Sepsis neutropénique

Frédéric Pène

Médecine intensive - Réanimation, Hôpital Cochin, AP-HP. Centre

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Déclaration de liens

- **Gilead: consultant, interventions congrès, participations congrès**

Febrile neutropenia vs. neutropenic sepsis

Non-complicated FN

- Clinical documentation 30%
- Microbiological documentation <20%
  - 60% Gram + cocci
  - 40% Gram-neg bacilli
  - <5% fungi
- Specific fever 10%
- Fever of unknown origin 40%

→ Mortality < 5%

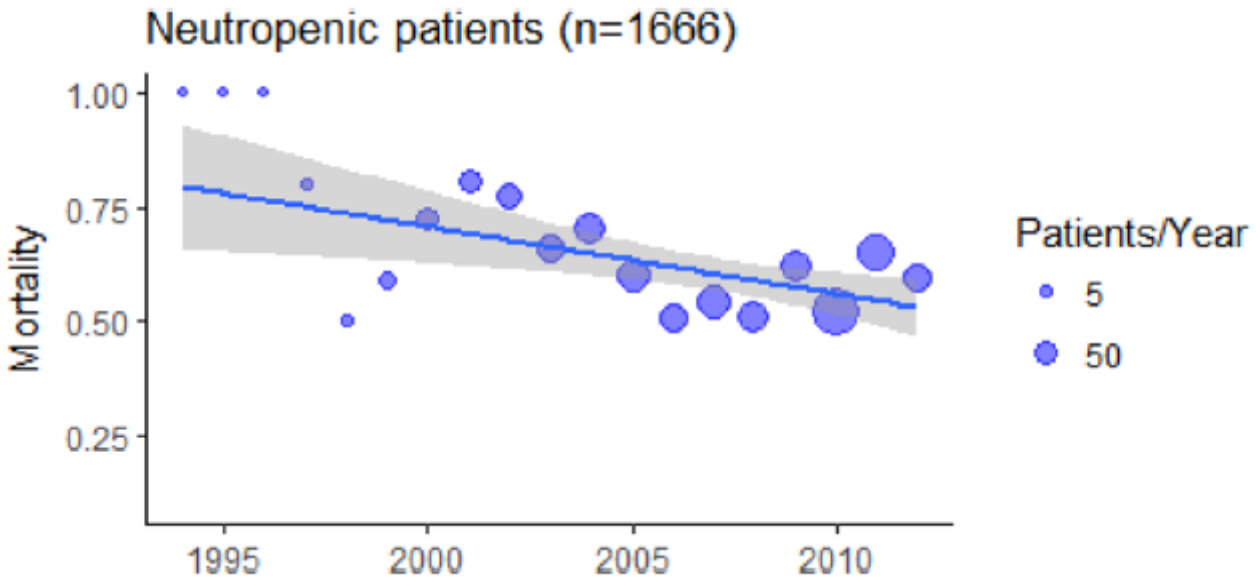
Neutropenic sepsis

- Clinical documentation 85%
  - Lung 70%
  - Abdomen 20%
  - Soft tissue / catheter 4% / 3%
- Microbiological documentation 55%
  - 75% Gram-neg bacilli
  - 25% Gram + cocci
  - >10% fungi

→ Mortality up to 40%

Pène, Crit Care Med 2008; Legrand, Crit Care Med 2012; Lemiale, Crit Care Med 2020

En réanimation: un pronostic en amélioration



M. Darmon, Intensive Care Med (2019) 45:977-987

Sepsis neutropénique: quelles spécificités?

- **Risque infectieux**
- **Traitements anti-infectieux**
- **Défaillances d'organes**
- **Traitement immuno-stimulant**
- **Mesures d'isolement**

Sepsis neutropénique: quelles spécificités?

