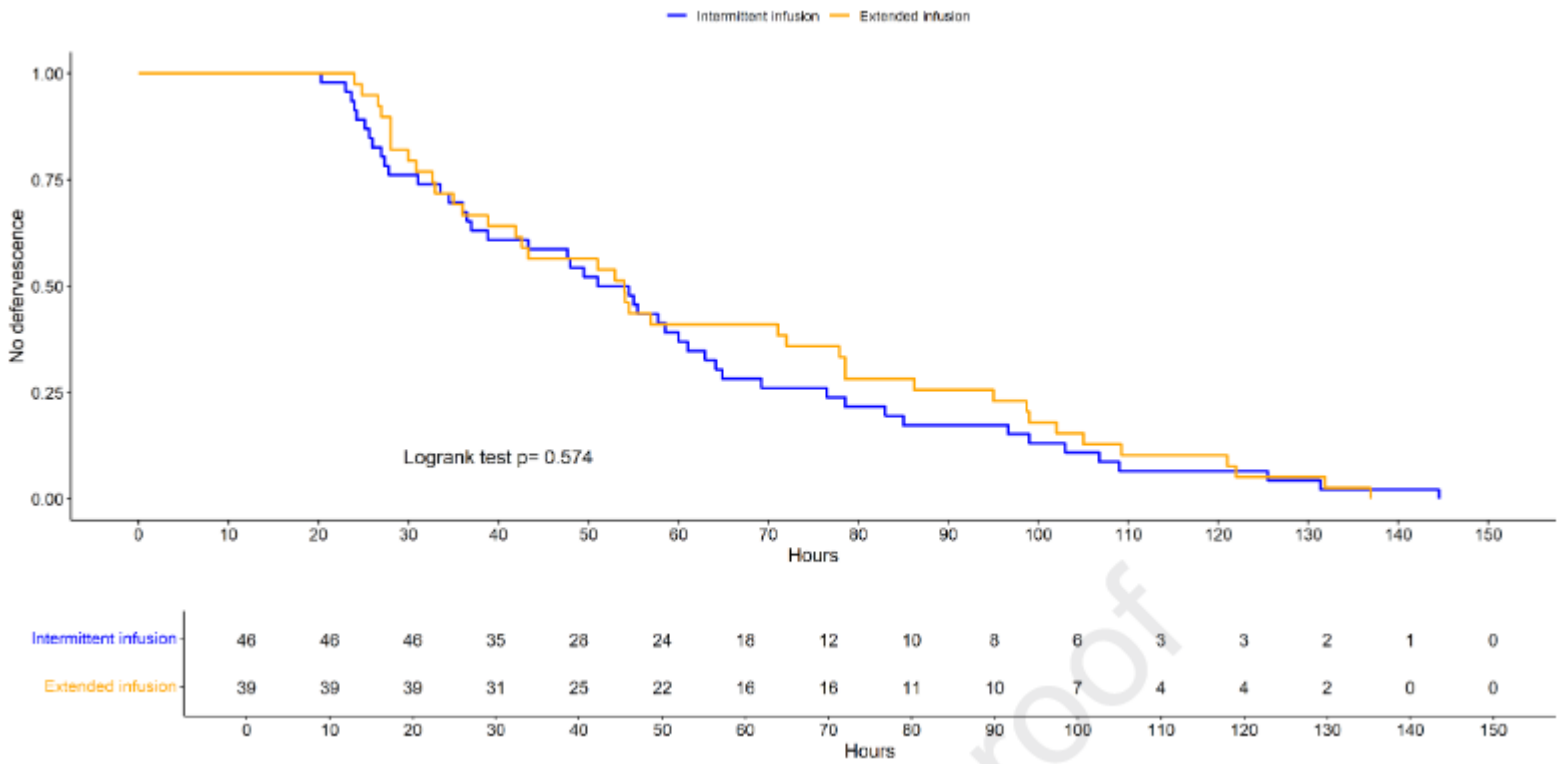
Intervention and Control

At FN onset, the BLA of choice was administered within 30 minutes in all patients. For patients in the EI group, time was equal to half of the time of the dosing interval. For patients in the II group, the BLA was administered in 30 minutes. Dosage was the recommended for treating *Pseudomonas aeruginosa*: piperacillin-tazobactam 4g/6h, cefepime 2g/8h and meropenem 1g/8h; or adjusted according to renal function (Table S4).

- Critères de jugement:
  1)Succès a J5: apyrexie, pas de modification d'ATB
  2)Delai d'apyrexie, délai de decroissance CRP, resolution des symptomes, objectif PK/PD: 100%t> CMI, mortalité

Table 1: Baseline characteristics at febrile neutropenia onset in the intention-to-treat population

	Extended infusion (n=77)	Intermittent infusion (n=73)
Initial antibiotic therapy		
Cefepime	5 (6.5%)	2 (2.7%)
Cefepime + amikacin	32 (41.6%)	35 (48.0%)
Cefepime + vancomycin	5 (6.5%)	2 (2.7%)
Cefepime + daptomycin	0	1 (1.3%)
Cefepime + amikacin + vancomycin	1 (1.3%)	1 (1.3%)
Cefepime + amikacin + daptomycin	3 (3.9%)	2 (2.7%)
Piperacillin-tazobactam	14 (18.2%)	17 (23.3%)
Piperacillin-tazobactam + amikacin	4 (5.4%)	4 (5.5%)
Piperacillin-tazobactam + vancomycin	3 (3.9%)	2 (2.7%)
Piperacillin-tazobactam + daptomycin	1 (1.3%)	0
Piperacillin-tazobactam + amikacin + daptomycin	1 (1.3%)	0
Meropenem	7 (9.1%)	4 (5.5%)
Meropenem + vancomycin	1 (1.3%)	3 (4.11%)



- Pas de différence: (effectif? Bitherapie? Heterogénéité?)
  - Sauf pour la PK/PD théorique de 100%> CMI(pyo)=> interet en probabiliste?
  - Même pour la monothérapie (14/22 vs 14/18)

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Journal of Antimicrobial Chemotherapy

A meropenem pharmacokinetics model in patients with haematological malignancies

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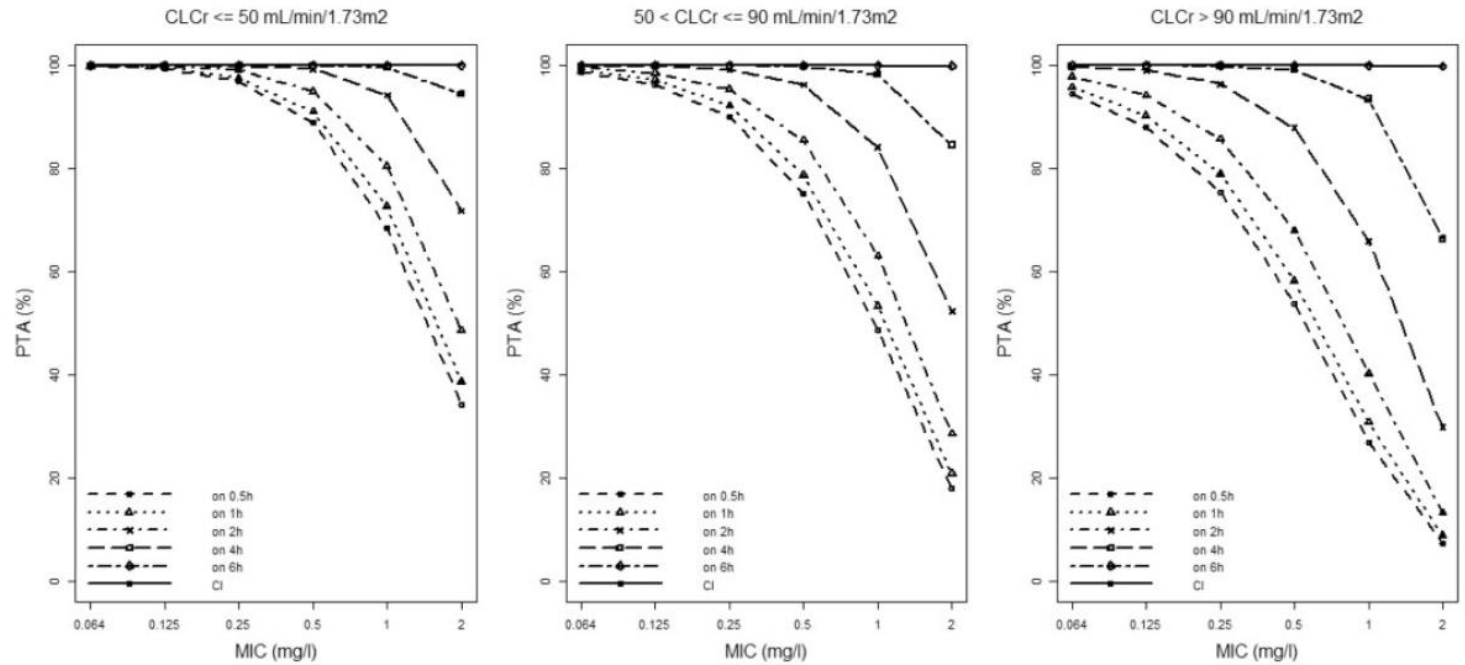


Figure 4. PTA versus MIC, for meropenem 2 g q8h administered according to different durations of infusion. We represented PTA versus MIC for different durations of infusion (0.5 h, 1 h, 2 h, 4 h, 6 h and continuous infusion) in three different categories of renal function [$CL_{CR} \leq 50$ mL/min/1.73 m^2 (left panel), $50 < CL_{CR} \leq 90$ mL/min/1.73 m^2 (central panel) and $CL_{CR} > 90$ mL/min/1.73 m^2 (right panel)]. CI, continuous infusion.

Bêta-lactamines – MEROPENEME chez le neutropénique

Effect of meropenem administration in extended infusion on the clinical outcome of febrile neutropenia: a retrospective observational study

Csaba Fehér[1]*, Montserrat Rovira[2,3], Alex Soriano[1,3,4], Jordi Esteve[2,3], José Antonio Martínez[1,3], Francesc Marco[5,6], Enric Carreras[2,3], Carmen Martínez[2,3], Francesc Fernández-Avilés[2,3], María Suárez-Lledó[2,3] and Josep Mensa[1,3]

Rétrospectif monocentrique
N=164 ; HSCT & Induction LAM
1gx3/j
Bolus vs Perfusion de 4h

Table 3. Main outcomes according to meropenem administration method

	SI (*N*=88)	EI (*N*=76)	*P*
Treatment success by day 5, *n* (%)	36 (40.9)	52 (68.4)	**<0.001**
Antibiotic change by day 5[a], *n* (%)	44 (50.0)	20 (26.3)	**0.002**
LOS (days), median (IQR)	35 (28–48)	32 (27–39)	0.053
Deaths, *n* (%)			
none	75 (85.2)	69 (90.8)	0.278
occurring on days 0–30	1 (1.1)	3 (3.9)	
occurring on days 31–100	12 (13.6)	4 (5.3)	

Table 4. Results of the four multivariate analyses of factors associated with treatment success on day 5 of antibiotic therapy

	I[a] (*N*=164)			II[b] (*N*=150)			III[c] (*N*=121)			IV[d] (*N*=67)		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Extended meropenem infusion	3.13	1.61	6.10	3.52	1.74	7.11	3.81	1.67	8.69	5.58	1.83	16.99
Non-catheter infectious focus	0.46	0.22	0.95	0.50	0.23	1.07	0.23	0.06	0.86	—	—	—
Grade III–IV mucositis	0.24	0.08	0.79	0.25	0.07	0.78	0.36	0.15	0.85	—	—	—

N, sample size.
[a]The entire study population.
[b]Microbiologically documented infections and fever of unclear aetiology.
[c]Microbiologically documented infections caused by meropenem-susceptible microorganisms and fever of unclear aetiology.
[d]Cases treated with meropenem as monotherapy.

Fehér, JAC, 2014

Meropenem MERONEM®

Hôpital Cochin Port-Royal AP-HP

Dose de charge* : 2 g en perfusion de 5 minutes **immédiatement suivie** d'une administration IVSE

Administration IVSE : Perfusion prolongée dépendante des situations suivantes

Posologie initiale* : 2 g x 3 / 24h puis à adapter aux dosages

Concentration plasmatique maximale pour limiter une toxicité rénale **< 44 mg/L**

Une voie d'administration dédiée est disponible

IVSE **pendant 8 heures** toutes les 8h

L'idéal

Aucune voie d'administration dédiée n'est disponible

L'alternative

IVSE **pendant 6 heures** toutes les 8h
(2h x 3 /jr pour perfuser d'autres médicaments)

Seulement les jours où un médicament incompatible en Y doit être passé > 2h

IVSE **pendant 4 ou 5 heures** toutes les 8h

L'exception

Quand prélever pour le dosage ?	
IVSE de 8 heures	**IVSE de ≤ 6 heures**
N'importe quel moment mais attendre ≥ 5h après un changement de posologie	Juste avant la reprise de la perfusion (à la fin de l'interruption)

Quoi qu'il en soit, toujours :
- Doser au J2 de l'initiation et de chaque changement de posologie
- Doser en cas d'anomalie rénale ou hépatique
- Remplir tous les renseignements de la feuille de prélèvement
- Prélever en périphérique, sur le bras opposé à la perfusion

Médicaments **compatibles** pour injection en Y du meropenem

Atenonol	Fluconazole	Magnesium sulfate
Cimetidine	Furosémide	Metoclopramide
Dexamethasone	Gentamicine	Morphine sulfate
Digoxine	Héparine Sodique	Phenobarbital sodium
Dobutamine	Insuline	Ranitidine
Dopamine	Linezolide	Vancomycine

Médicaments **incompatibles** pour injection en Y du meropenem

Aciclovir	Calcium gluconate	Metronidazole
Amphotéricine B	Diazepam	Ondansetron
		Sang et dérivés

Compatibilité **inconnue** pour injection en Y

En cas de doute, ne pas administrer par la même voie des médicaments ayant un pH éloigné (meropenem : 7,3 < pH < 8,3).
Favoriser la prudence : contrôler visuellement et passer autant que possible les produits séparément.

* Posologies recommandées pour le patient normo-rénal

Si DFG < 50 mL/min/1,73 m² → DC de 1 g suivi d'une perfusion IVSE de 1 g x 3 / 24h

Rappels

Meropenem / MERONEM®	
Présentation	1 g, poudre pour solution injectable
Reconstitution	1 g de poudre avec 20 mL d'**EPPI**
Dilution	Dans **NaCl 0,9%** pour une concentration finale max < 40 mg/mL
Surveillance	Bilans rénal et hépatique

D. Bouscary, A. Contejean, I. Ducamp, J. Decroocq & J. Zerbit. Mars 2021

Open Forum Infectious Diseases

MAJOR ARTICLE

The Dose-Dependent Efficacy of Cefepime in the Empiric Management of Febrile Neutropenia: A Systematic Review and Meta-Analysis

Nikolaos Andreatos,[a] Myrto Eleni Flokas,[a] Anna Apostolopoulou, Michail Alevizakos, and Eleftherios Mylonakis

Infectious Diseases Division, Warren Alpert Medical School of Brown University, Rhode Island Hospital, Providence

32 essais, 5724 patients

⇒ Efficacité clinique (succès clinique sans modification) identique aux autres trts: TZP, Carba

⇒ Plus gde mortalité (RR=1,32)=> 2g/12h monothérapie, différence s'efface si 2g/8h

⇒ Mortalité sous FEP > carbapénèmes

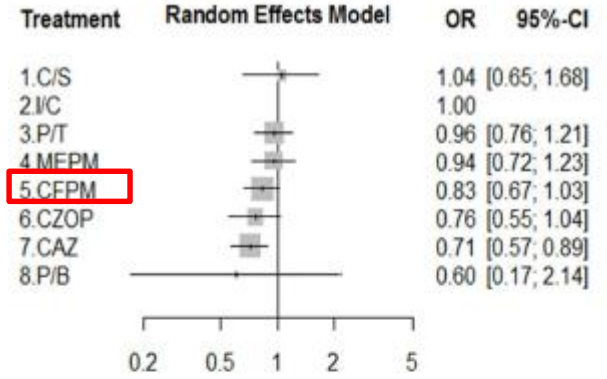
⇒ Echec de traitement des infection documentée plus grand sous FEP que carba mais 2g/12h

⇒ Forte doses de FEP: plus de toxicité associé au trt

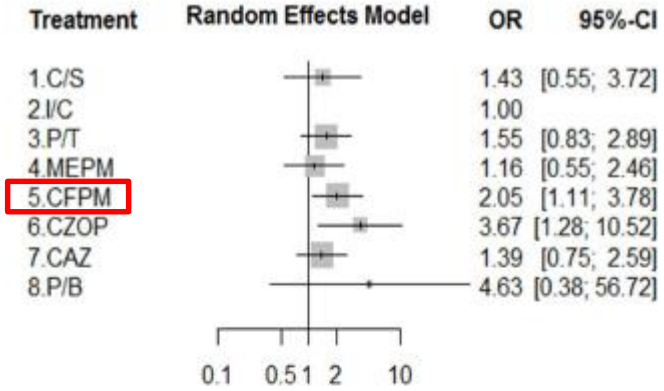
⇒ Faible dose: moins de toxicité associée

⇒ Question de l'index thérapeutique?