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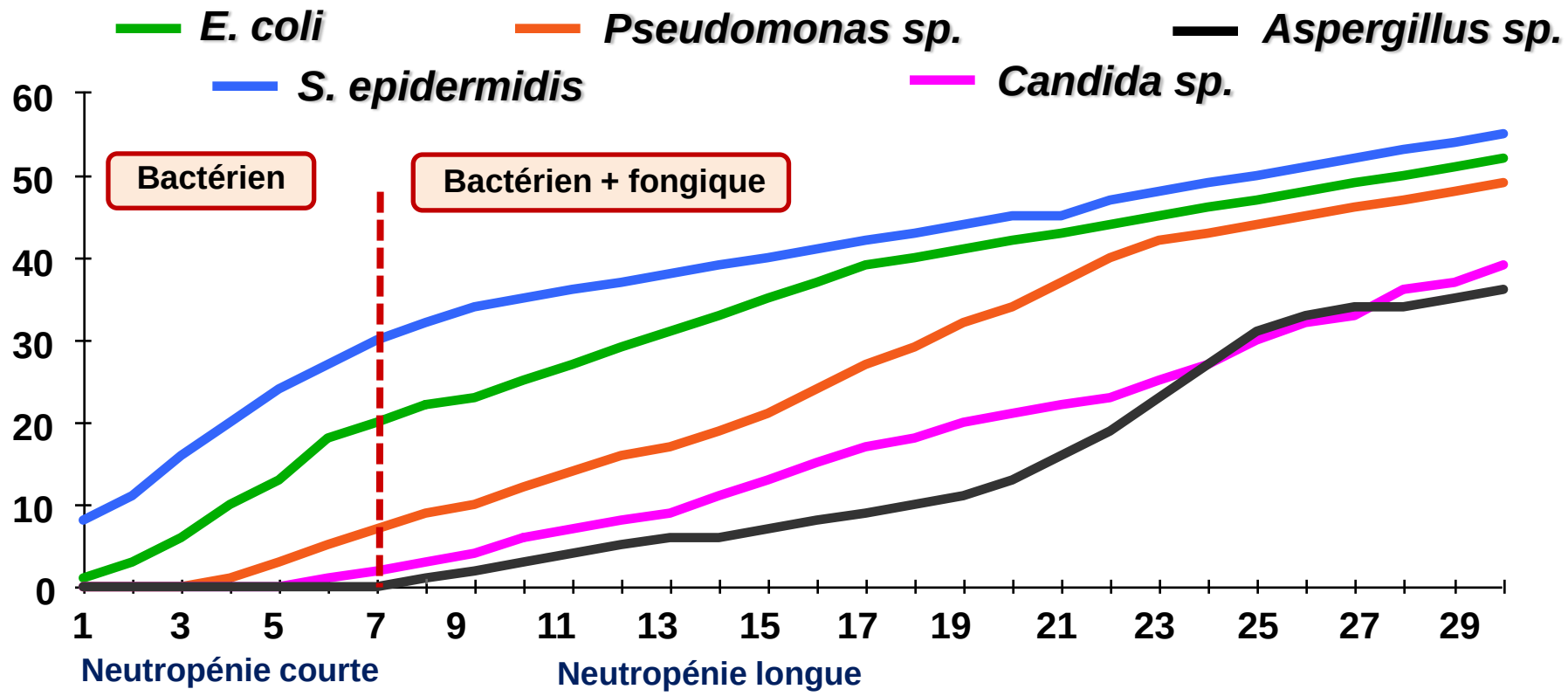
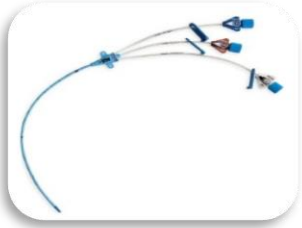
Risques infectieux de la neutropénie

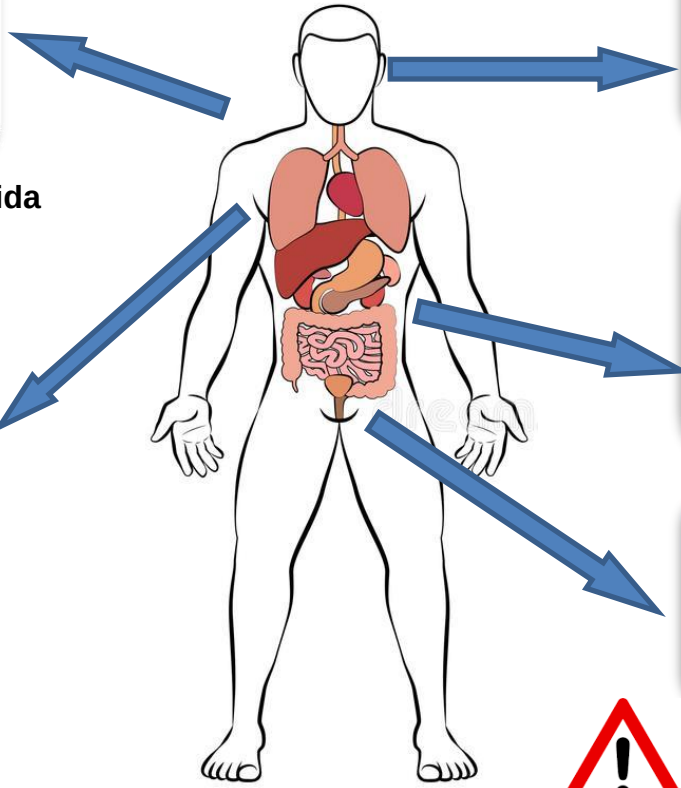


Sites infectieux chez le neutropénique



BGN, *S. aureus*, Candida

BGN, streptocoques, *Aspergillus*



streptocoques anaérobies *S. aureus*

BGN anaérobies entérocoques *Candida*

BGN anaérobies streptocoques entérocoques

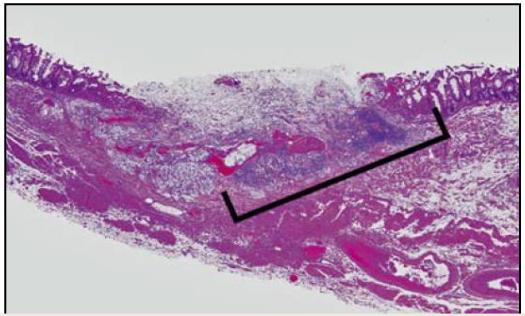
Polymicrobien

Am J Surg Pathol • Volume 39, Number 12, December 2015

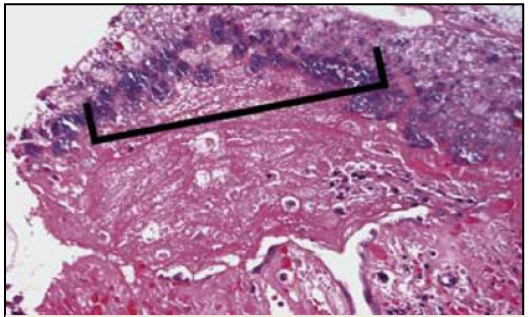
Neutropenic Enterocolitis

New Insights Into a Deadly Entity