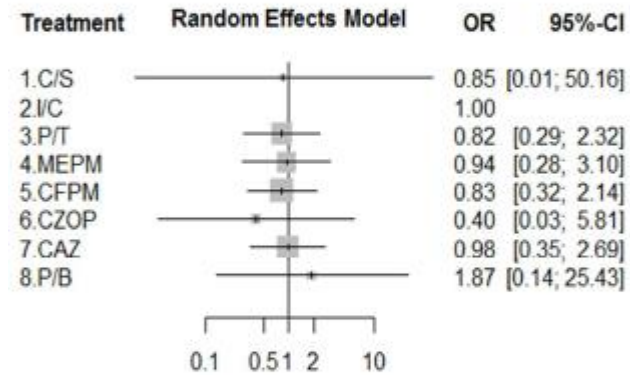
Treatment success without modification



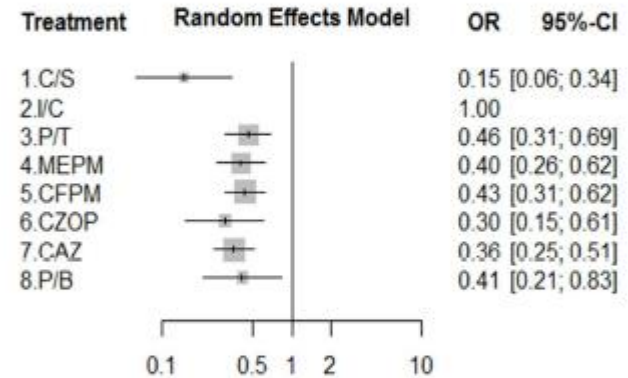
All-cause death



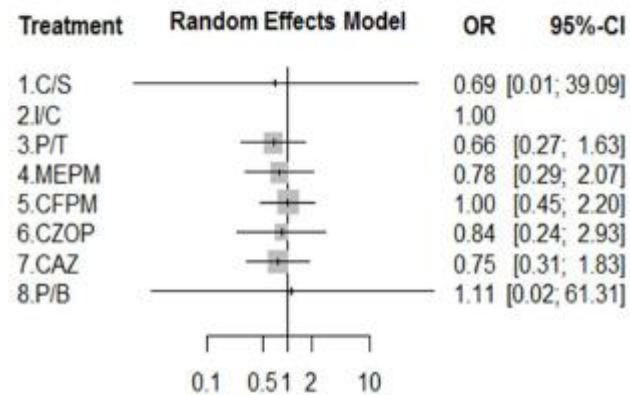
Infection-related death



Any adverse event



Adverse evenet leading to discontinuation



C/S: Cefoperazone/Sulbactam. CAZ: Ceftazidime. CFPM: Cefepime. CZOP: Cefozopran. I/C: Imipenem/Cilastatin. MEPM: Meropenem P/B: Panipenem/betamipron. P/T: Piperacillin/Tazobactam. OR: odds ratio.

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Letter to the editor

Comparison of antipseudomonal β-lactams for febrile neutropenia empiric therapy: authors' response

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https://doi.org/10.1093/jac/dkad166 Advance Access publication 1 June 2023

Journal of Antimicrobial Chemotherapy

Advances in antibacterial treatment of adults with high-risk febrile neutropenia

Adrien Contejean [1,2,3]*, Alexis Maillard [2], Etienne Canouï [2], Solen Kernéis[3,4,5], Bruno Fantin[3,6], Didier Bouscary[3,7], Perrine Parize [8], Carolina Garcia-Vidal[9,10] and Caroline Charlier [2,3,11,12]

Table 2. Proposed dosage and infusion modalities of parenteral antibiotics in patients with high-risk febrile neutropenia and no otherwise specified condition

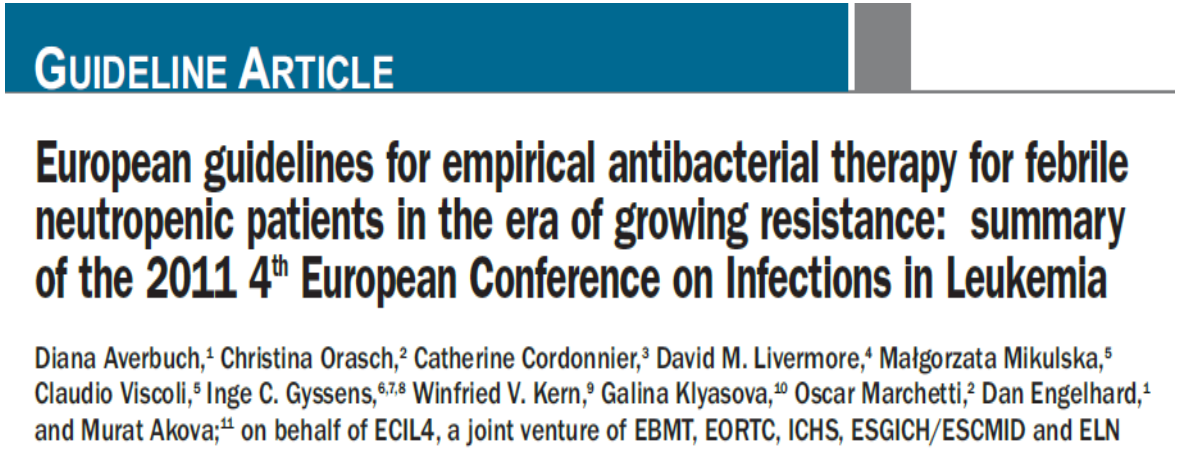
Antibiotics	Infusion modalities	Administration rules	Stability	Therapeutic drug monitoring	References
Piperacillin/ tazobactam	4 g loading dose over 30 min 12 g/day CI	Dilution in saline serum C_{max} 80 mg/mL + 10 mg/mL	24 h at 25°C	Piperacillin concentration at steady state (≥24 h)	76,78–80
Cefepime	2 g loading dose over 30 min 6 g/day CI	Dilution in saline serum C_{max} 50 mg/mL Administration in three separate infusions over 8 h	8 h at 25°C	Cefepime concentration at steady state (≥24 h)	78–83
Ceftazidime	2 g loading dose over 30 min 6 g/day CI	Dilution in saline serum C_{max} 80 mg/mL Administration in three separate infusions over 8 h	8 h at 25°C	Ceftazidime concentration at steady state (≥24 h)	78–80,84
Meropenem	2 g loading dose over 30 min 6 g/day CI	Dilution in saline serum C_{max} 50 mg/mL Administration in three separate infusions over 8 h	8 h at 25°C	Meropenem concentration at steady state (≥24 h)	80,85,86
Vancomycin	25 mg/kg loading dose over 2 h (max. 2 g) 40 mg/kg/day CI	Dilution in saline serum or G5% C_{max} 40 mg/mL	48 h at 25°C	Vancomycin concentration at steady state (24 h after loading dose)	78,79,87–91
Daptomycin	10 mg/kg/day over 30 min	Dilution in saline serum C_{max} 500 mg/50 mL	12 h at 25°C	Efficacy: 24 h AUC/MIC or daptomycin concentration at peak (30 min after the end of infusion) Toxicity: daptomycin trough concentration, before subsequent infusion	63,79,92–95
Amikacin	30 to 35 mg/kg/day over 30 min	Dilution in saline serum or G5% C_{max} 20 mg/mL	24 h at 25°C	Efficacy: amikacin concentration at peak (30 min after the end of infusion) Toxicity: amikacin trough concentration, before subsequent infusion	64,65
Gentamicin	6 to 7 mg/kg/day over 30 min	Dilution in saline serum or G5% C_{max} 10 mg/mL	24 h at 25°C	Efficacy: gentamicin concentration at peak (30 min after the end of infusion) Toxicity: gentamicin trough concentration, before subsequent infusion	64,65,79

G5%, Glucose 5%.

Table 1. Main pharmacological modifications of antibiotics in febrile neutropenia

Pharmacological modifications	Involved antibiotics	References
Increase in volume of distribution	β-Lactams[a] Glycopeptides Daptomycin Aminoglycosides	57–65
Increase in drug clearance and decrease in elimination half-life	β-Lactams[a] Glycopeptides Daptomycin Aminoglycosides	57–65
Decrease in peak concentration (C_{max})	Daptomycin Aminoglycosides	63–65
Decrease in AUC	Glycopeptides Daptomycin	61–63
Decrease in post-antibiotics effect	Carbapenems Aminoglycosides	66,67

Problème de la NF en hématologie…



GUIDELINE ARTICLE

European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia

Diana Averbuch,[1] Christina Orasch,[2] Catherine Cordonnier,[3] David M. Livermore,[4] Małgorzata Mikulska,[5] Claudio Viscoli,[5] Inge C. Gyssens,[6,7,8] Winfried V. Kern,[9] Galina Klyasova,[10] Oscar Marchetti,[2] Dan Engelhard,[1] and Murat Akova;[11] on behalf of ECIL4, a joint venture of EBMT, EORTC, ICHS, ESGICH/ESCMID and ELN

- Nécessité d'épargne des carbapenemes
- Augmentation des BMR (BLSE, Pyo Cefta-R, ERV)
- Propose 2 attitudes: escalade/ desescalade

Averbuch et al, ECIL-4, Haematologica 2013

Doit- on couvrir les BMR?

- Vaste débat…
- Chez le neutropénique:

Support Care Cancer (2016) 24:253–259
DOI 10.1007/s00520-015-2772-z

ORIGINAL ARTICLE

Fecal ESBL *Escherichia coli* carriage as a risk factor for bacteremia in patients with hematological malignancies

Patricia Cornejo-Juárez[1] · Juan Antonio Suárez-Cuenca[2] · Patricia Volkow-Fernández[1] · Jesús Silva-Sánchez[3] · Humberto Barrios-Camacho[3] · Esmeralda Nájera-León[4] · Consuelo Velázquez-Acosta[1] · Diana Vilar-Compte[1]

J Antimicrob Chemother 2014; **69**: 3387–3392
doi:10.1093/jac/dku305 Advance Access publication 6 August 2014

Journal of Antimicrobial Chemotherapy

A multicentre cohort study on colonization and infection with ESBL-producing Enterobacteriaceae in high-risk patients with haematological malignancies

Maria J. G. T. Vehreschild[1,2]*, Axel Hamprecht[1,3], Lisa Peterson[1,4], Sören Schubert[1,5], Maik Häntschel[1,6], Silke Peter[1,7], Philippe Schafhausen[1,8], Holger Rohde[1,9], Marie v. Lilienfeld-Toal[1,10,11], Isabelle Bekeredjian-Ding[1,12], Johannes Libam[1,2], Martin Hellmich[1,13], Jörg J. Vehreschild[1,2], Oliver A. Cornely[1,2,14,15] and Harald Seifert[1,3]

Eur J Clin Microbiol Infect Dis (2011) 30:355–360
DOI 10.1007/s10096-010-1093-x

ARTICLE

Risk factors for, and clinical relevance of, faecal extended-spectrum β-lactamase producing *Escherichia coli* (ESBL-EC) carriage in neutropenic patients with haematological malignancies

M. Arnan · C. Gudiol · L. Calatayud · J. Liñares · M. Á. Dominguez · M. Batlle · J. M. Ribera · J. Carratalà · F. Gudiol

Micozzi *et al. BMC Infect Dis* (2021) 21:1079
https://doi.org/10.1186/s12879-021-06747-8

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Reduced mortality from KPC-*K.pneumoniae* bloodstream infection in high-risk patients with hematological malignancies colonized by KPC-*K.pneumoniae*

Alessandra Micozzi[1*], Giuseppe Gentile[1], Stefania Santilli[2], Clara Minotti[3], Saveria Capria[3], Maria Luisa Moleti[3], Walter Barberi[3], Claudio Cartoni[3], Silvia Maria Trisolini[3], Anna Maria Testi[1], Anna Paola Iori[3], Giampaolo Bucaneve[4] and Robin Foà[1]

› Infection. 2022 Jan 10. doi: 10.1007/s15010-021-01753-z. Online ahead of print.

Predictive value of surveillance cultures for bacteremia caused by extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales among patients with hematological diseases

Takuya Hattori [1], Tatsunori Goto [2], Masahide Osaki [2], Yukiyasu Ozawa [2], Koichi Miyamura [2]

Affiliations + expand

PMID: 35013943 DOI: 10.1007/s15010-021-01753-z

Doit- on couvrir les BMR?

- Chez le neutropenique, le portage rectal d'une BMR semble être associé a une augmentation du risque de bactériémie à ce germe (contrairement au non neutropénique…)

- L'echec du traitement probabiliste initial est un FDR de mortalité => problème des BLSE, KPC, ERV, SARM et Pyo CAZ-R…

Elting et al. Clin Infect Dis 1997
Ariffin et al. Int J Infect Dis 1999
Tumbarello et al. Antimicrob Agents Chemother 2006
Ortega et al. J Antimicrob Chemother 2009
Trecarichi et al. J Infect 2009
Martinez et al. Antimicrob Agents Chemother 2010
Trecharichi et al. Haematologica 2011

Facteurs de risque orientant l'ATB:

Table 2. Major factors to consider when choosing empirical therapy for febrile neutropenic patients, based on the literature review (6, 8, 9, 18-24, 26, 31, 35-43, 51, 53, 54).

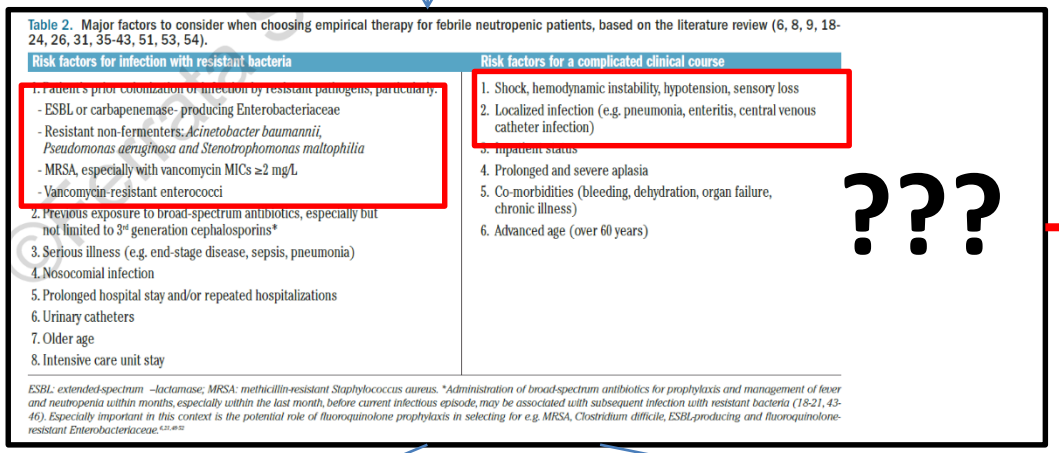
Risk factors for infection with resistant bacteria	Risk factors for a complicated clinical course
1. Patient's prior colonization or infection by resistant pathogens, particularly: - ESBL or carbapenemase- producing Enterobacteriaceae - Resistant non-fermenters: *Acinetobacter baumannii, Pseudomonas aeruginosa and Stenotrophomonas maltophilia* - MRSA, especially with vancomycin MICs ≥2 mg/L - Vancomycin-resistant enterococci	1. Shock, hemodynamic instability, hypotension, sensory loss 2. Localized infection (e.g. pneumonia, enteritis, central venous catheter infection)
2. Previous exposure to broad-spectrum antibiotics, especially but not limited to 3rd generation cephalosporins*	3. Inpatient status
3. Serious illness (e.g. end-stage disease, sepsis, pneumonia)	4. Prolonged and severe aplasia
4. Nosocomial infection	5. Co-morbidities (bleeding, dehydration, organ failure, chronic illness)
5. Prolonged hospital stay and/or repeated hospitalizations	6. Advanced age (over 60 years)
6. Urinary catheters	
7. Older age	
8. Intensive care unit stay	

*ESBL: extended-spectrum –lactamase; MRSA: methicillin-resistant Staphylococcus aureus. *Administration of broad-spectrum antibiotics for prophylaxis and management of fever and neutropenia within months, especially within the last month, before current infectious episode, may be associated with subsequent infection with resistant bacteria (18-21, 43-46). Especially important in this context is the potential role of fluoroquinolone prophylaxis in selecting for e.g. MRSA, Clostridium difficile, ESBL-producing and fluoroquinolone-resistant Enterobacteriaceae.*[6,21,48-52]

Averbuch et al, ECIL-4, Haematologica 2013

2 approches:

Neutropénie fébrile à haut risque (hématologie+++)



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2. Previous exposure to broad-spectrum antibiotics, especially but not limited to 3rd generation cephalosporins* 3. Serious illness (e.g. end-stage disease, sepsis, pneumonia) 4. Nosocomial infection 5. Prolonged hospital stay and/or repeated hospitalizations 6. Urinary catheters 7. Older age 8. Intensive care unit stay	

*ESBL: extended-spectrum –lactamase; MRSA: methicillin-resistant Staphylococcus aureus. *Administration of broad-spectrum antibiotics for prophylaxis and management of fever and neutropenia within months, especially within the last month, before current infectious episode, may be associated with subsequent infection with resistant bacteria (18-21, 43-46). Especially important in this context is the potential role of fluoroquinolone prophylaxis in selecting for e.g. MRSA, Clostridium difficile, ESBL-producing and fluoroquinolone-resistant Enterobacteriaceae.*

???

Examen (bi)quotidien
Screening du portage

-pas de FDR de forme compliquée
-pas d'ATCD de colonisation/ infection à BMR
-écologie locale favorable

Escalade

-FDR de forme compliquée
-ATCD de colonisation/ infection à BMR
-écologie locale défavorable

Désescalade

Averbuch et al, ECIL 2011, Haematologica 2013

Escalade vs Desescalade

Escalade= Monothérapie empirique	**Désescalade: mono-bithérapie large spectre**		
Ceftazidime **AI** **Céfépime** **Pipéracilline/Tazobactam** Ticarcilline/ clavulanate Piperacilline+ gentamicine	- Choc septique - BLSE + - Ecologie BLSE	-BGN non fermentant (écologie, colonisation/infection antérieure, carbapeneme<1mois) - Carbapénémase?	-Sepsis sévère -Pneumonie -SARM/ ERV -Peau/ KT
	Carbapénème **BII**	**β-lactam anti-pyo** **BIII** + **Aminoside/ FQ**	**Ajout anti Gram +** (Vanco/dapto) **CIII**
		Colistine **BIII** + **β-lactam** **+/- rifampicine…**	

ET ON REEVALUE+++

Averbuch et al, ECIL-4, Haematologica 2013

L’épargne des Carbapénèmes:

- **Colonisation** connue à entérobactérie(s) **BLSE**
- Les “**graves**” : choc septique, pneumonie
- Centres à **forte prévalence** de BLSE dans les neutropénies fébriles basés sur les chiffres de suivi

Averbuch et al, ECIL-4, Haematologica 2013
Freifeld et al, CID 2011

L’adjonction d’aminoside:

- Chez les “**graves**” : choc septique, pneumonie
- Si probabilité significative de **BGN non fermentants** basée sur: Epidémiologie locale
- Colonisation
- Usage de carbapénème dans le mois précédent
- Si utilisation PIPERACILLINE ou TICARCILLINE **sans** inhibiteurs de B Lactamines (tazobactam ou acide clavulanique)

Averbuch et al, ECIL-4, Haematologica 2013
Freifeld et al, CID 2011
Schnell et al, ann intensiv care 2016

Aminosides chez le patient neutropénique

Situations in which combination with an aminoglycoside is indicated as the first-line regimen BIII for all

1. Seriously-ill patients e.g. *severe sepsis, septic shock or*
2. If resistant non-fermenters (*Pseudomonas aeruginosa or Acinetobacter* spp.) are likely, based upon:
   a. *Local epidemiology*
   b. *Previous colonization or infection with these pathogens*
   c. *Previous use – during the last month – of carbapenems*

ECIL 2011

Choc septique + neutropénie : facteurs associés à la mortalité	OR (IC95%) multivarié	p-value
Bêta-lactamine empirique seule	0.41 (0.08-2.16)	0.294
Bêta-lactamine empirique + aminoside	**0.32 (0.18-0.57)**	**<0.001**
Aminoside comme seul ATB actif	**15.24 (1.73-134.45)**	**0.014**

Chumbita, AAC, 2021

ction anti-Gram+

Table 4. Indications for Addition of Antibiotics Active Against Gram-Positive Organisms to the Empirical Regimen for Fever and Neutropenia

- Hemodynamic instability or other evidence of severe sepsis
- Pneumonia documented radiographically
- Positive blood culture for gram-positive bacteria, before final identification and susceptibility testing is available
- Clinically suspected serious catheter-related infection (eg, chills or rigors with infusion through catheter and cellulitis around the catheter entry/exit site)
- Skin or soft-tissue infection at any site
- Colonization with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, or penicillin-resistant *Streptococcus pneumoniae* (see text)
- Severe mucositis, if fluoroquinolone prophylaxis has been given and ceftazidime is employed as empirical therapy

re intention globalement

SA

pectée

ue **pea**

Situations in which antibiotics *vs.* resistant Gram-positive bacteria is indicated to combine in the first-line regimen CIII for all

1. Hemodynamic instability or other evidence of severe sepsis, septic shock or pneumonia *or*
2. Colonization with MRSA or VRE *or*
3. Suspicion of serious catheter-related infection *e.g. chills or rigors with infusion through catheter and cellulitis around the catheter exit site or*
4. Skin or soft-tissue infection at any site

- **Pneumonie** documentée radiologiquement,
- Instabilité
- **Cocci G+** e
- Notion de

RV-2—Glycopeptide antibiotic adjunctive agents (or other agents active against resistant aerobic gram-positive cocci) should probably be considered for the following specific clinical indications

V-2-a—Suspected catheter-related infection (Grade 2+, strong agreement)

V-2-b—Skin or soft tissue infection (Grade 2+, strong agreement)

V-2-c—Severe sepsis or septic shock (Grade 2+, weak agreement)

V-2-d—Use of antipseudomonal -lactam agent with insufficient anti-gram-positive activity (ceftazidime, for example) (Grade 2+, weak agreement)

V-2-e—Grade III or IV mucositis (Grade 2+, weak agreement)

V-2-f—Known colonization with methicillin-resistant Staphylococcus aureus (Grade 2+, weak agreement)

Averbuch et al, ECIL-4, Haematologica 2013
Freifeld et al, CID 2011
Schnell et al, ann intensiv care 2016

Cochrane Library

Cochrane Database of Systematic Reviews

Empirical antibiotics targeting gram-positive bacteria for the treatment of febrile neutropenic patients with cancer (Review)

Beyar-Katz O, Dickstein Y, Borok S, Vidal L, Leibovici L, Paul M

Beyar-Katz O, Dickstein Y, Borok S, Vidal L, Leibovici L, Paul M.

Empirical antibiotics targeting gram-positive bacteria for the treatment of febrile neutropenic patients with cancer.

Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD003914.

DOI: 10.1002/14651858.CD003914.pub4.

Key results: mortality did not differ between patients groups. Antibiotic treatment was more frequently modified among patients who did not initially receive specific antibiotics against gram-positive bacteria, but overall treatment failures were not different. We attempted to examine the durations of fever and hospital stay, but these were not consistently reported. The addition of specific antibiotics against gram-positive bacteria resulted in more adverse events, mainly rash. We conclude that antibiotic treatment directed against resistant gram-positive bacteria can await identification of specific bacteria and need not be given routinely prior to bacterial identification.

J0 : antibiothérapie probabiliste
NF à haut risque

Aucun signe de gravité

Cas général
(y compris colonisation à EBLSE
Si pas d'antibiothérapie préalable)
TAZOCILLINE**
4g/6h IVSE sur 4h†

Antibiothérapie large spectre < 3mois*
ET colonisation connue à EBLSE
MEROPENEME†
Dose de Charge de 2g sur 5 minutes puis 2g/8h IVSE sur 8h†

≥ 1 signe de gravité

Pas de colonisation connue à EBLSE
TAZOCILLINE**
4g/6h IVSE sur 4h†
+ AMIKACINE ***
30mg/kg x1 IVL sur 30min

Colonisation connue à BLSE
MEROPENEME†
Dose de Charge de 2g sur 5 minutes puis 2g/8h IVSE sur 8h†
+ AMIKACINE ***
30mg/kg x1 IVL sur 30 min

**Antibiothérapie large spectre : Fluoroquinolone, Céphalosporine de 3ème génération, Piperacilline/Tazobactam*

*** Attention incompatibilité de Piperacilline/Tazobactam avec : bicarbonate, ringer lactacte, produits sanguins labiles, Albumine*

**** Une deuxième dose d'Amikacine sera à discuter en fonction de la persistance des signes de gravité*

† *Les alternatives et modalités administration de Piperacilline/Tazobactamet du meropénème sont disponible en appendices*

SIGNES DE GRAVITE

- PAS < 90mmHg ou marbrures ou lactates artériels ≥ 2mmol/L
- SpO2 < 92% en AA ou FR ≥ 22/min ou signes de lutte respiratoires
- troubles de vigilance

INDICATIONS de la VANCOMYCINE*

Signes de gravité **ET** colonisation à SARM

OU VVC suspecte

OU Infection de la peau ou des tissus mous

En perfusion continue : 25mg/kg en dose de charge IVSE sur 1h puis 40mg/kg/24h IVSE

Prévoir un dosage plasmatique de vancomycine à H24 avec objectifs 25-35mg/l.

En perfusion discontinue : 20mg/kg/12h sur une perfusion de 1h minimum, sans dépasser 10 mg/minute

Prévoir un dosage plasmatique en résiduel de vancomycine à H24 avec objectifs 15-20mg/l.

* **Attention sur-risque d'insuffisance rénale de l'association Vancomycine / Pipéracilline**

- Si utilisation de VANCOMYCINE nécessaire, préférer l'associer à une autre bêta-lactamine large spectre (CEFEPIME ou CEFTAZIDIME ou MEROPENEME si indication)
- Si patient sous PIPERACILLINE/TAZOBACTAM non modifiable, préférer l'utilisation de DAPTOMYCINE 10mg/kg/j en remplacement de la VANCOMYCINE (en l'absence d'infection pulmonaire)

Existe-t-il une orientation clinique?

- Cutanée: anti gram+
- Digestive: métronidazole, CD
- Fongique: rarement en urgence
- Pulmonaire: PCP, intracellulaire, légionellose
- Infection Virale: Herpes
- Neurologique: Listeria, herpes (Tazobactam ne passe pas dans les méninges…)

M.D 50 ans, suite

- Un traitement Probabiliste par méropènème est débuter devant la NF à haut risque non grave colonisé à BLSE.

- 24h plus tard patient toujours fébrile à 40°c avec des frissons et une altération de l'état générale

=> **Quelle est votre attitude?**

M.D 50 ans, suite

- Un traitement probabiliste par méropènème est débuter devant la NF à haut risque non grave colonisé à BLSE.
- 24h plus tard patient toujours fébrile (40°c)+ frissons:
  - Hémocultures + KT et periph sans différentiel
  - Cocci + en chainette et BGN sur flacon aérobie

    => **Quelle est votre attitude?**

M.D 50 ans, suite

- Le traitement par vancomycine est débuté
- Ajout Ceftazidime au meropénème *(P.aéruginosa*)
- 1 dose d'amikacine

MAIS

Pour le micro-organisme no. 1 Pseudomonas aeruginosa

Technique : diffusion	DIFFUSION
Ticarcilline	R (Diff.:18.00)
Ticarcilline + ac. clavulanique	R (Diff.:15.00)
Pipéracilline	R (Diff.: 6.00)
Pipéracilline + tazobactam	R (Diff.:14.00)
Ceftazidime	R (Diff.:14.00) (CMI:12.00
Ceftolozane/Tazobactam	S (CMI: 3.00) CC: 4 mg/L
Aztréonam	I (Diff.:22.00)
Céfépime	R (Diff.:17.00) (CMI:16.00
Imipénème	R (Diff.:11.00)
Méropénème	I (Diff.:19.00)
Tobramycine	R (Diff.: 6.00)
Amikacine	S (Diff.:21.00)
Ciprofloxacine	R (Diff.: 6.00)
Lévofloxacine	R (Diff.: 6.00)
Colistine	S (CMI: 3.00) CC: 4 mg/L

Pour le micro-organisme no. 2 Enterococcus gallinarum

Technique : diffusion	DIFFUSION
Ampicilline	S
Amoxicilline	S
Céfotaxime	R
Gentamicine	I
Lévofloxacine	S (CMI: 2.00) CC: 4 mg/L
Erythromycine	R (Diff.: 6.00)
Lincomycine	R (Diff.: 6.00)
Linézolide	S (Diff.:20.00)
Teicoplanine	S (Diff.:18.00)
Vancomycine	R (Diff.:13.00)
Nitrofuranes	S (Diff.:22.00)
Rifampicine	S (Diff.:30.00)

Pour le micro-organisme no. 2 Enterococcus faecium

Technique : diffusion	DIFFUSION
Pénicilline G	R (Diff.: 6.00)
Ampicilline	R
Amoxicilline	R
Céfotaxime	R
Gentamicine	I
Lévofloxacine	S (Diff.:18.00) (CMI: 2.
Erythromycine	R (Diff.: 6.00)
Lincomycine	R (Diff.: 6.00)
Pristinamycine	S (Diff.:23.00)
Linézolide	S (Diff.:23.00)
Teicoplanine	S (Diff.:18.00)
Vancomycine	S (Diff.:19.00)
Nitrofuranes	R (Diff.:15.00)
Rifampicine	R (Diff.:15.00)

Que faites- Vous?

CAT (si patient toujours fébrile) à 48h

- REEXAMINER le patient
- REPRELEVER, Récupérer les résultats
- Rechercher infection fongique, foyer profond
  - Ag aspergillaire, TDM thoracique, +/- LBA
  - Imagerie abdominopelvienne, ETT (EI), doppler veineux (cathéter)
- Sur le plan thérapeutique
  - Adaptation si documentation
  - Pas d'escalade ATB si patient stable
  - Discuter traitement antifongique probabiliste

Les grands messages des recommandations: rééval à 48h

The further management of febrile neutropenic patients should be based on their clinical course and microbiological results.

a) If a pathogen is identified

Whatever the initial approach was (escalation or de-escalation) the patient should be treated according to the organism identified (assuming it is a plausible pathogen) using narrower-spectrum agents, guided by *in vitro* susceptibility tests, including minimum inhibitory concentrations (MIC) when available, and based on knowledge on drugs with specific activities **AI**.

Consultation with an infectious diseases expert/clinical microbiologist is recommended, if available.

b) Escalation approach, no bacteria documented (Figure 1)

Broadening of initial antibiotic regimen is recommended only for a deteriorating patient. The appropriateness of the antibiotic choice for CDI should be assessed. It is important to emphasize that continuing fever in a stable patient is not a criterion to escalate antibiotics, but diagnostic efforts should be continued, including repeated blood and other cultures (sampling any focus repeatedly at the discretion of the physician), and possibly including seeking fungal or viral infections, serum fungal diagnostic tests (galactomannan or β-(1-3)-D glucan assays), chest X-rays and eventually computed tomography (CT) scans of the lungs, abdomen, sinuses and brain. The number of blood

c) De-escalation approach, no bacteria documented (Figure 2)

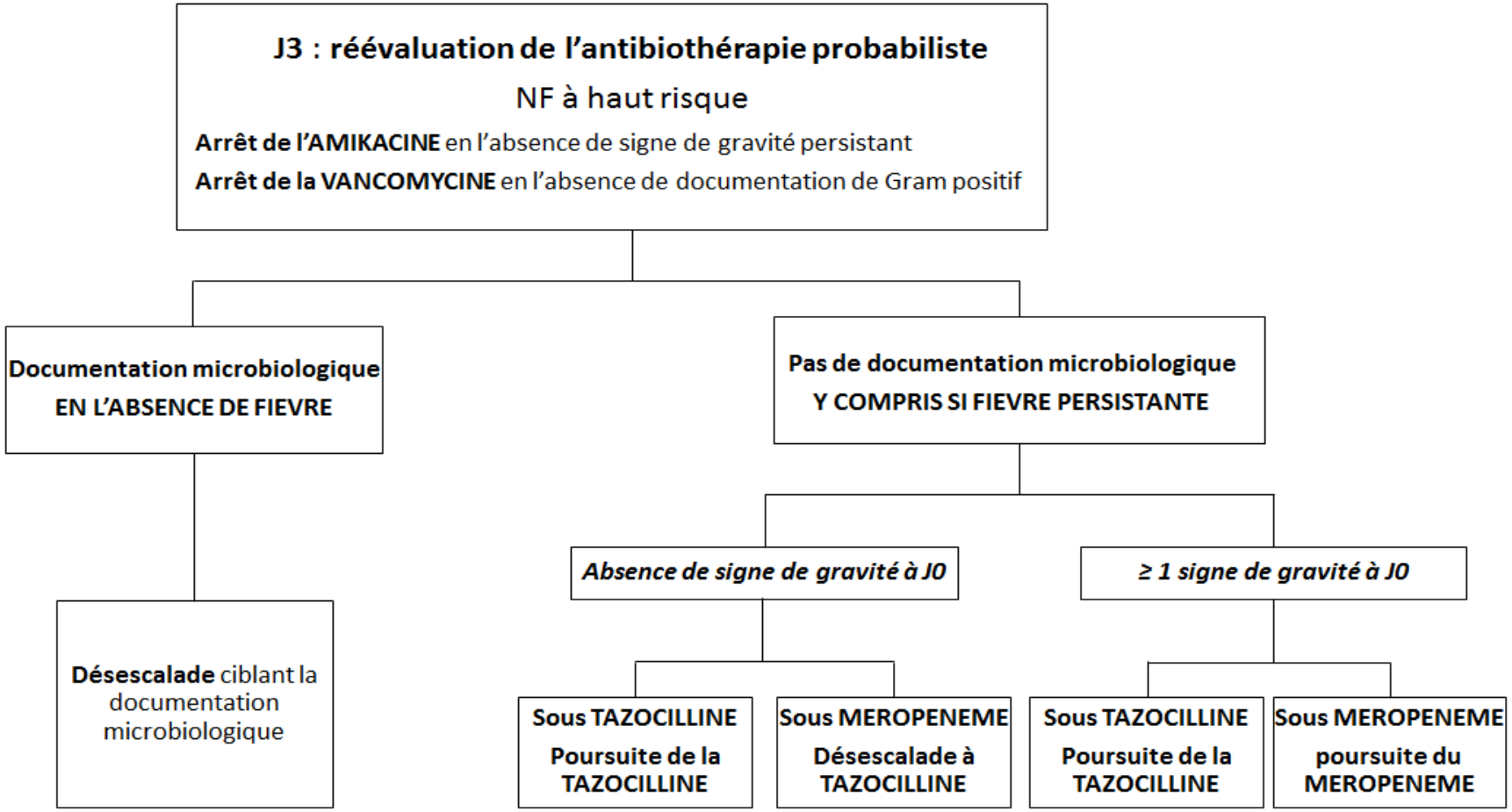
If a de-escalation approach was chosen based on severe illness at presentation (e.g. septic shock) and the patient has stabilized on treatment, no change in initial therapy is recommended, even if blood or other cultures remain negative.

If a de-escalation approach was chosen based on known colonization or previous infection with resistant bacteria and the patient was stable at presentation, streamlining of initial therapy should be considered (Figure 2) including: i) discontinuation of any aminoglycoside, quinolone, colistin or any antibiotic directed against resistant Gram-positive pathogens, if given in combination; or ii) for patients with FUO initially treated with a carbapenem, change to a narrower-spectrum agent, e.g. cefepime, ceftazidime, piperacillin-tazobactam, cefoperazone-sulbactam or ticarcillin-clavulanate (the last two agents are not available in many European countries). Diagnostic efforts should be continued, including repeated cultures (sampling any focus repeatedly at the discretion of the physician) and possibly including seeking fungal or viral infections, serum fungal diagnostic tests (galactomannan or β-(1-3)-D glucan assays), chest X-rays and eventually a CT scan of the lungs, abdomen, sinuses and brain.