Taha Sachak, MD, Michael A. Arnold, MD, PhD,*† Bita V. Naini, MD,‡*

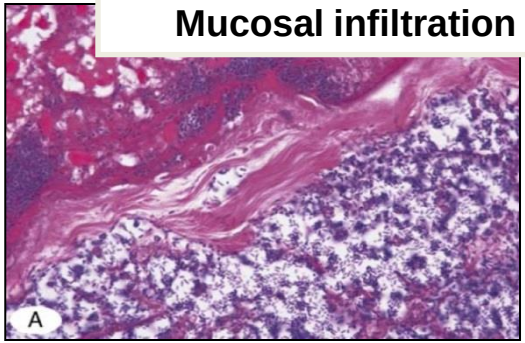


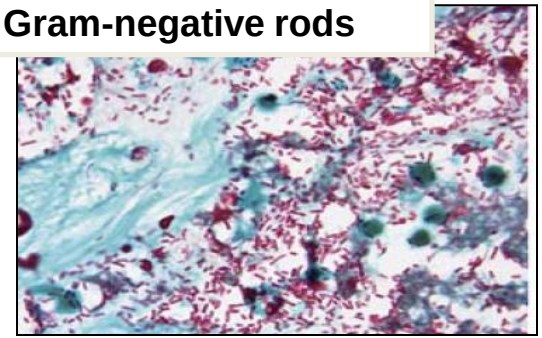
Patchy necrotic ulcerations

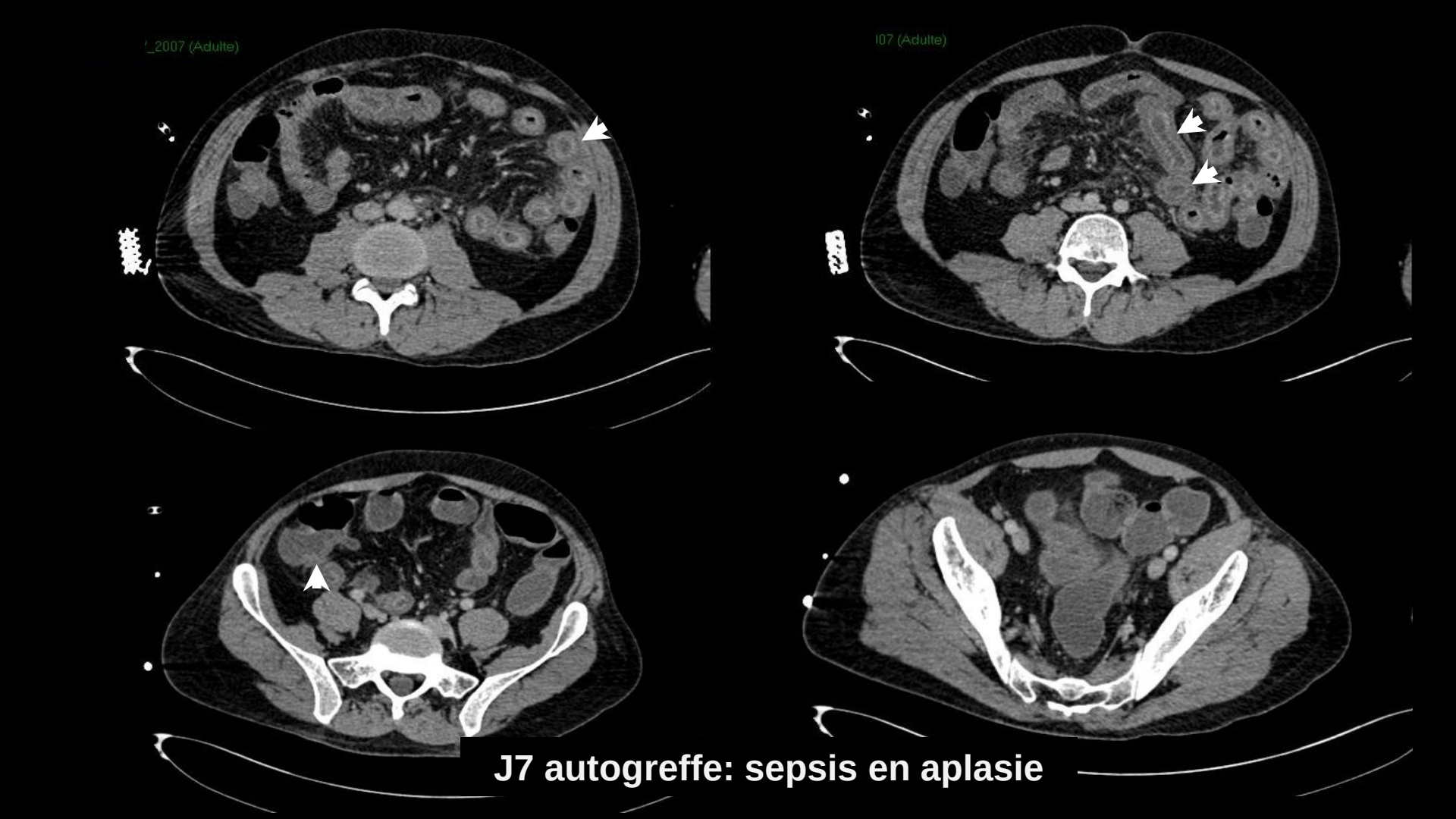


Necrosis and hemorrhage

Mucosal infiltration by Gram-negative rods

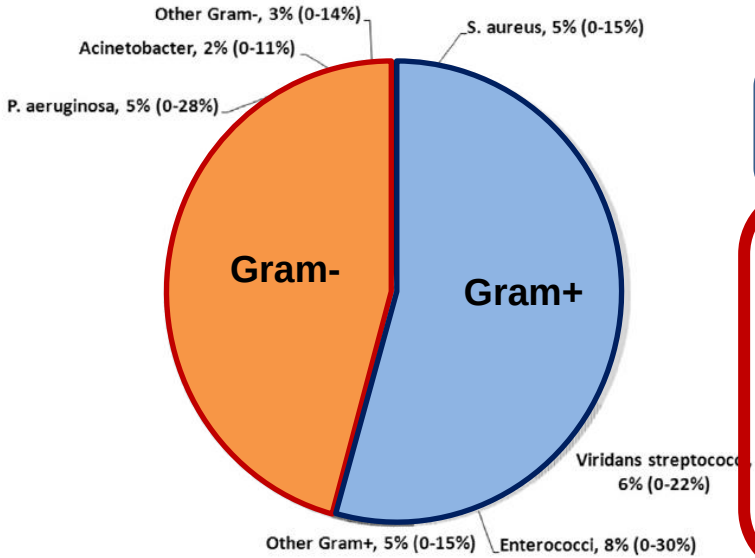






J7 autogreffe: sepsis en aplasie

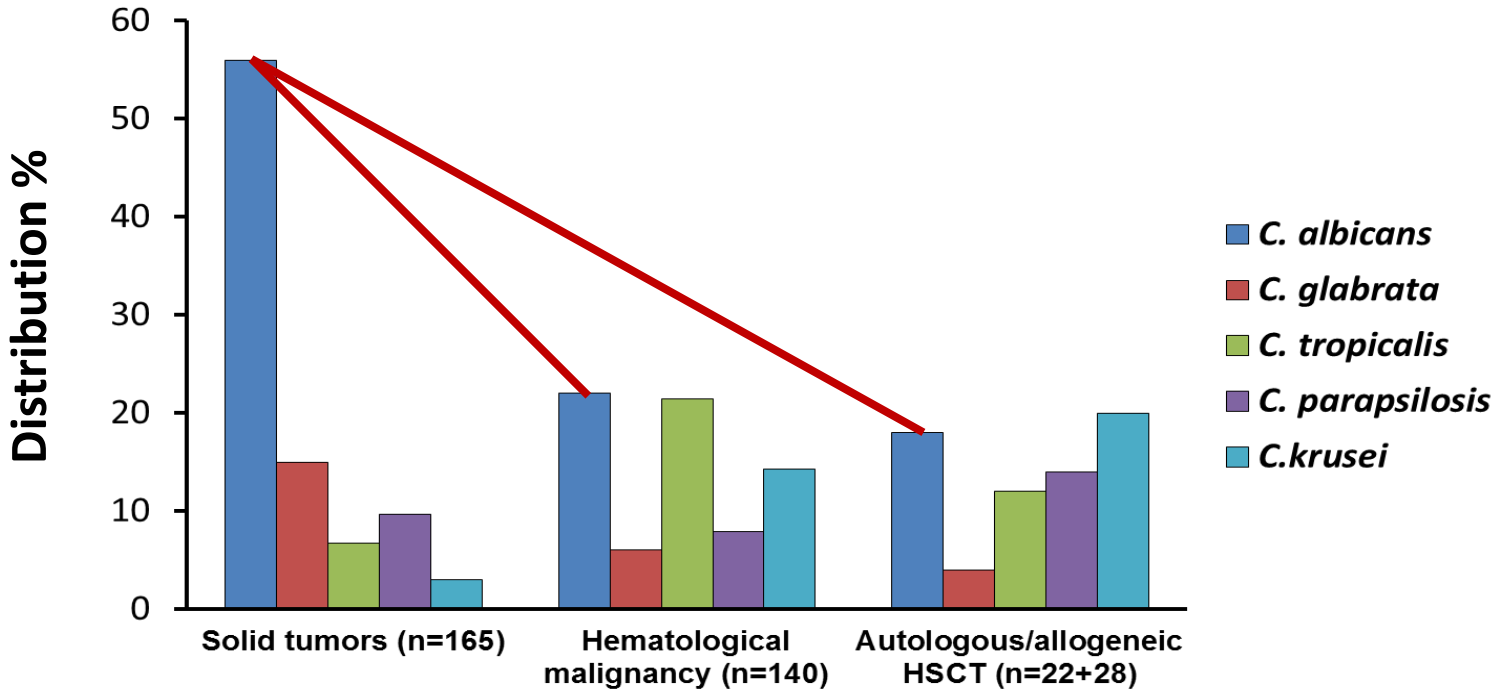
Current epidemiology and resistance in bacterial isolates in onco-hemato patients