Averbuch et al, ECIL-4, Haematologica 2013

Réévaluation de l'antibiothérapie à 48-72 heures

La persistance de la fièvre (ou l'apyrexie puis réapparition de la fièvre sous l'antibiothérapie initiale) en l'absence de dégradation clinique, ne constitue pas en elle-même une indication à modifier l'antibiothérapie (sauf dans le cas d'une colonisation rectale à *E. BLSE* avec persistance de symptômes, où se pose la question de prendre en compte la colonisation)



DESESCALADE D'ANTIBIOTHERAPIE UNIQUEMENT APRES ACCORD DU SENIOR D'HEMATOLOGIE

Si persistance de la fièvre à J3-J5

- Refaire une paire d'hémoculture
- Répéter les prélèvements en fonction des points d'appel clinique
- Bilan à la recherche d'une infection fongique
  - TDM sinus + TAP
  - Antigène galactomannane deux jours de suite
  - β-1,3 D glucane sanguin
  - PCR sanguine pour aspergillus et mucorales
  - Discuter prélèvement invasif en fonction du TDM (LBA)

Chemtouh R, Bernard S, Kernéis S; Procédure Hôpital Cochin 2019

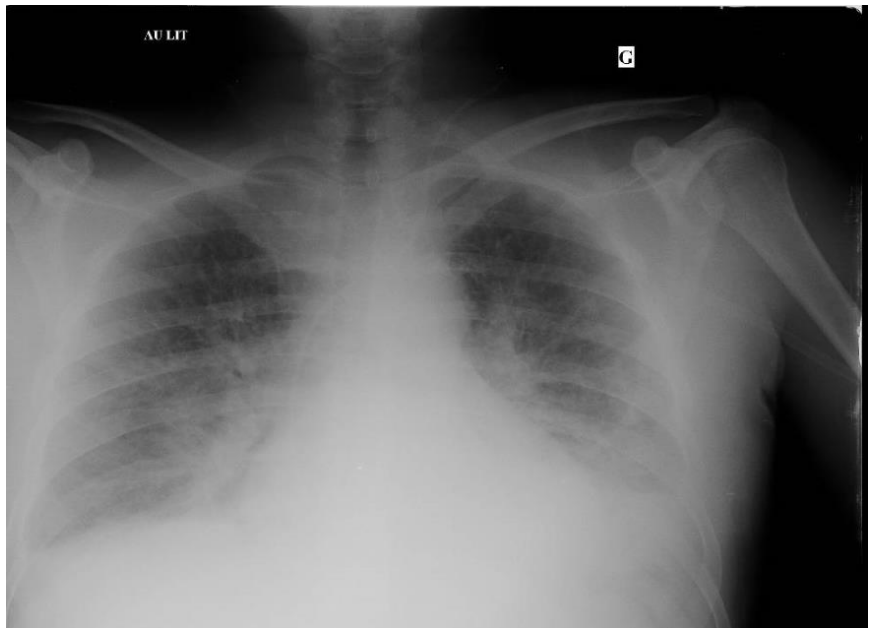
M.D 50 ans, suite

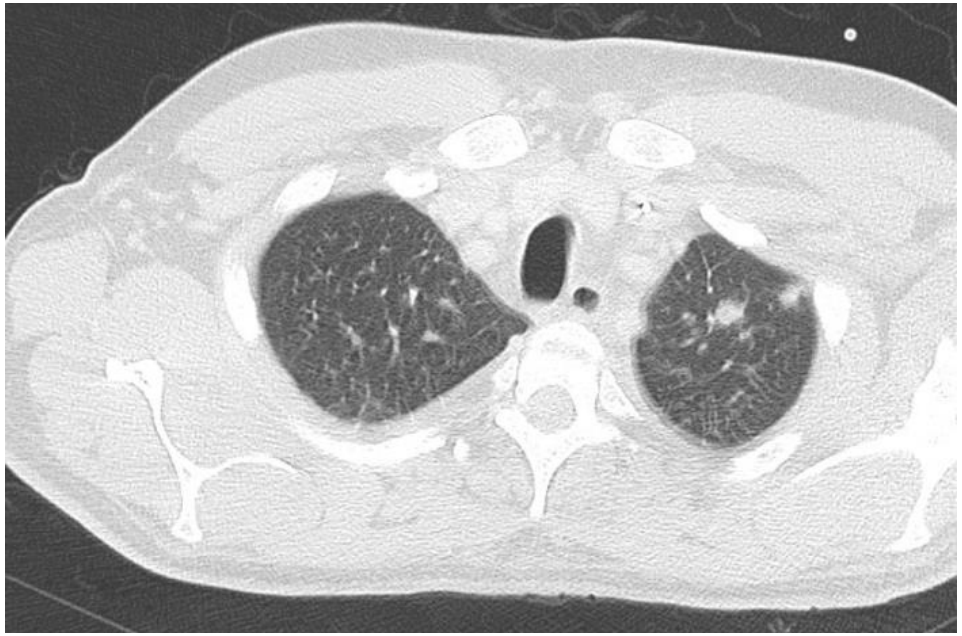
- Le traitement a été modifié par
  - Ceftolozane- tazobactam + 2j d'amikacine
  - Targocid
- Evolution clinique initialement favorable
- 48h plus tard:
  - Dégradation: fievre à 39°c
  - Insuffisance respiratoire aigue

=> Que faites-vous?

M.D 50 ans, suite

- Hemocultures négatives, ECBU negatif
- Antigénuries négatives, antigénémie negative
- PCR virales respiratoires : rhinovirus positif
- PCR virales dans le sang négatives (CMV, EBV, HSV)
- LBA: négatif (bactério, myco, mycobactérie)





CAT si patient toujours fébrile à 4-5j

- REEXAMINER le patient
- REPRELEVER, Récupérer les résultats
- Rechercher infection fongique, foyer profond
  - Ag aspergillaire, TDM thoracique, +/- **LBA**
  - **TDM**, ETT (EI), doppler veineux (cathéter)
- Sur le plan thérapeutique
  - Adaptation si documentation
  - Pas d'escalade ATB si patient stable
  - Discuter traitement antifongique probabiliste
  - Avis réa (pneumopathie/ entérocolite)/ chirurgien (enterocolite)

TABLEAU II

Causes de fièvre persistante chez le patient neutropénique après initiation d'une antibiothérapie empirique [13]

Causes infectieuses de fièvre persistante
Posologie ou concentration sérique d'antibiotique inadaptée
Diarrhée à *Clostridium difficile*
Pathogène résistant à l'antibiothérapie initiée : BMR, mycobactérie, légionnelle, mycoplasme, *Chlamydia pneumoniae*, Bartonella
Infection fungique : levures (Candida, cryptocoque), champignons (Aspergillus, zygomycetes)
Infection parasitaire : toxoplasmose
Infection virale : herpes virus (CMV, EBV, HHV6, HSV, VZV), virus *influenza*, para-influenza, VRS
Persistance du foyer infectieux : cathéter
Infection incontrôlée : endocardite, péritonite
Causes non infectieuses de fièvre persistante
Fièvre post-transfusionnelle
Syndrome d'activation macrophagique
Thrombose veineuse profonde
Fièvre médicamenteuse
Maladie du greffon contre l'hôte chez le patient allogreffé
Pancréatite
Maladie maligne sous-jacente, rechute
Sortie d'aplasie

Saillard et al, Bull cancer 2015

Table 3. Clinical hypotheses if patient is still febrile at Day 3

Hypotheses	Complementary investigations
Underdosed antibiotics	Therapeutic drug monitoring
Inappropriate antibiotic therapy	Repeat blood cultures
Uncontrolled focal infection	Full body tomography
	Consider [^{18}F]FDG-PET-CT scan
	Therapeutic drug monitoring
	Consider central venous catheter withdrawal and culture
	Search for *Clostridioïdes difficile* infection
Thrombosis (+/– septic) of central venous catheter	Central catheter Doppler ultrasound
	Repeat blood cultures
Undocumented MDR bacteria	Repeat blood cultures
Insufficient antibacterial spectrum	
Viral infection	Nasopharyngeal swab with PCR test
(flu, respiratory syncytial virus, SARS-CoV-2, etc.)	
Invasive fungal infection	Sinus and chest tomography
(aspergillosis, mucormycosis, invasive candidiasis, etc.)	Galactomannan antigen
	Aspergillus sp. blood PCR
	Mucor sp. blood PCR
	β-D-Glucan
	Repeat blood cultures

Contejean et al, JAC 2023

Dans la NF, ne pas oublier le fongique…

- TT probabiliste/préemptif
  - Sur T°, Ag, βDG, image TDM…..
  - Ambisome ou caspo
  - Scanner thoracique rapide
    - Si pas d'anomalies, arrêt AF (repasser en prophylaxie s'il y en avait une)
    - Si anomalie, discuter LBA et passer en traitement
- Curatif
  - Asperg: vori, sinon ambisome, sinon caspo mais bof
  - Candida: caspo, sinon ambisome, sinon vori. Adapte
- GM et βDG 2/sem si neutropénie
- Scanner facile
- Dosage systématique posa/vori (po et IV)

Table 3 ECIL 3 guidelines on empirical antifungal treatment in neutropenic patients with persistent or relapsing fever (the updated items are reported in bold italic)

Antifungal agent	*Daily dose*	*Level of recommendation*	*CDC grading Level of evidence for*	
			Efficacy	*Safety*
Liposomal ampho B	3 mg/kg	A[a]	I	I
Caspofungin	50 mg	A[a,b]	I	I
ABCD	4 mg/kg	B[c]	I	I
ABLC	5 mg/kg	B[c]	I	I
Itraconazole	200 mg i.v.	B[b,e]	I	I
Voriconazole	2 × 3 mg/kg i.v.	B[b,d,e]	I	I
Micafungin	***100 mg***	***B***	***II***	***II***
Ampho B deoxycholate	0.5–1 mg/kg	B[c]/D[f]	I	I
Fluconazole	400 mg i.v.	C[b,e,g]	I	I

Chen *et al. BMC Infectious Diseases* (2017) 17:159
DOI 10.1186/s12879-017-2263-6

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Empiric treatment against invasive fungal diseases in febrile neutropenic patients: a systematic review and network meta-analysis

Ken Chen[1], Qi Wang[2], Roy A. Pleasants[3], Long Ge[2], Wei Liu[1], Kangning Peng[4] and Suodi Zhai[1*]

Diapo empruntée à S.Alfandari
Maertens J et al, ECIL 3, BMT 2011

M.D 50 ans, suite

- Apres un traitement par:
  - Ceftolozane/tazobactam+
  - Targocid+
  - Rovamycine
  - Antifongique: voriconazole puis ambisome

    ⇒**M.D est apyrétique et va mieux**

    ⇒**Que fait-on de tous ces anti-infectieux et pour quelle durée?**

Durée de traitement:

22. In patients with clinically or microbiologically documented infections, the duration of therapy is dictated by the particular organism and site; appropriate antibiotics should continue for at least the duration of neutropenia (until ANC ⩾ 500 cells/mm^3) or longer if clinically necessary (B-III).

23. In patients with unexplained fever, it is recommended that the initial regimen be continued until there are clear signs of marrow recovery; the traditional endpoint is an increasing ANC that exceeds 500 cells/mm^3 (B-II).

Duration of targeted therapy for microbiologically documented infections.

Antibiotic treatment should be continued for at least 7 days, until the infection is microbiologically eradicated and all clinical signs of infection are resolved, with the patient afebrile for at least 4 days **BIII**. If the patient is still neutropenic and antibiotic therapy is stopped, (s)he should be kept hospitalized under close observation for at least 24-48 hours. If fever recurs, antibiotics should be re-started urgently after obtaining blood cultures and performing other relevant evaluation based on clinical judgment.

Duration of antibacterial treatment

Empirical antibiotics can be discontinued after 72 h or more of intravenous administration in patients who have been hemodynamically stable since presentation and have been afebrile for 48 h or more, irrespective of their neutrophil count or expected duration of neutropenia **BII**. The patient should be kept hospitalized under close observation for at least a further 24-48 h if the patient is still neutropenic when antibiotic therapy is stopped. If fever recurs, antibiotics should be re-started urgently, after obtaining blood cultures and clinical evaluation. Centers that give prophylactic antibacterial agents should consider renewing this regimen upon discontinuation of the empirical therapy if the patient is still neutropenic **CIII**.

⇒ 2 écoles, un débat…

Averbuch et al, ECIL-4, Haematologica 2013
Freifeld et al, CID 2011

Durée de traitement:

Discontinuation of empirical antibiotic therapy in neutropenic acute myeloid leukaemia patients with fever of unknown origin: is it ethical?

J.-B. Micol[1], C. Chahine[1], P.-L. Woerther[2], D. Ghez[1], F. Netzer[3], C. Dufour[4], M. Merad[5], F. Blot[6], E. Chachaty[2], S. de Botton[1] and B. Gachot[6]

1) *Service d'Hématologie,* 2) *Laboratoire de Microbiologie,* 3) *Service de Pharmacie,* 4) *Service de Pédiatrie,* 5) *Service des Urgences and* 6) *Département de Soins Aigus, Gustave Roussy Cancer Campus Grand Paris, Villejuif, France*

Discontinuation of empirical antibiotic therapy in neutropenic leukaemia patients with fever of unknown origin is ethical

C. Orasch[1], D. Averbuch[2], M. Mikulska[3], C. Cordonnier[4], D. M. Livermore[5], I. C. Gyssens[6,7,8], G. Klyasova[9], D. Engelhard[2], W. Kern[10], C. Viscoli[3], M. Akova[11] and O. Marchetti[1] for the 4th European Conference on Infections in Leukemia (ECIL-4), a joint venture of Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (IDWP-EBMT), Infectious Diseases Group of the European Organization for Research and Treatment of Cancer (IDG-EORTC), International Immunocompromised Host Society (ICHS), European Leukemia Net (ELN) and European Study Group on Infections in Immunocompromised Hosts of the European Society for Clinical Microbiology and Infectious Diseases (ESGICH-ESCMID)

⇒ 2 écoles, un débat…

⇒ 7 patients avec arrêt ATB , 4 rechutes précoces

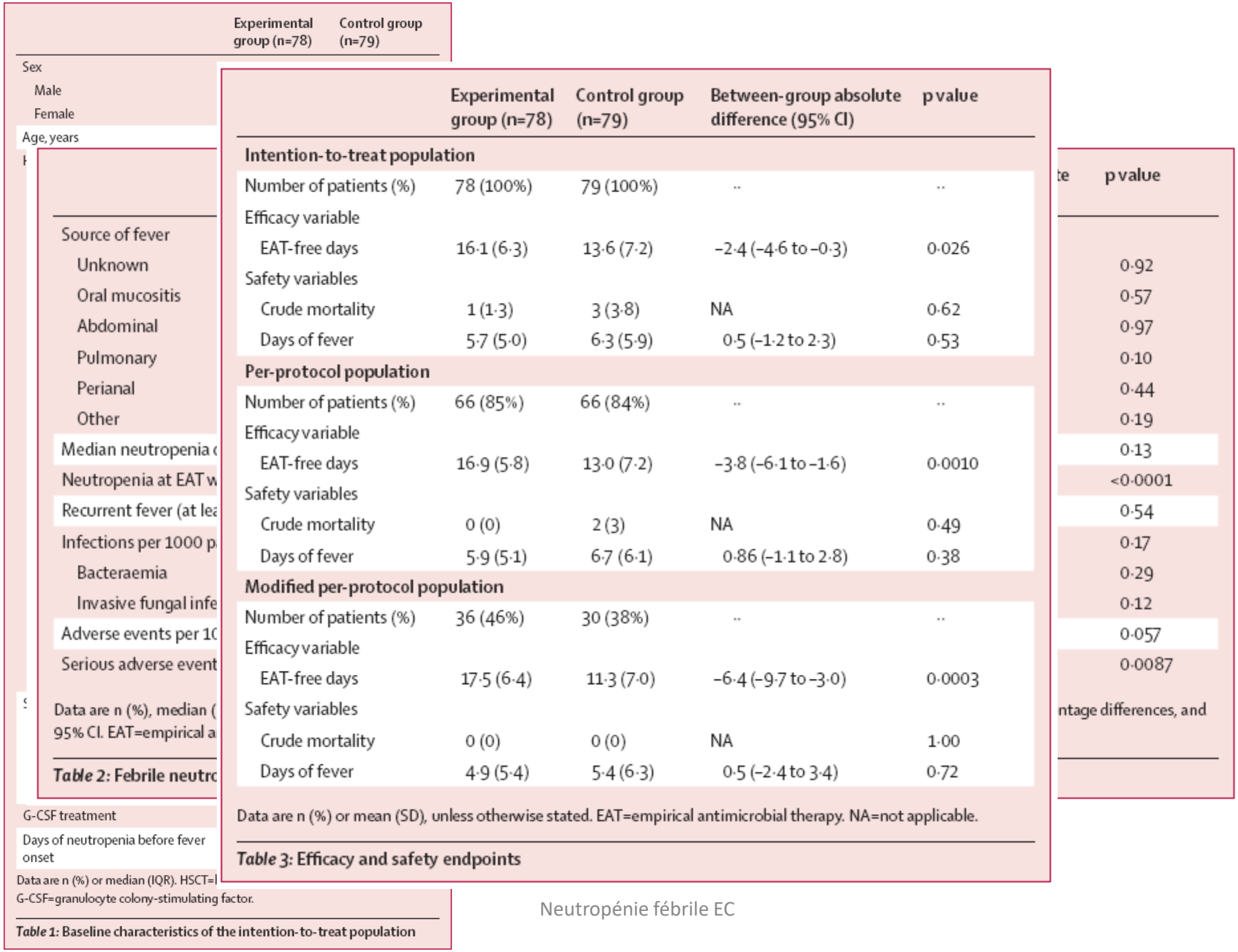
⇒ En pratique: se poser la question, si tout les critères sont remplis: discuter l'arrêt des ATB.

⇒ Les autres possibilité: maintien ATB large spectre, reprise ATB prophylaxie.

Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial

Manuela Aguilar-Guisado, Ildefonso Espigado, Almudena Martín-Peña, Carlota Gudiol, Cristina Royo-Cebrecos, José Falantes, Lourdes Vázquez-López, María Isabel Montero, Clara Rosso-Fernández, María de la Luz Martino, Rocío Parody, José González-Campos, Sebastián Garzón-López, Cristina Calderón-Cabrera, Pere Barba, Nancy Rodríguez, Montserrat Rovira, Enrique Montero-Mateos, Jordi Carratalá, José Antonio Pérez-Simón, José Miguel Cisneros

NF à haut risque
Randomisation 1:1: durée de trt selon IDSA (jusque PNN>500) vs ECIL 4 (arrêt à 72h)
Primary endpoint: nbre de jour sans ATB
Critère secondaire: mortalité et nbre d'épisode de NF, cutoff de PCT
Essai randomisé, de supériorité
Avril 2012 a mai 2016
157 patients



	Experimental group (n=78)	Control group (n=79)	Between-group absolute difference (95% CI)	p value
Intention-to-treat population				
Number of patients (%)	78 (100%)	79 (100%)	..	..
Efficacy variable				
EAT-free days	16·1 (6·3)	13·6 (7·2)	−2·4 (−4·6 to −0·3)	0·026
Safety variables				
Crude mortality	1 (1·3)	3 (3·8)	NA	0·62
Days of fever	5·7 (5·0)	6·3 (5·9)	0·5 (−1·2 to 2·3)	0·53
Per-protocol population				
Number of patients (%)	66 (85%)	66 (84%)	..	..
Efficacy variable				
EAT-free days	16·9 (5·8)	13·0 (7·2)	−3·8 (−6·1 to −1·6)	0·0010
Safety variables				
Crude mortality	0 (0)	2 (3)	NA	0·49
Days of fever	5·9 (5·1)	6·7 (6·1)	0·86 (−1·1 to 2·8)	0·38
Modified per-protocol population				
Number of patients (%)	36 (46%)	30 (38%)	..	..
Efficacy variable				
EAT-free days	17·5 (6·4)	11·3 (7·0)	−6·4 (−9·7 to −3·0)	0·0003
Safety variables				
Crude mortality	0 (0)	0 (0)	NA	1·00
Days of fever	4·9 (5·4)	5·4 (6·3)	0·5 (−2·4 to 3·4)	0·72

Data are n (%) or mean (SD), unless otherwise stated. EAT=empirical antimicrobial therapy. NA=not applicable.

Table 3: Efficacy and safety endpoints

	Experimental group (n=78)	Control group (n=79)
Sex		
Male		
Female		
Age, years		
Source of fever		
Unknown		
Oral mucositis		
Abdominal		
Pulmonary		
Perianal		
Other		
Median neutropenia		
Neutropenia at EAT		
Recurrent fever (at lea		
Infections per 1000 p		
Bacteraemia		
Invasive fungal infe		
Adverse events per 1		
Serious adverse event		
G-CSF treatment		
Days of neutropenia before fever onset		

Data are n (%), median (95% CI. EAT=empirical a

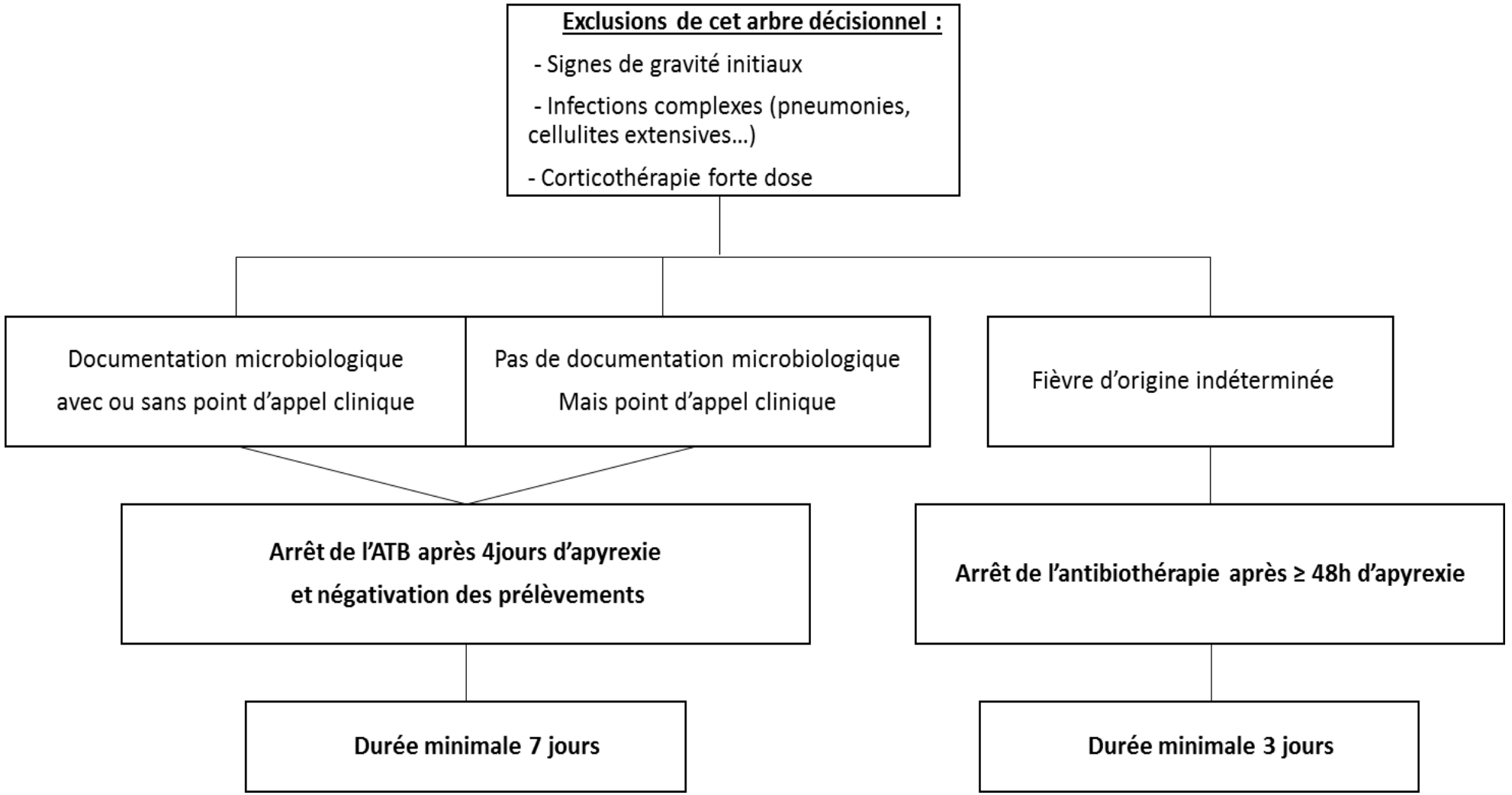
Data are n (%) or median (IQR). HSCT= G-CSF=granulocyte colony-stimulating factor.

Table 2: Febrile neutrc

Table 1: Baseline characteristics of the intention-to-treat population

te	p value
	0·92
	0·57
	0·97
	0·10
	0·44
	0·19
	0·13
	<0·0001
	0·54
	0·17
	0·29
	0·12
	0·057
	0·0087

ntage differences, and


Exclusions de cet arbre décisionnel :
- Signes de gravité initiaux
- Infections complexes (pneumonies, cellulites extensives…)
- Corticothérapie forte dose
Documentation microbiologique avec ou sans point d'appel clinique
Pas de documentation microbiologique Mais point d'appel clinique
Fièvre d'origine indéterminée
Arrêt de l'ATB après 4jours d'apyrexie et négativation des prélèvements
Arrêt de l'antibiothérapie après ≥ 48h d'apyrexie
Durée minimale 7 jours
Durée minimale 3 jours

European Journal of Clinical Microbiology & Infectious Diseases
https://doi.org/10.1007/s10096-018-3328-1

ORIGINAL ARTICLE

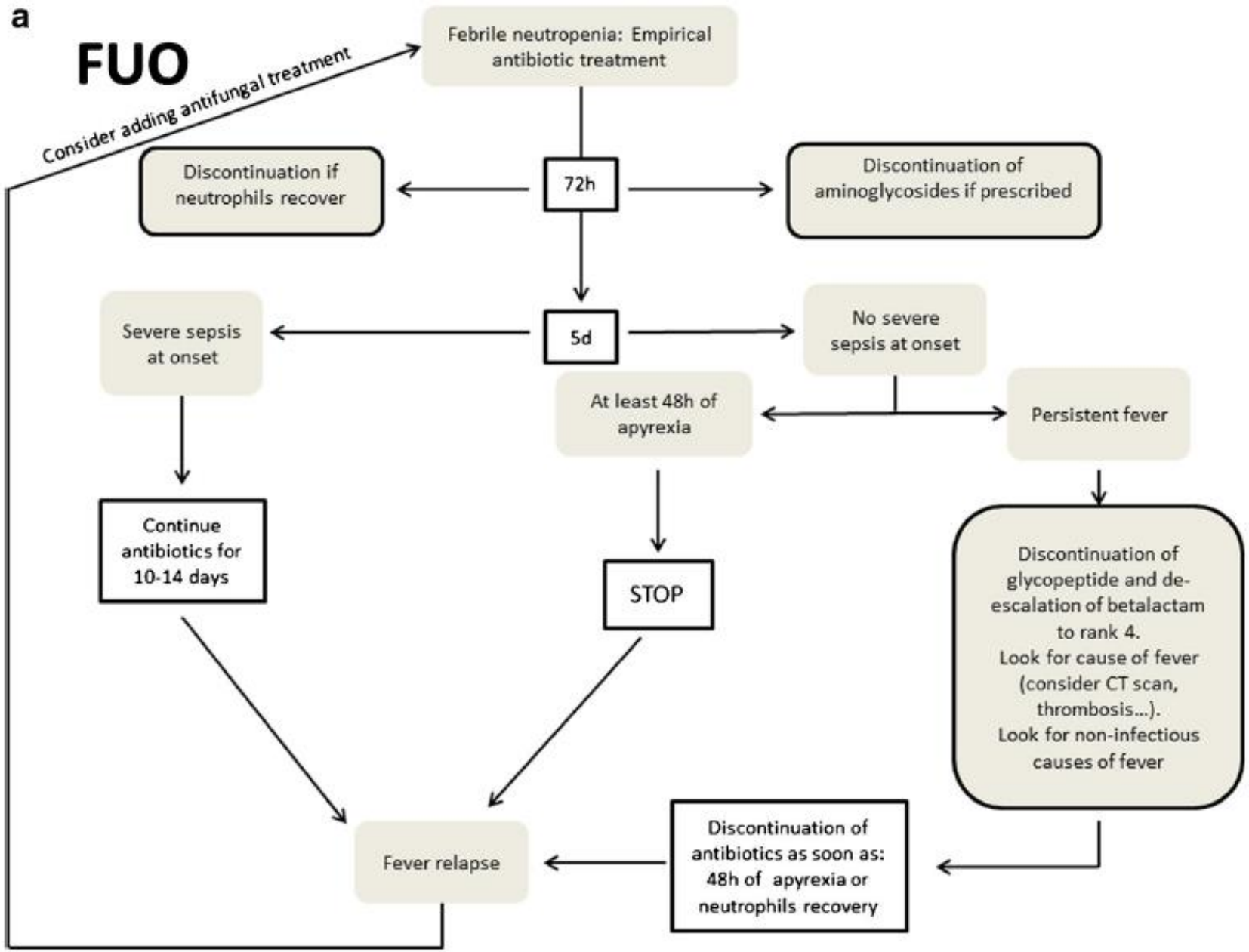
De-escalation and discontinuation strategies in high-risk neutropenic patients: an interrupted time series analyses of antimicrobial consumption and impact on outcome

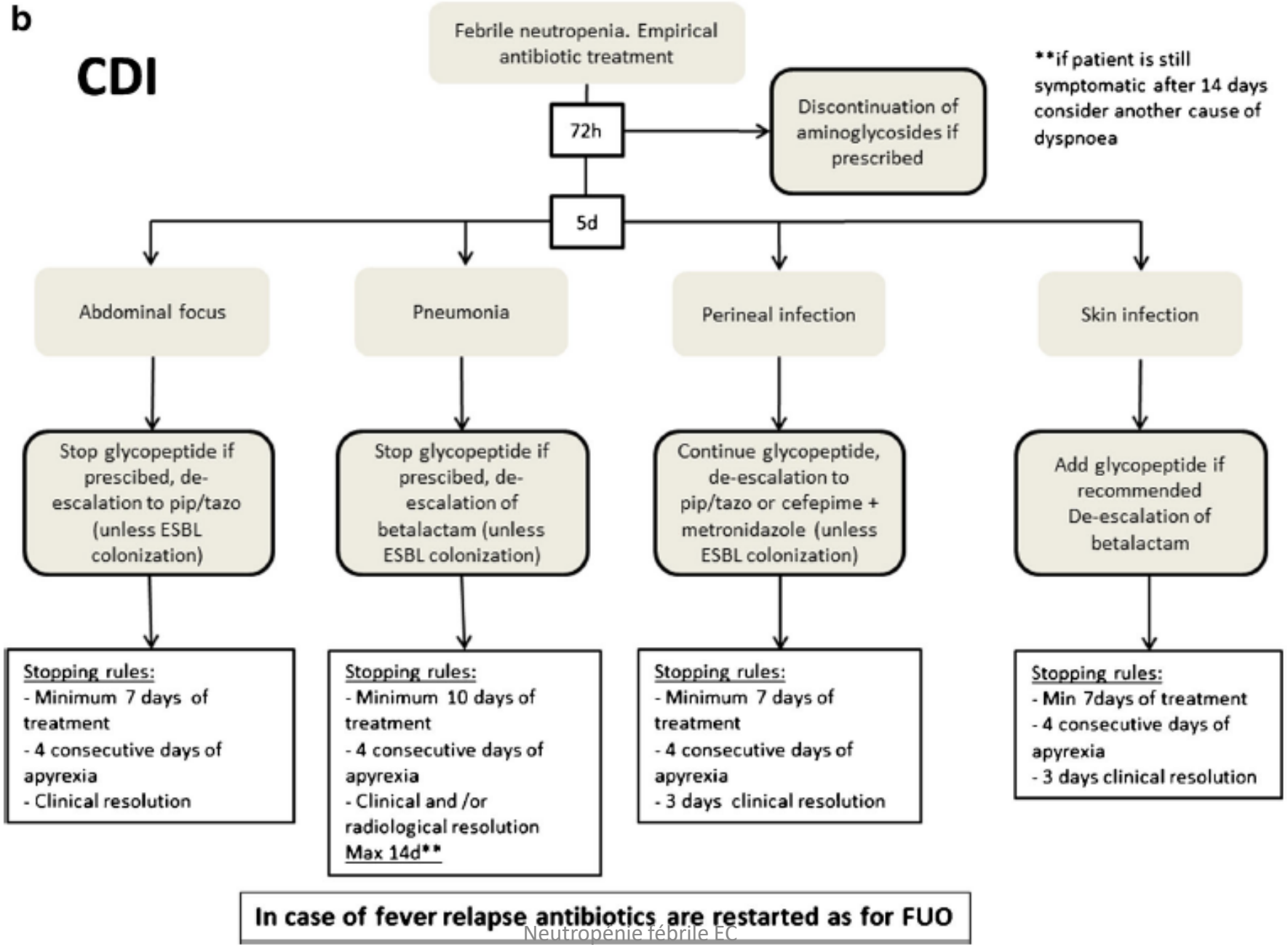
Giulia la Martire[1,2] · Christine Robin[1,3] · Nadia Oubaya[4] · Raphaël Lepeule[5] · Florence Beckerich[1,3] · Mathieu Leclerc[1,3] · Walid Barhoumi[1] · Andréa Toma[1] · Cécile Pautas[1] · Sébastien Maury[1,3] · Wiem Akrout[6] · Catherine Cordonnier-Jourdin[6] · Vincent Fihman[7,8] · Mario Venditti[2] · Catherine Cordonnier[1,3]

Received: 13 June 2018 / Accepted: 10 July 2018

Implémentation dans un service d'hémato (HCST, LAM) d'un EMI avec les reco de l'ECIL:

- étude type avant/ après
- Critère de jugement principal: la conso ATB
- critère secondaires: acceptation, nombre de jours sans ATB, incidence d'ICD, bactériémie et séjour en ICU, mortalité, prix ATB


a
FUO
Consider adding antifungal treatment
Febrile neutropenia: Empirical antibiotic treatment
72h
Discontinuation if neutrophils recover
Discontinuation of aminoglycosides if prescribed
5d
Severe sepsis at onset
No severe sepsis at onset
At least 48h of apyrexia
Persistent fever
Continue antibiotics for 10-14 days
STOP
Discontinuation of glycopeptide and de-escalation of betalactam to rank 4.
Look for cause of fever (consider CT scan, thrombosis...).
Look for non-infectious causes of fever
Fever relapse
Discontinuation of antibiotics as soon as: 48h of apyrexia or neutrophils recovery


b
CDI
Febrile neutropenia. Empirical antibiotic treatment
72h
Discontinuation of aminoglycosides if prescribed
**if patient is still symptomatic after 14 days consider another cause of dyspnoea
5d
Abdominal focus
Pneumonia
Perineal infection
Skin infection
Stop glycopeptide if prescibed, de-escalation to pip/tazo (unless ESBL colonization)
Stop glycopeptide if prescibed, de-escalation of betalactam (unless ESBL colonization)
Continue glycopeptide, de-escalation to pip/tazo or cefepime + metronidazole (unless ESBL colonization)
Add glycopeptide if recommended De-escalation of betalactam
Stopping rules:
- Minimum 7 days of treatment
- 4 consecutive days of apyrexia
- Clinical resolution
Stopping rules:
- Minimum 10 days of treatment
- 4 consecutive days of apyrexia
- Clinical and /or radiological resolution
Max 14d**
Stopping rules:
- Minimum 7 days of treatment
- 4 consecutive days of apyrexia
- 3 days clinical resolution
Stopping rules:
- Min 7days of treatment
- 4 consecutive days of apyrexia
- 3 days clinical resolution
In case of fever relapse antibiotics are restarted as for FUO