Pathogen and studies	Type of resistance	Adults median rate of resistance (range)
S. aureus	MRSA	56% (18–100%)[a]
CNS	MR-CNS	80% (33–100%)[c]
Enterococci	VRE	23% (0–50%)[e]
Gram-negatives	Fluoroquinolone-resistant	41% (18–74%)[g]
Gram-negatives	Carbapenem-resistant	20% (11–72%)[i]
Gram-negatives	Aminoglycoside-resistant	28% (6–41%)[j]
Gram-negatives	Ceftazidime-resistant	43% (17–45%)[l]
Enterobacteriaceae	ESBL-producing	34% (16–44%)[m]
Enterobacteriaceae	Fluoroquinolone-resistant	56% (28–87%)[p]
P. aeruginosa	Fluoroquinolone-resistant	53% (7–72%)[q]
P. aeruginosa	Carbapenem-resistant	44% (3–66%)[s]

Mikulska (on behalf of ECIL4), J Infection 2014

Epidemiology and Outcome of Fungemia in a Cancer Cohort of the Infectious Diseases Group (IDG) of the European Organization for Research and Treatment of Cancer (EORTC 65031)



Cornely, CID 2015

Sepsis neutropénique: quelles spécificités?

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- **Mesures d’isolement**

Djamel Mokart
Colombe Saillard
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Laurent Chow-Chine
Jean-Paul Brun
Marion Faucher
Jean-Louis Blache
Didier Blaise
Marc Leone

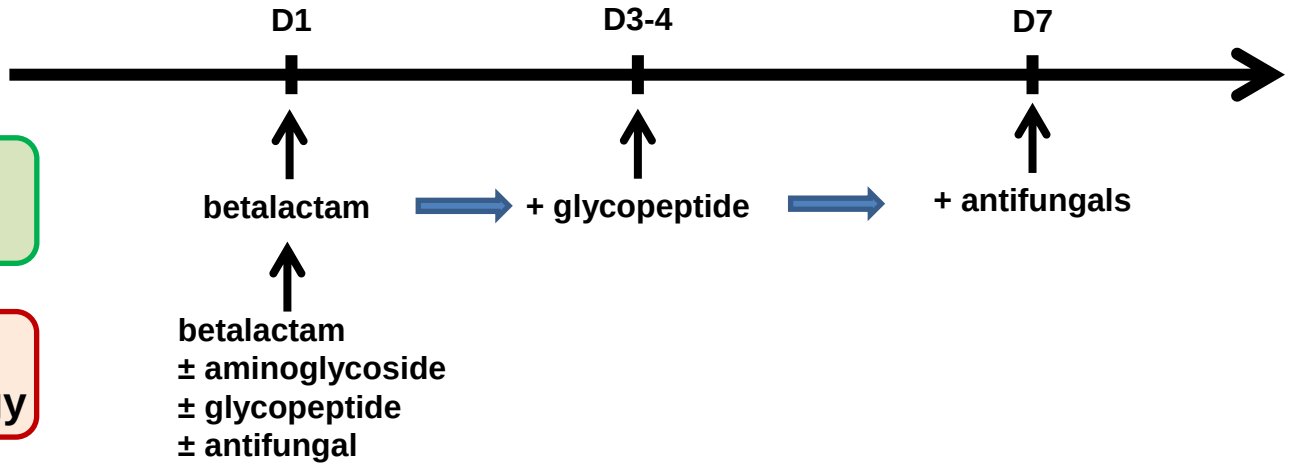
Neutropenic cancer patients with severe sepsis: need for antibiotics in the first hour

ICU mortality	Odds ratio	95 % confidence interval	*p*
Efficacy of the first antimicrobial treatment in the ICU			
Appropriate	1	Reference	
Inappropriate	6.4	1.6–26	0.01
Empirical	0.7	0.2–2.5	0.63
SOFA score at admission (per point)	1.4	1.2–1.6	<0.001
Non-fermentative Gram-negative bacilli	4.8	1.3–18	0.02
Interval between the first signs of sepsis in ICU and antimicrobial initiation >1 h	10	2.5–33	0.002

Intensive Care Med (2014) 40:1173–1174

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. Ra
Kenneth V. Rolston,[6] Jo-Anne H. Young,[7] and John R. Wingard[8]