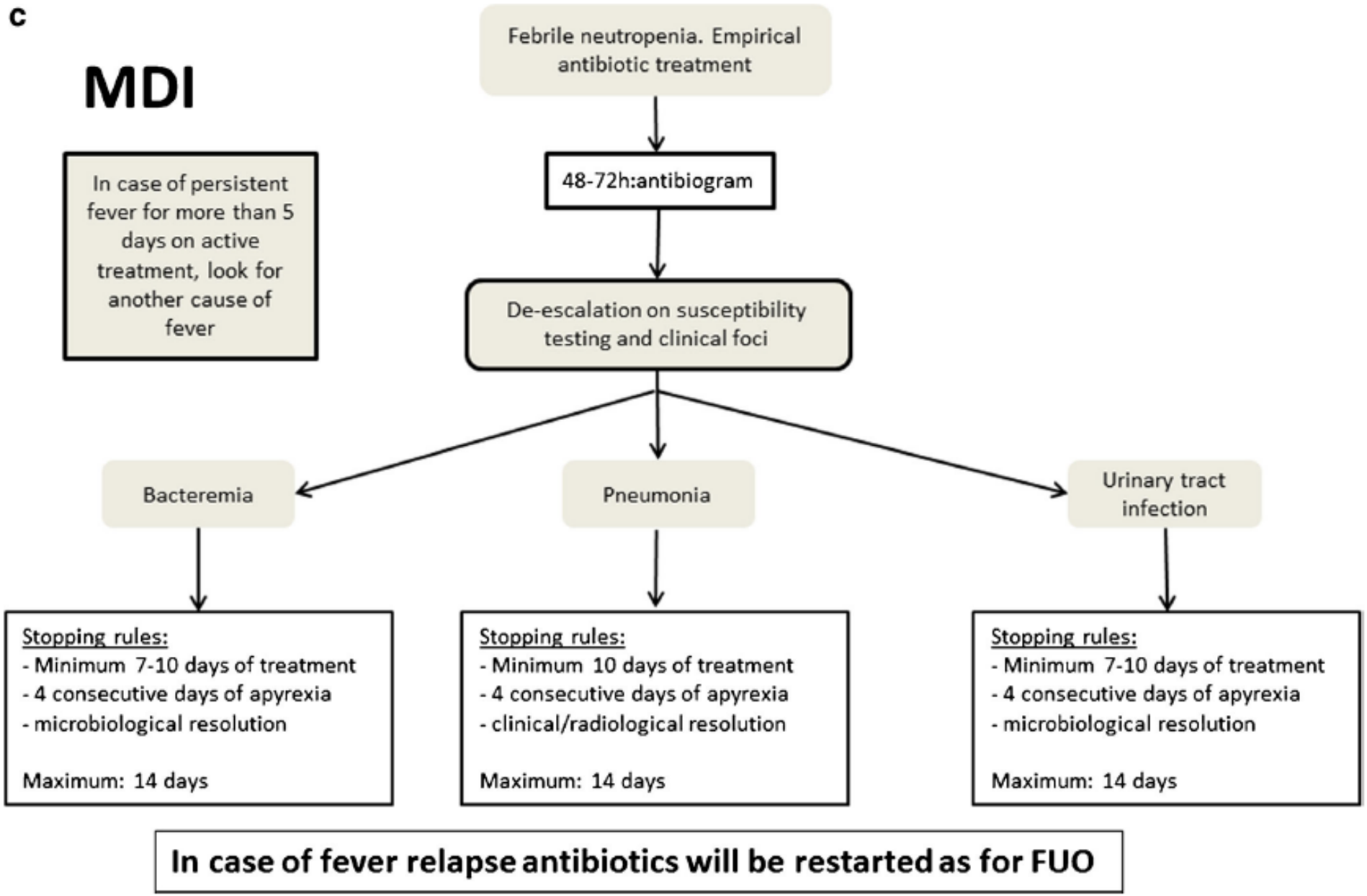
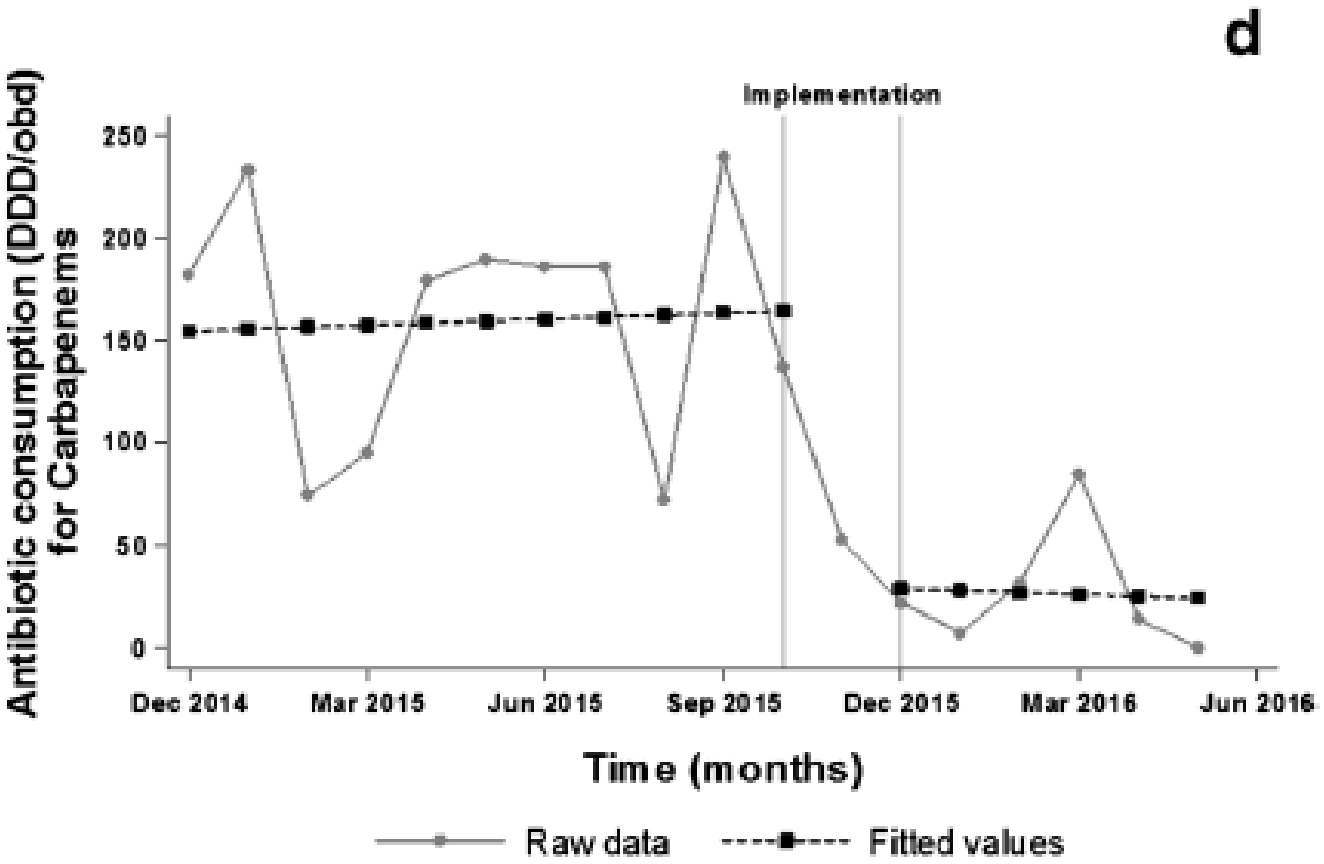


Fig. 1 continued.



Prix: de 85 keuros à 42 k euros…

Accepted Manuscript

Effect of an Antimicrobial Stewardship Programme on Antimicrobial Utilisation and Costs in Patients with Leukaemia: A Retrospective Interventional Controlled Study

Miranda So, BScPhm, PharmD, Muhammad Mamdani, PharmD, MA, MPH, Andrew Morris, MD SM, Tim Lau, BSc(Pharm), PharmD, Raewyn Broady, MBChB, Uday Deotare, MD, Jennifer Grant, MD, CM, Dennis Dong Hwan Kim, MD, PhD, Aaron D. Schimmer, MD, PhD, Andre Schuh, MD, Salomeh Shajari, BSc, Marilyn Steinberg, RN, Chaim M. Bell, MD, PhD, Shahid Husain, MD, MS

Open Forum Infectious Diseases

MAJOR ARTICLE

Safety and Efficacy of Antibiotic De-escalation and Discontinuation in High-Risk Hematological Patients With Febrile Neutropenia: A Single-Center Experience

Receiv
Revise
Accept

Anke Verlinden,[1,2] Hilde Jansens,[2,3] Herman Goossens,[2,3] Sébastien Anguille,[1,2] Zwi N. Berneman,[1,2] Wilfried A. Schroyens,[1,2] and Alain P. Gadisseur[1]

[1]Department of Haematology, Antwerp University Hospital, Edegem, Belgium, [2]Vaccine and Infectious Disease Institute, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium, and [3]Department of Infection Control and Microbiology, Antwerp University Hospital, Edegem, Belgium

- étude rétrospective, durée de 8 ans et utilise 2 groupes contrôles
- dans l'unité où l'intervention a lieu, les prescriptions d'antibiotiques sont effectuées par des médecins internistes chargé des soins de support et non par les hématologues, ce qui est une situation différente des services d'hématologie français.
- réduction significative de 278 à 247 DDDJ/100 patients jours ($p<0,01$) : cette réduction porte sur les prescriptions d'antibiotiques mais non sur les prescriptions d'antifongiques.
- Le coût des traitements anti-infectieux est réduit significativement de 17% par jour de prescription (- 21% pour les antibiotiques), dans le groupe intervention, contrairement aux groupes contrôles.
- aucun impact clinque délétère de l'intervention n'est observé : la mortalité et la durée de séjour restent stables. Il n'y a pas d'impact sur le taux d'infections à *difficile*. Moins de mortalité dans le papier « belge » ….

American Journal of Infection Control ■■ (2017) ■■-■■

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journal homepage: www.ajicjournal.org

Major Article

Implementation of an antimicrobial stewardship program for patients with febrile neutropenia

Bahar Madran RN [a], Şiran Keske MD [a], Gizem Tokça RN [a], Ebru Dönmez RN [a], Burhan Ferhanoğlul MD [b], Mustafa Çetiner MD [c], Nil Molinas Mandel MD [d], Önder Ergönül MD, MPH [e,*]

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[d] Medical Oncology Department, American Hospital, Istanbul, Turkey
[e] Infectious Diseases and Clinical Microbiology Department, School of Medicine, Koç University, Istanbul, Turkey

Table 1
Characteristics of the patients

Characteristic	Total (N = 95)	Pre-ASP (n = 50)	Post-ASP (n = 45)	*P* value
Age, mean ± SD (minimum-maximum), y	57 ± 15 (21-82)	57 ± 17 (18-82)	56 ± 15 (21-84)	.781
Female sex	41 (43)	25 (50)	16 (36)	.156
No. of FN attacks per patient (minimum-maximum)	1.6 (1-5)	1.63 (1-5)	1.57 (1-4)	.725
Duration of neutropenia per FN attack, d	4.2	4.9	3.5	.100
Diagnosis				
Leukemia	35 (37)	22 (44)	13 (29)	.127
Lymphoma	26 (27)	12 (24)	14 (31)	.437
Multiple myeloma	6 (6)	3 (6)	3 (6)	.893
Solid tumors	4 (4)	2 (4)	2 (4)	.914
Comorbidities				
Diabetes mellitus	14 (13)	8 (16)	6 (13)	.714
Chronic heart disease	27 (28)	16 (32)	11 (23)	.414
MASCC score <21 (high risk)	81 (85)	45 (90)	36 (80)	.352
Fatality	20 (21)	15 (30)	5 (11)	.024

NOTE. Values are n (%) or as otherwise indicated.
ASP, antimicrobial stewardship program; *FN*, febrile neutropenia; *MASCC*, Multinational Association of Supportive Care in Cancer.

Table 2
Appropriateness of antimicrobials

	Pre-ASP appropriateness/FN attack (%)	Post-ASP appropriateness/FN attack (%)	*P* value
Appropriateness of antimicrobials			
Appropriate empirical use (step 1)	60/78 (77)	52/71 (73)	.603
Appropriate adding or changing antimicrobial (step 2)	19/36 (53)	35/43 (81)	.006
Appropriate continuation or de-escalation or discontinuation (step 3)	32/60 (53)	60/71 (85)	<.001

ASP, antimicrobial stewardship program; *FN*, febrile neutropenia.

Table 4. Main antimicrobial stewardship interventions to consider in patients with febrile neutropenia

Clinical situation	Intervention	References
Fever of unknown origin	Consider stopping antibiotics after at least 3 days of treatment and 48 h of apyrexia	9,10,120–124
CDI or MDI with no severity criteria	Consider the same treatment duration as in non-neutropenic patients if the patient gets at least 4 days of apyrexia and clinical and microbiological resolution Consider de-escalation to targeted therapy against documented bacteria	9,10,25,120,121,123,12
Fever persistence or breakthrough under broad-spectrum antibiotics AND no new clinical sign AND no severity criteria AND no MDR bacteria colonization	Do not consider antibiotic escalation	9,10,120,121
Ongoing combination of anti-Gram-positive and anti-*P. aeruginosa* β-lactam antibiotics and no microbiological documentation at Day 3	Consider stopping anti-Gram-positive antibiotics and pursuing only anti-*P. aeruginosa* β-lactam	9,10,120,121
Ongoing carbapenem AND no microbiological documentation at Day 3 AND patient is stable	Consider de-escalation to a narrower-spectrum β-lactam covering *P. aeruginosa*	10,120,121
Ongoing aminoglycosides	Consider stopping aminoglycosides at Day 2 or 3 when patient is stable	10,120,121
Pneumonia or cutaneous cellulitis	Consider tailored-fit treatment based on bronchoscopy and broncho-alveolar lavage samples	120
Initial severity criteria or corticosteroids	Sometimes excluded from published local guidelines Consider tailored-fit treatment	120,121

CDI, clinically documented infection; MDI, microbiologically documented infection.

Contejean et al, JAC 2023

Contejean *et al.*
Antimicrobial Resistance & Infection Control
https://doi.org/10.1186/s13756-022-01084-0

RESEARCH

Antimicrobial s
neutropenia pa

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Anne Casetta[7], Lise Willems[2], Etier
Jeanne Reboul-Marty[10], Rui Batista

Table 1 Overall population characteristics (per patients) and comparison of hospital stays between pre- and post-intervention periods

Patients characteristics	Pre-intervention period Jan–Oct 2018 N = 164 patients	Post-intervention period Jan–Oct 2019 N = 148 patients	p value
Age (year); Median [IQR]	60.4 [49.4–71.9]	65.2 [54.3–72.8]	0.049
Sex (female); N (%)	78 (47.6)	65 (43.9)	0.60
Charlson comorbidity index; Median [IQR]	2 [2–4]	2 [2–6]	0.54
Number of stays; Median [IQR]	1 [1–2]	1 [1–2]	0.49
Hematological disease; N (%)			0.44
Myeloma	37 (22.6)	45 (30.4)	
Acute myeloid leukemia	31 (18.9)	32 (21.6)	
Aggressive lymphoma	28 (17.1)	26 (17.6)	
Indolent lymphoma	20 (12.2)	9 (6.1)	
ALL/LBL	18 (11)	11 (7.4)	
Myelodysplastic syndrome	7 (4.3)	9 (6.1)	
Hodgkin lymphoma	6 (3.7)	4 (2.7)	
Aplastic anemia	5 (3)	5 (3.4)	
Other	12 (7.3)	7 (4.7)	
Hospital stays characteristics	**Pre-intervention period Number of hospital stay = 273**	**Post-intervention period Number of hospital stay = 217**	**p-value**
Total number of patient-days	3180	3129	–
Cause of hospitalization; N (%)			0.28
Intensive or induction chemotherapy	57 (20.9)	38 (17.5)	
Leukemia consolidation chemotherapy	32 (11.7)	27 (12.4)	
Chemotherapy (other)	67 (24.5)	49 (22.6)	
Autologous BMT	51 (18.7)	48 (22.1)	
Transfusion	9 (3.3)	9 (4.1)	
Palliative care	4 (1.5)	5 (2.4)	
Aplasia	1 (0.4)	5 (2.4)	
Antithymocyte globulin + ciclosporin	1 (0.4)	4 (1.8)	
Other	51 (18.6)	32 (14.7)	
Number of stays with febrile episode; N (%)	118 (43.2)	116 (53.5)	0.031