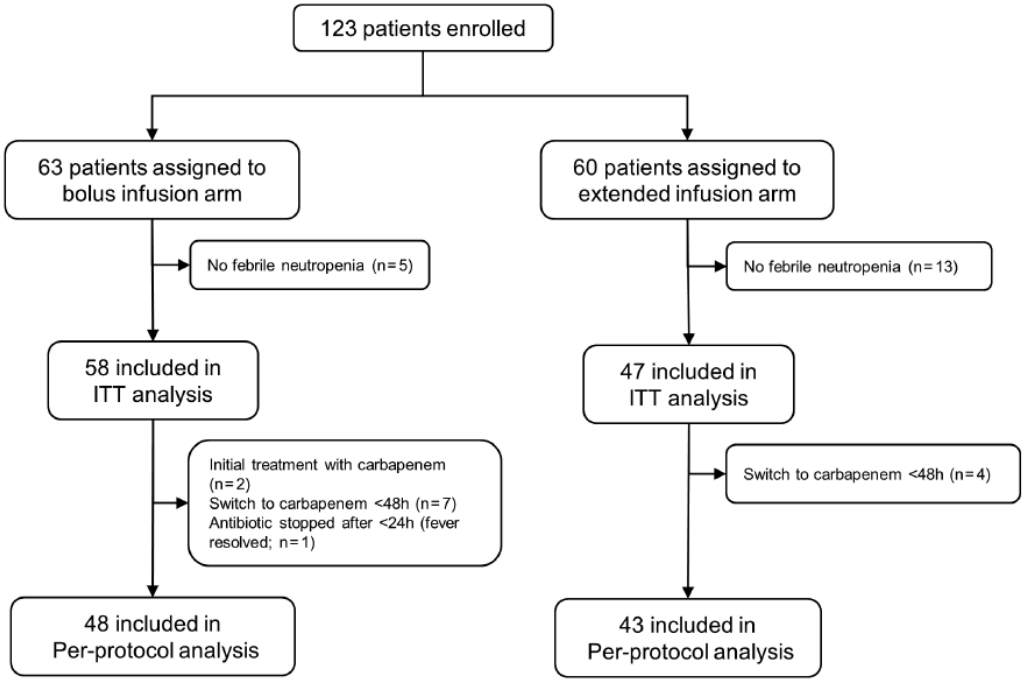
Documentation? → **De-escalation?**

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

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]

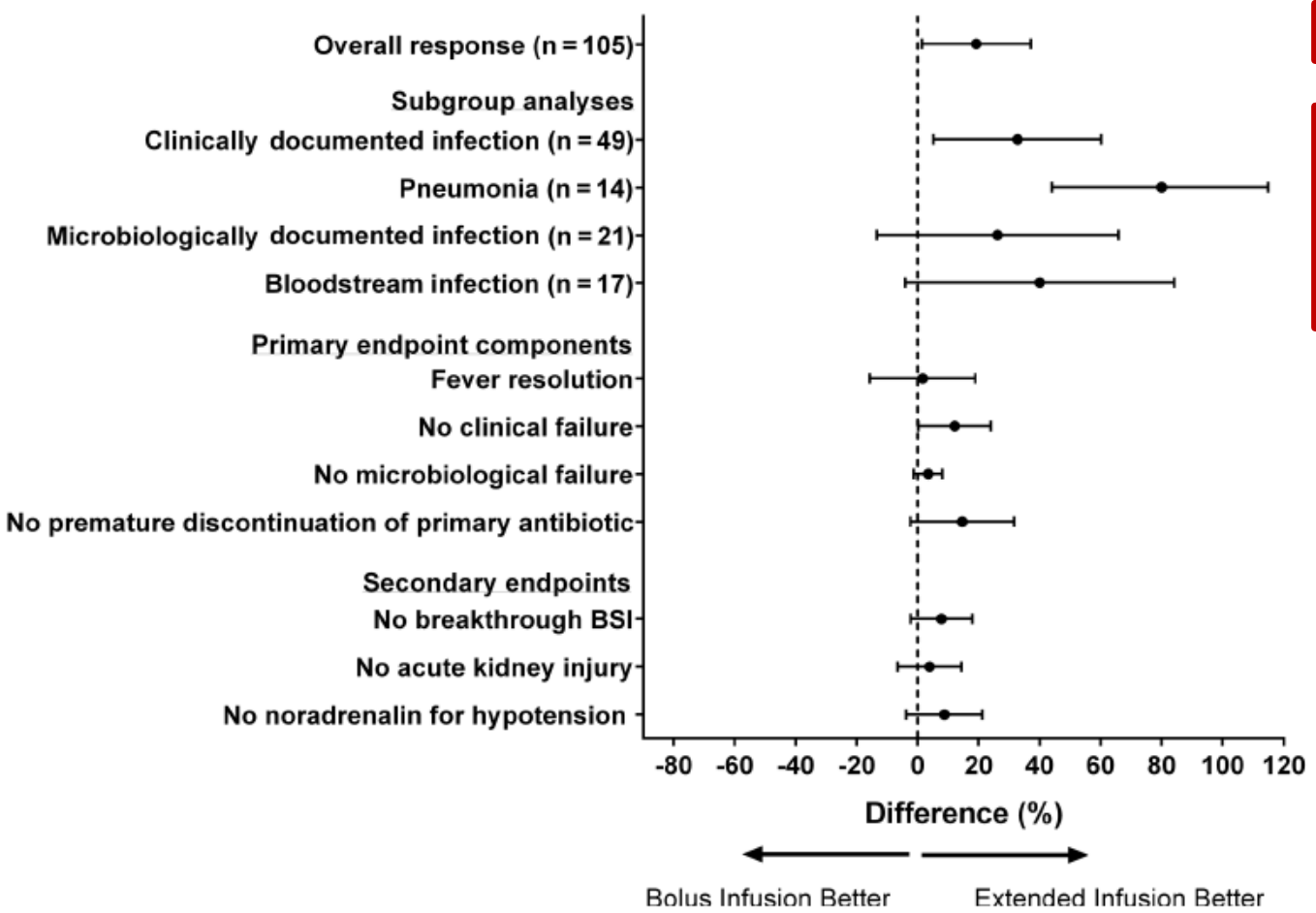
[1]Bone Marrow Transplantation Unit, Tel Aviv Medical Center, [2]Sackler Faculty of Medicine, Tel Aviv University, and [3]Infectious Diseases Unit, Tel Aviv Medical Center, Israel