ALL: Acute lymphoblastic leukemia; LBL: Lymphoblastic lymphoma

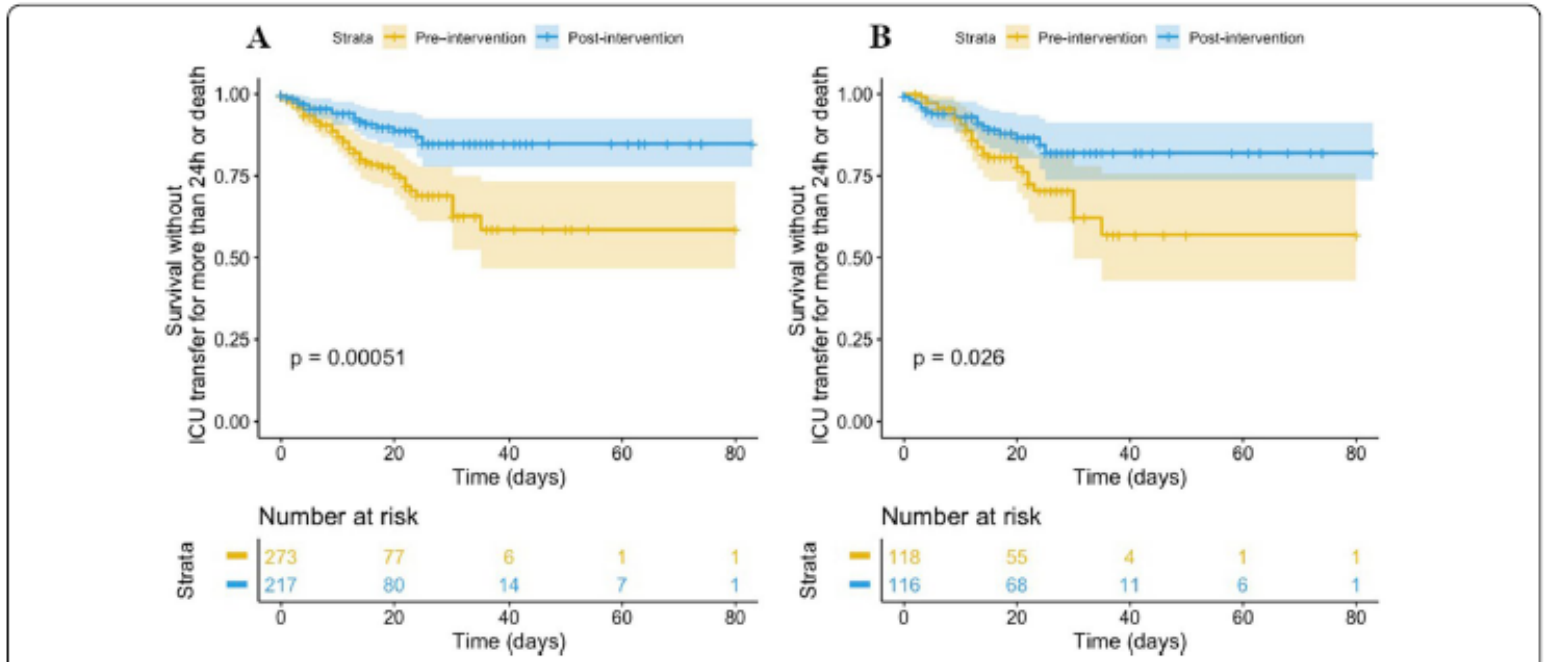


Fig. 2 Kaplan–Meier curves for occurrence of a negative outcome (ICU transfer for more than 24 h or death). A: Overall study population; B: Hospital stays with at least one febrile episode. Log-rank tests were used for statistical comparisons. Faded areas represent the 95% confident interval of each curve

Table 3 Outcomes

Outcome	Pre-intervention period Number of hospital stays = 273	Post-intervention period Number of hospital stays = 217	p-value
Length of stay (days); Median [IQR]	9 [3–19]	13 [3–21]	0.061
Clostridioides difficile infections; N (%)	4 (1.5)	6 (2.8)	0.35
Invasive infection with ESBL-PE; N (%)	9 (3.3)	2 (0.9)	0.12
Meropenem-resistant isolates among *Pseudomonas aeruginosa* infections; N (%)	4/5 (80)	2/8 (25)	0.10
Transfer to the ICU for more than 24 h or death; N (%)	49 (17.9)	18 (8.3)	0.0020
Transfer to the ICU for more than 24 h; N (%)	42 (15.4)	10 (4.6)	0.00022
Death; N (%)	14 (5.1)	8 (3.7)	0.59

Comparison of outcomes in the pre- and post-intervention periods in terms of length of stay, infectious complications and ICU transfer or death

ICU: Intensive Care Unit

del

I]	p-value
9 [−16.90;+6.71]	0.34
.34 [−32.48;−2.21]	0.03
.73 [−93.15;−2.31]	0.04
9 [−2.05;+11.82]	0.14
9 [−36.98;+41.96]	0.89
9 [−24.81;+36.80]	0.66
5 [−10.57;+6.47]	0.59
8 [−20.93;+1.97]	0.09
.91 [−117.45;+77.63]	0.64

D/1000 patient-days in both pre-
DDD/1000 patient-days in the

eraci

Conclusion

Implementation of a de-escalation and discontinuation strategy based on ECIL4 guidelines for patients with high-risk FN in our center was feasible, safe, and led to a significant decrease in glycopeptide and carbapenem consumption at the scale of an intensive hematology unit. The overall standard of care was impacted, with significantly less ICU transfers after the intervention. Also, it was accompanied by a trend towards fewer meropenem-resistant *Pseudomonas aeruginosa* infections, although larger studies are warranted to confirm this observation. A multidisciplinary approach, with endorsement of guidelines by both hematology and AMS teams, and close collaboration for patient care appear to be key factors in the success of such programs in this specific population.

Conclusion

- Urgence thérapeutique
- Examen clinique+ Prélèvement
- Escalade/ désescalade selon protocole
- Optimisation des anti-infectieux
- Coopération multidisciplinaire
- Réévaluation+++

Je vous remercie de votre attention.

infections et greffe d'organe

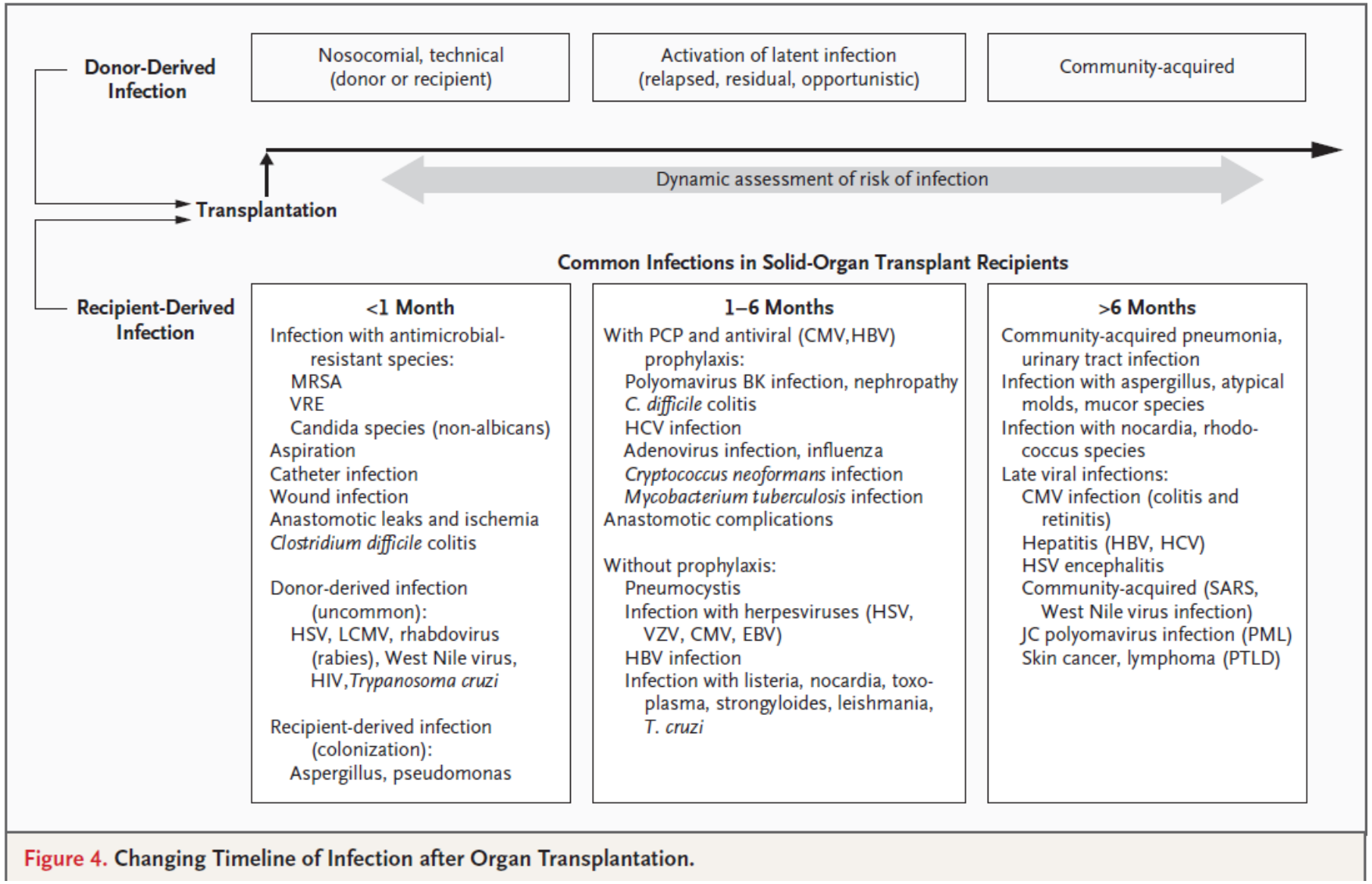
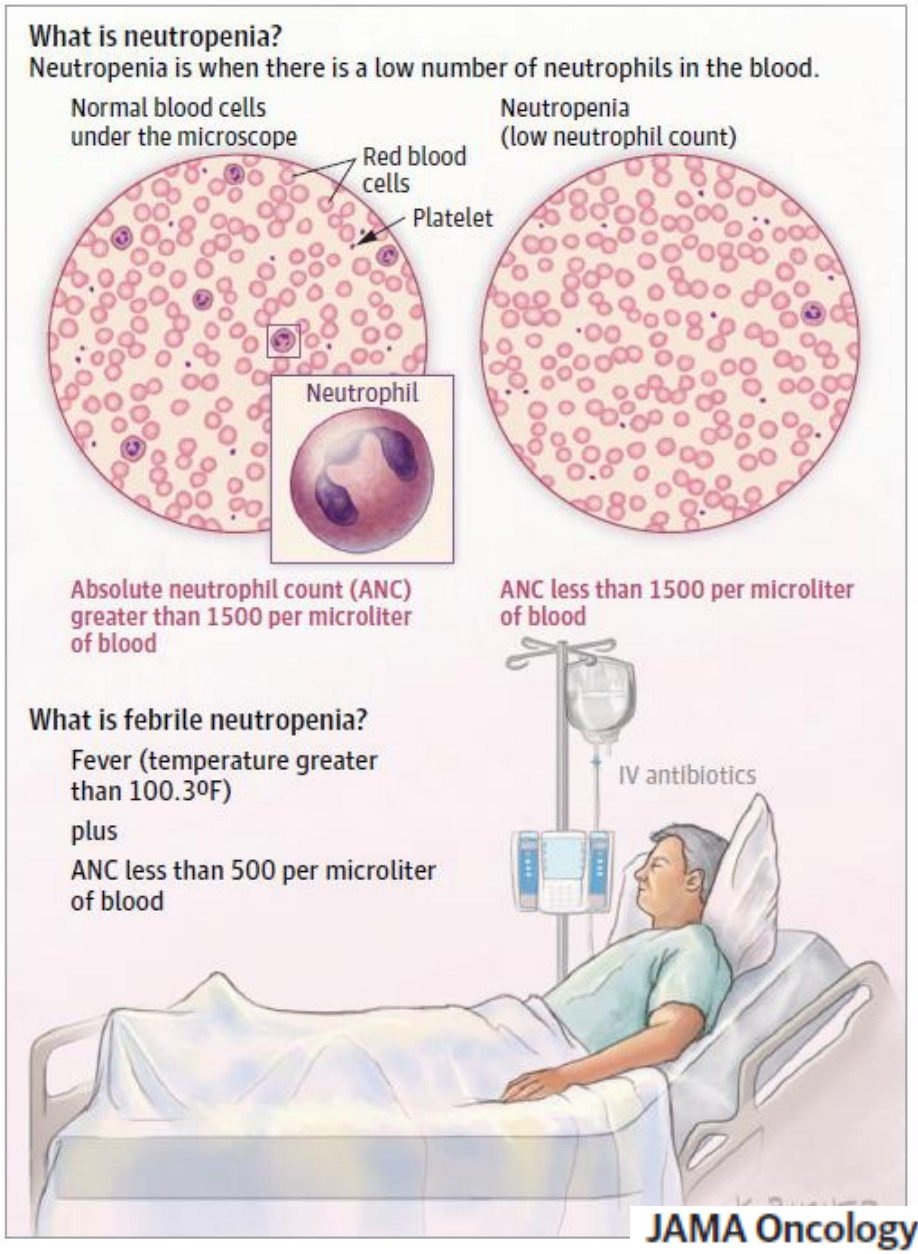


Figure 4. Changing Timeline of Infection after Organ Transplantation.

Fishman, NEJM 2007

Recommandations: ATBP

- Leucémie aig
  - Prophy
    - M
    - Ep
    - Inf
    - Inf
    - Inf
    - L'u
  - Allogreffe:
  - A débuter a
    - Sortie
    - Début



- La meille des patients

Freifeld et al, CID 2011

JAMA Oncology Published online July 27, 2017

Antibioprophylaxie

25. Fluoroquinolone prophylaxis should be considered for high-risk patients with expected durations of prolonged and profound neutropenia (ANC ≤100 cells/mm^3 for >7 days) (**B-I**). Levofloxacin and ciprofloxacin have been evaluated most comprehensively and are considered roughly equivalent, although levofloxacin is preferred in situations with increased risk for oral mucositis-related invasive viridans group streptococcal infection. A systematic strategy for monitoring the development of fluoroquinolone resistance among gram-negative bacilli is recommended (**A-II**).

26. Addition of a gram-positive active agent to fluoroquinolone prophylaxis is generally not recommended (**A-I**).

27. Antibacterial prophylaxis is not routinely recommended for low-risk patients who are anticipated to remain neutropenic for <7 days (**A-III**).

opinion.

A-2a. Antibacterial prophylaxis should use an orally administered, systemically absorbed fluoroquinolone to prevent invasive infection by Gram-negative bacilli of outpatients with profound neutropenia expected to last for ≥ 7 days associated with severe mucositis (eg, from primary or salvage remission-induction therapy for acute leukemia, dose-intensive postremission consolidation for acute leukemia, or HSCT); prophylaxis may be less effective in environments where > 20% of Gram-negative bacilli are resistant to fluoroquinolones

Freifeld et al, CID 2011
Flowers et al, ASCO, JCO 2013

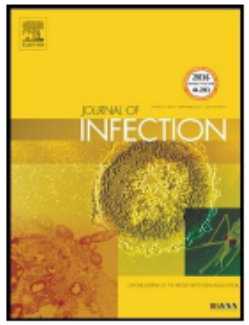
Risques de l'antibioprophylaxie

- Sélection de BGN FQ-R
  - Dissémination autres patients/unités/germes
  - Impose dépistage résistance/suivi écologie
- Baisse de la « résistance à la colonisation »
  - Risque accru *Clostridium difficile*
  - Autres germes entériques
- Perte d'une classe pour le traitement probabiliste

- **Peu employée (et de moins en moins) en France**

Diapo empruntée à S.Alfandari
Freifeld et al, CID 2011

Accepted Manuscript



Title: Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines

Author: Malgorzata Mikulska, Diana Averbuch, Frederic Tissot, Catherine Cordonnier, Murat Akova, Thierry Calandra, Marcello Ceppi, Paolo Bruzzi, Claudio Viscoli, European Conference on Infections in Leukemia (ECIL)

PII: S0163-4453(17)30322-5
DOI: https://doi.org/doi:10.1016/j.jinf.2017.10.009
Reference: YJINF 4004

To appear in: *Journal of Infection*

Accepted date: 13-10-2017

Highlights

- The role of fluoroquinolone prophylaxis (FQ-P) during neutropenia in the times of increasing antibiotic resistance has to be established.
- In observational and randomized studies published after 2005, FQ-P had no effect on mortality, but it reduced the rate of bloodstream infections and episodes of fever.
- No effect of background rate of resistance of *E. coli* to FQs was shown for the setting with FQ resistance rate below 27%
- Use of FQ prophylaxis should depend on local epidemiology and policy on antimicrobial use

Du nouveau dans la prophylaxie?