Primary study endpoint

overall response on day 4, defined as a composite of 4 criteria:

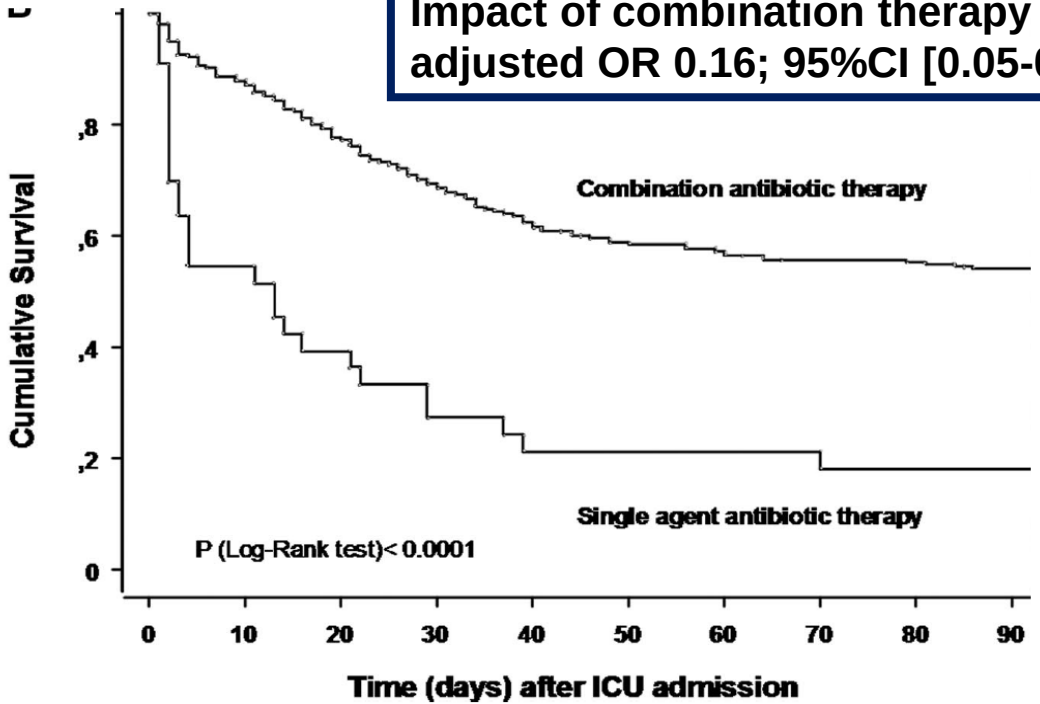
- **resolution of fever for at least 24 hours**
- **microbiological eradication : sterile cultures on day 4**
- **clinical response: resolution of signs and symptoms of infection**
- **no need for a change in the antibiotic regimen**


Overall response (n = 105)
Subgroup analyses
Clinically documented infection (n = 49)
Pneumonia (n = 14)
Microbiologically documented infection (n = 21)
Bloodstream infection (n = 17)
Primary endpoint components
Fever resolution
No clinical failure
No microbiological failure
No premature discontinuation of primary antibiotic
Secondary endpoints
No breakthrough BSI
No acute kidney injury
No noradrenalin for hypotension
-80 -60 -40 -20 0 20 40 60 80 100 120
Difference (%)
Bolus Infusion Better
Extended Infusion Better
55% vs. 74%
35% vs. 68%
0% vs. 80%
18% vs. 44%
10% vs. 50%

Survival in neutropenic patients with severe sepsis or septic shock

Matthieu Legrand, MD; Adeline Max, MD; Vincent Peigne, MD; Eric Mariotte, MD; Emmanuel Canet, MD; Alexandre Debrumetz, MD; Virginie Lemiale, MD; Amélie Seguin, MD; Michael Darmon, MD; Benoît Schlemmer, MD; Élie Azoulay, MD, PhD