Supportive Care in Cancer
https://doi.org/10.1007/s00520-017-3976-1

ORIGINAL ARTICLE

Levofloxacin for febrile neutropenia prophylaxis in acute myeloid leukemia patients associated with reduction in hospital admissions

Samantha S. F. Lee [1] · Adrienne E. Fulford [2] · Maureen A. Quinn [2] · Jamie Seabrook [3] · Irina Rajakumar [4]

Received: 28 May 2017 / Accepted: 13 November 2017

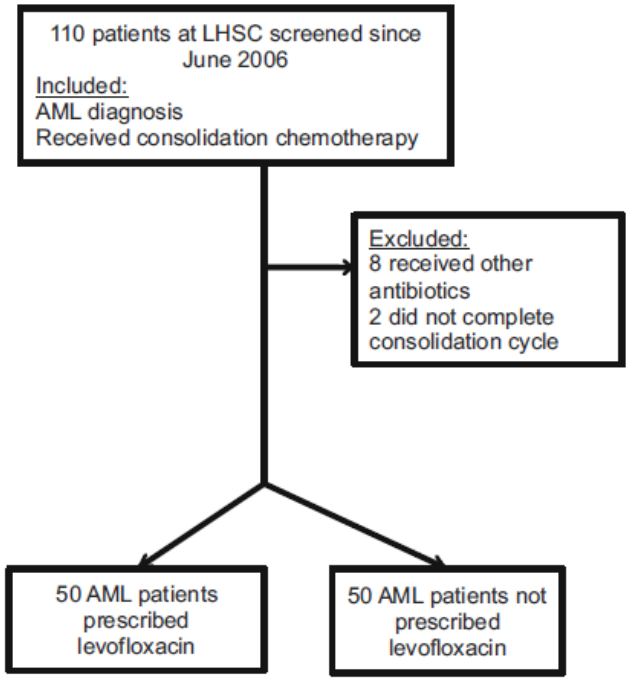


Table 3 Outcomes after the first consolidation cycle only (primary analysis)

	Levofloxacin ($n = 50$)	No levofloxacin ($n = 50$)	p value
Hospital readmission for febrile neutropenia (%)	**42.0**	**72.0**	**0.002**
Total antibiotic treatment days (mean)	10.19	10.90	0.690
Day of readmission after discharge from receiving consolidation (mean)	11.44	11.86	0.805
Rate of positive bacterial culture in readmitted FN patients (%, n)	18.8 (3)	31.0 (9)	0.372
CDAD within 30 days from consolidation chemotherapy (n)	0	1	NA
Proportion of isolates empirically covered by levofloxacin	2/3	11/14	NA
Proportion of isolates resistant to levofloxacin (in cultures where levofloxacin susceptibility reported)	1/2	5/11	NA

Original Article

JOURNAL OF ONCOLOGY PHARMACY PRACTICE

J Oncol Pharm Practice
0(0) 1–7

DOI: 10.1177/1078155217735153
journals.sagepub.com/home/opp
SAGE

Impact of fluoroquinolone prophylaxis on infectious-related outcomes after hematopoietic cell transplantation

Support Care Cancer
DOI 10.1007/s00520-017-3797-2

CrossMark

ORIGINAL ARTICLE

Moxifloxacin versus levofloxacin or ciprofloxacin prophylaxis in acute myeloid leukemia patients receiving chemotherapy

Daniel J. Przybylski[1,2] · David J. Reeves[1,2]

of febrile ne
transplant r

Rosa Rönkkö, Aun
Nousiainen, Esa Ja

To cite this article: Ro
Esa Jantunen & Sari Hä
febrile neutropenia in a
10.1080/23744235.201

To link to this article:

chemotherapy-induced neutropenia

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Autres prophylaxies

- Vaccination (grippe, DTCP, VHB, pneumocoque…)
- Hépatites virales
- Pneumocystose=> en hématologie
- HSV/VZV=> en hématologie
- Infections fongiques=> neutropénie de longue durée.
- **Hygiène, gestion de l'environnement: surtout en hématologie**
- GCSF…

Freifeld et al, CID 2011
Maertens J et al, ECIL 3, BMT 2011
Flowers et al, ASCO, JCO 2013
Maertens J et al, JAC 2016
HCSP 2012
Mallet et al, Lancet inf dis 2016

A-1a. FNE risk should be systematically assessed (in consultation with infectious disease specialists as needed), including patient-, cancer-, and treatment-related factors (see Table 2); G-CSF prophylaxis should be used before neutropenia develops for patients who meet criteria specified in the ASCO WBC growth factors guideline

A-2b. Use an orally administered triazole antifungal or parenterally administered echinocandin in the outpatient setting as prophylaxis against opportunistic yeast infection in those with profound neutropenia and mucositis expected to last for ≥ 7 days in environments with > 10% risk of invasive *Candida* infection; a mold-active triazole is recommended in environments with a substantial risk (> 6%) for invasive aspergillosis

A-2c. Prophylaxis with trimethoprim-sulfamethoxazole should only be used if risk for pneumonia from *Pneumocystis jirovecii* is > 3.5% (eg, patients administered regimens with ≥ 20 mg of prednisone equivalents daily for ≥ 1 month or those based on purine analogs); additional details and alternatives for patients with sulfa-based hypersensitivities are provided in the full guideline online

A-2d. Lamivudine is recommended as prophylaxis in patients at substantial risk for reactivation of HBV infection

A-2e. A nucleoside analog is recommended to prevent herpesvirus infection in those at risk

A-2f. Influenza immunization should use trivalent inactivated vaccine; in select circumstances after proven exposure of a susceptible patient with cancer, a neuraminidase inhibitor (eg, oseltamivir, zanamivir) may be offered

A-3a. All health care workers should follow hand hygiene guidelines including handwashing practices to reduce exposure through contact transmission and respiratory hygiene/cough etiquette guidelines to reduce exposure through droplet transmission

A-3b. Outpatients with neutropenia from cancer therapy should avoid prolonged contact with environments that have high concentrations of airborne fungal spores (eg, construction and demolition sites)

A-3c. None of the following measures are routinely necessary to prevent infection of afebrile outpatients with a malignancy and neutropenia: protected environments (HEPA filters with or without laminar air flow), respiratory or surgical masks (to prevent invasive aspergillosis), footwear exchange at entry and exit, and the neutropenic diet or similar nutritional interventions; gowning and gloving should only be considered in accordance with local infection prevention and control practices for antibiotic-resistant organisms such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, or extended-spectrum β-lactamase–producing and carbapenemase-producing Gram-negative bacilli

Flowers et al, ASCO, JCO 2013

Vaccinations des patients traités par chimiothérapie pour tumeur solide ou hémopathie maligne

La chimiothérapie induit une déplétion lymphocytaire immédiate avec une baisse du nombre et de la fonctionnalité des lymphocytes TCD4 pendant toute la durée du traitement et persistant les mois suivants.

→ **Il est donc recommandé de mettre à jour, si possible, les vaccinations avant de débuter la chimiothérapie.**

Les vaccins vivants atténués sont contre-indiqués en cours de chimiothérapie et pendant au moins six mois après son arrêt.

VACCINS VIVANTS ATTÉNUÉS (uniquement 6 mois après la chimiothérapie)

BCG	Contre-indiqué.
ROR	Adultes nés depuis 1980. Au moins six mois après l'arrêt de la chimiothérapie : - vaccination complète avant traitement : une dose ; - non préalablement vaccinés ou vaccinés avec une dose : schéma général à deux doses espacées d'au moins un mois.
Varicelle	Chez les sujets non immuns, un an après la chimiothérapie : - systématiquement chez les patients à risque de rechute et sans antécédent de varicelle ; - selon les recommandations particulières du calendrier vaccinal en vigueur chez les patients considérés guéris.
Fièvre jaune	Pourra être réalisé au moins 6 mois après la chimiothérapie.

VACCINS INACTIVÉS

	EN COURS DE CHIMIOTHÉRAPIE	APRÈS LA CHIMIOTHÉRAPIE
dTPca*	Non indiqué.	tumeur solide M3 | hémopathie maligne M6
Pneumocoque	M0 13-valent + > M2 23-valent Pour les enfants âgés de + de 5 ans et pour les adultes non préalablement vaccinés	Rappel : Il paraît souhaitable pour les personnes âgées de + de 2 ans et présentant des facteurs de risque d'infection sévère à pneumocoque : M3 13-valent + > M2 23-valent
Hépatite B	Vaccination si risque d'exposition au VHB + contrôle sérologique 4 sem. après, M0 + M1 + M6 + M7 Contrôle des anticorps	Si risque d'exposition au VHB : dose de rappel M6
Méningocoque C conjugué	Non indiqué.	Patients vaccinés ou non M3 2 à 24 ans
Grippe saisonnière	annuelle à l'automne ou, à défaut, en période épidémique.**	

Vaccination et patients greffés de cellules souches hématopoïétiques (CSH)

Les patients ayant bénéficié d'une greffe de CSH sont considérés comme naïfs par rapport aux antigènes vaccinaux. Ils doivent donc être vaccinés avec des schémas de primovaccination.
Les vaccins **vivants atténués** sont **contre-indiqués** pendant au **moins deux ans après la greffe**, voire davantage en cas de réaction du greffon contre l'hôte.
Les vaccinations à réaliser en priorité dans l'année suivant la greffe de CSH sont les vaccinations contre les infections à pneumocoque et *Haemophilus influenzae* de type b, et la vaccination antigrippale par le vaccin inactivé. Les autres vaccins recommandés devront être administrés dès que possible.

VACCINS INACTIVÉS ET SOUS-UNITAIRES

	RECOMMANDATIONS/DÉLAI APRÈS LA GREFFE	SCHÉMA
Pneumocoque	Pour tous les patients greffés de CSH. ⏳ = 3 mois post-greffe	M3 + M4 + M5 + M12 * 13-valent 13-valent 13-valent 23-valent
Grippe inactivée (vaccin injectable)	Pour tous les patients greffés de CSH annuellement à vie. ⏳ = 6 mois post-greffe **	Selon le schéma du calendrier vaccinal en vigueur en fonction de l'âge
Haemophilus influenzae de type b	Pour tous les patients greffés de CSH. ⏳ = 6 mois post-greffe	M6 + M7 + M8 + M18
dTP***	Pour tous les patients greffés de CSH. ⏳ = 6 à 12 mois post-greffe	M0 + M1 + M2 + M12
Méningocoque	Pour tous les patients greffés de CSH. ⏳ = 12 à 18 mois post-greffe	**Pour les patients âgés de plus de 1 an et les adultes non préalablement vaccinés :** tétravalent conjugué ACWY M0 + M6 — La fréquence des rappels reste à préciser. **Vaccin méningocoque B :** M0 + M1 + M2 + M12
Hépatite B	Pour tous les patients greffés de CSH jusqu'à l'âge de 16 ans, et les patients âgés de 16 ans ou plus à risque d'exposition. ⏳ = **À partir de 6 mois post-greffe**	M6 + M7 + M8 + M18
HPV (Papillomavirus humain)	Pour les jeunes filles dès l'âge de 9 ans et jusqu'à 19 ans révolus. ⏳ = **À partir de 6 mois post-greffe**	+ +

VACCINS VIVANTS ATTÉNUÉS

	RECOMMANDATIONS/DÉLAI APRÈS LA GREFFE	SCHÉMA
ROR	Pour tous les patients greffés de CSH. ⏳ = **Au moins 24 mois**, en l'absence de cGVH et de traitement immunosuppresseur.	M0 + ≥ M1
Varicelle	Uniquement pour les patients greffés de CSH séronégatifs pour la varicelle. ⏳ = **Au moins 24 mois**, en l'absence de cGVH et de traitement immunosuppresseur.	M0 + M2

Hépatites virales (en hématologie)

Panel: ECIL-5 recommendations for the management of HBV infection in patients with haematological malignancy

The Infectious Diseases Society of America grading system for ranking recommendations includes three strengths of recommendation (grade A: good evidence to support a recommendation for or against use; grade B: moderate evidence to support a recommendation for or against use; grade C: poor evidence to support a recommendation) and three levels of quality of evidence (level 1: evidence from at least one properly, randomised, controlled trial; level 2: evidence from at least one well designed clinical trial, without randomisation; from cohort or case-controlled analytic studies [preferably from more than one centre]; from multiple time series; or from dramatic results of uncontrolled experiments; level 3: evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees)

Indications for screening
- All patients needing chemotherapy or immunosuppressive therapy (A I)

Screening parameters
- HBsAg, anti-HBc, anti-HBs; HBV DNA if anti-HBc detected
- Expert evaluation of all anti-HBc patients is recommended (A I)

Vaccination
- Vaccination of anti-HBc-negative and anti-HBs-negative patients before and after HSCT is recommended (A I); double vaccine doses (40 µg) may be required to achieve an anti-HBs response in immunocompromised patients (at 0, 1, 2, and 6 months)
- Vaccination of anti-HBc-negative and anti-HBs-negative stem cell donors before HSC harvesting should be considered (B III); an accelerated single-dose (20 µg) 3-week (at 0, 10, and 21 weeks) schedule may be an alternative to the conventional 6-month protocols

Indication for treatment
- All HBsAg-positive patients (A I)
- Biological agents: all anti-HBc-positive patients (A II)
- Stem cell transplantation: all anti-HBc-positive patients (A I)
- All HBsAg-negative, anti-HBc-negative, and anti-HBs-negative recipients receiving anti-HBc-positive grafts (A III); vaccination and the addition of hepatitis B immune globulin can be considered in this setting (B III)

Start of antiviral treatment
- At the start of immunosuppressive therapy (A II)

Choice of antiviral drug
- Tenofovir or entecavir (A I); drug dosing should follow standard recommendations

Duration of antiviral treatment
- Until haematological cure is pronounced and 1 year after withdrawal of immunosuppressive treatment (B III)
- Antivirals may be given for longer periods in HSCT recipients with chronic GvHD and patients exposed to depleting antibodies (A III)

Treatment monitoring
- 3-monthly monitoring of HBV DNA and ALT; monthly monitoring of HBV DNA and ALT after the withdrawal of antiviral treatment (A II)

ECIL-5=European Conference on Infection in Leukaemia. HSCT=haemopoietic stem cell transplant. HBV=hepatitis B virus. GvHD=graft-versus-host disease. ALT=alanine aminotransferase.

-VHC: surveillance et trt après l'hémopathie
-VHE: diminuer l'Immunosuppression+/- ribavirine
-VHA: vaccination si a risque
-VHD: cf VHB

Mallet et al, Lancet inf dis 2016

Prophylaxie anti-fongique:

Table 2 ECIL 3 Guidelines on antifungal primary prophylaxis in hematology patients (the items in bold italic have been introduced at ECIL 3)

Antifungal drug	*Grading*	*Comments*
Leukemia patients, induction chemotherapy		
Fluconazole (50–400 mg/day)	CI	Azoles should not be used empirically in case of prevoius azole prophylaxis Combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections
Itraconazole oral solution (2.5 mg/kg b.i.d.)	CI	May be limited by drug interactions and/or patient tolerability Azoles should not be used empirically in case of prior azole prophylaxis It is recommended to monitor serum drug concentrations
Posaconazole (200 mg t.i.d.)	AI	Azoles should not be used empirically in case of previous azole prophylaxis It is recommended to monitor serum drug concentrations
Echinocandins IV	Insufficient data	
Polyenes IV	CI	Includes low doses of conventional ampho B and lipid formulations
Aerosolized liposomal ampho B combined with oral fluconazole	***BI***	***The ECIL recommendation for aerosolized amphotericin B deoxycholate is DI***
Allogeneic HSCT recipients, initial neutropenic phase		
Fluconazole (400 mg q.d. i.v. or oral)	AI	Azoles should not be used empirically in case of previous azole prophylaxis Combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections
Itraconazole (200 mg i.v. followed by oral solution 200 mg b.i.d.)[a]	BI	May be limited by drug interactions and/or patient tolerability Azoles should no It is recommende
Posaconazole	No data	
Voriconazole (200 mg b.i.d. oral)	***Provisional AI***	***Grading pending***
Micafungin (50 mg q.d. i.v.)	CI	
Polyenes i.v.	CI	Includes low dos
Aerosolized liposomal ampho B combined with oral fluconazole	***BII***	***The ECIL recom***
Allogeneic HSCT recipients, GVHD phase		
Fluconazole (400 mg q.d. i.v. or oral)	CI	Azoles should no
Itraconazole (200 mg i.v. followed by oral solution 200 mg b.i.d.)[a]	BI	May be limited b Azoles should no It is recommende
Posaconazole	AI	Azoles should no It is recommende
Voriconazole (200 mg b.i.d. oral)	***Provisional AI***	***Grading pending***
Echinocandins i.v.	Insufficient data	
Polyenes i.v.	CI	Includes low dos
Aerosolized liposomal ampho B combined with oral fluconazole	***Insufficient data***	

⇒ Uniquement en hématologie pour les aplasies de longue durée

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European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia

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Maertens J et al, ECIL 3, BMT 2011
Flowers et al, ASCO, JCO 2013

Pneumocystose

Table 1. ECIL guidelines in haematology patients at risk of *Pneumocystis* pneumonia: indication and duration of prophylaxis

	Adults		Children	
Indication for prophylaxis	disease/condition	duration of prophylaxis	disease/condition	duration of prophylaxis
Main (A)	ALL	from induction to end of maintenance	ALL	from induction to end of maintenance
	allogeneic HSCT	from engraftment to ≥6 months and as long as immunosuppression is ongoing	allogeneic HSCT	from engraftment to ≥6 months and as long as immunosuppression is ongoing
	alemtuzumab	>6 months after completion of treatment	alemtuzumab	
	fludarabine/cyclophosphamide/ rituximab	≥6 months after completion of treatment	SCID, WAS, X-linked agammaglobulinaemia, HLA II combined immunodeficiency	life-long or until restoration of underlying defect
	steroids (>20 mg/day prednisone for 4 weeks)		steroids (>0.4 mg/kg or 16 mg/day for ≥1 month)	
Optional (B)	Lymphoma treated with R-CHOP14 or escalated BEACOPP		AML	duration of chemotherapy
	nucleoside analogues (fludarabine, cladribine, mycophenolate mofetil)		solid tumours	duration of chemotherapy
	radiotherapy for brain tumours/ metastasis+ high-dose steroids			

HLA, human leucocyte antigen; SCID, severe combined immunodeficiency; WAS, Wiskott–Aldrich syndrome.

Table 3. Summary of the ECIL guidelines about choice of drugs and doses for PCP prophylaxis in haematology patients

	Adults		Children	
	drug grading	dose	drug grading	dose
First-line choice				
trimethoprim/sulfamethoxazole; all other alternatives are inferior (**A-II**)	**A-II**	one single-strength (80/400 mg) tablet/day or one double-strength tablet (160/800 mg)/day or thrice a week: **B-II**	**A-I**	150/750 mg/m^2/day in 1 or 2 doses/day or same dose 2 or 3 days/week: **A-I** 150/750 mg/m^2/day once a week: **B-II**
Second-line choice[a]				
dapsone	**A-II**	50 mg×2/day: **B-II**	**C-II**	2–4 mg/kg/day
atovaquone	**B-II**	1500 mg/day: **B-II**	**B-II**	30 mg/kg/day if >24 months of age 45 mg/kg/day if 4–24 months of age
pentamidine aerosols	**A-II**	300 mg once/month: **B-II**	**B-II**	300 mg once/month (age >5 years)
pentamidine intravenously	no data	—	**C-II**	4 mg/kg every 4 weeks

[a]Only in case of intolerance or severe adverse effects due to trimethoprim/sulfamethoxazole.

Maertens J et al, JAC 2016

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