Impact of combination therapy on mortality
adjusted OR 0.16; 95%CI [0.05-0.51], p=0.002



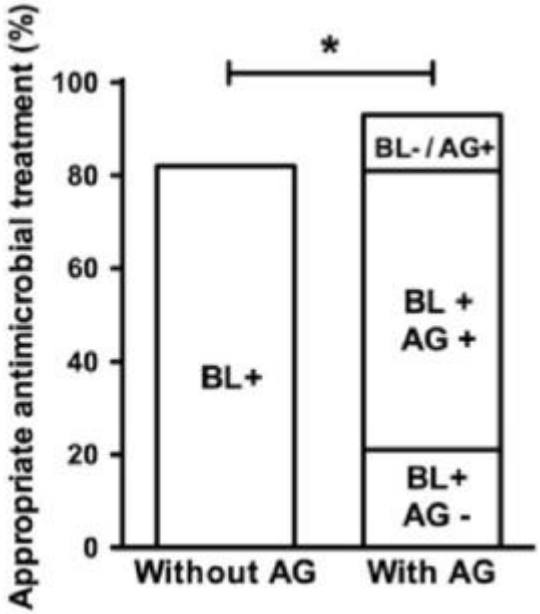
Crit Care Med 2012

RESEARCH LETTER Open Access

Aminoglycosides for the treatment of septic shock: a propensity-based study

Jean-François Llitjos[1,2,3*], Simon Meslin[1], Swann Bredin[1], Matthieu Jamme[4,5] and Frédéric Pène[1,2,3]

Llitjos *et al. Critical Care* (2020) 24:567
https://doi.org/10.1186/s13054-020-03284-9



	With aminoglycosides	Without aminoglycosides
All patients	**616**	**424**
In-ICU mortality	CSH 1.1; 95%CI 0.90–1.55, p=0.25	
Bacteremia	**241**	**106**
In-ICU mortality	CSH 1.03; 95%CI 0.64–1.66, p = 0.91	
Neutropenia	**91**	**38**
In-ICU mortality	CSH 1.11; 95%CI 0.75–1.62, p = 0.61	

Contrôle de la source

- **Entérocolite neutropénique**
  - **Traitement conservateur +++**
  - **Indications de chirurgie**
    - **Perforation**
    - **Nécrose intestinale**
    - **Dilatation colique majeure > 8cm**
    - **Hémorragie gastro-intestinae non contrôlée**
    - **Défaillance multi-viscérale?**
- **Infections des tissus mous**
  - **Excision chirurgicale des tissus infectés et nécrosés**
- **Voies veineuses**
  - **Retrait + culture**

Neutropénie et thrombopénie ne sont pas des contre-indications à la chirurgie

Désescalade antibiotique à 48-72h?

- **β-lactamine de spectre plus étroit**

  Préférer penicillines* + inhibiteurs de *β-lactamase aux cephalosporines ou carbapenemes

- **Arrêt des aminosides (si absence de Gram négatif documenté)**

- **Arrêt des glycopeptides en l'absence de Gram-positif résistant)**

Averbuch (ECIL4 guidelines), Haematologica 2013; 98 (12)

Intensive Care Med (2014) 40:41–49
DOI 10.1007/s00134-013-3148-9

ORIGINAL ARTICLE

Djamel Mokart
Géraldine Slehofer
Jérôme Lambert
Antoine Sannini
Laurent Chow-Chine
Jean-Paul Brun
Pierre Berger
Ségolène Duran
Marion Faucher
Jean-Louis Blache
Colombe Saillard
Norbert Vey
Marc Leone

De-escalation of antimicrobial treatment in neutropenic patients with severe sepsis: results from an observational study

Definitions of de-escalation

- Deleting one antibiotic of a combination regimen
- Using a betalactam with narrower spectrum

101 neutropenic patients with severe sepsis

- Pts with microbiological documentation
  - De-escalation 32/63 (51%)
  - In-ICU death 18%

- Pts without documentation
  - De-escalation 12/38 (32%)
  - In-ICU death 23%

Randomized DEP-OH study completed!

Sepsis neutropénique: quelles spécificités?

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Supports de défaillances d'organes

Défaillance	Etudes interventionnelles	Spécificités
Hémodynamique	Albumine vs. Ringer lactate [1] Vasopressine vs. noradrénaline [2]	Non
Respiratoire	VNI vs. O2 [3,4] OHD vs. O2 [5] OHD + VNI vs. OHD [6]	Pas de supériorité d'une stratégie non-invasive sur l'autre
Rénale	Non	Eviter anticoagulation chez le patient thrombopénique
Hématologique	Transfusion érythrocytaire [7,8] Seuils transfusionnels plaquettaire [9]	?

[1] Lee-Park, CCM 2019; [2] Hajjar, CCM 2019; [3] Hilbert, NEJM 2001; [4] Lemiale, JAMA 2015; [5] Azoulay, JAMA 2018; [6] Coudroy, Lancet Respir Med 2022; [7] Bergamin, CCM 2017; [8] Pène, NCT 03837171; [9] Pène, NCT06599385

Sepsis neutropénique: quelles spécificités?

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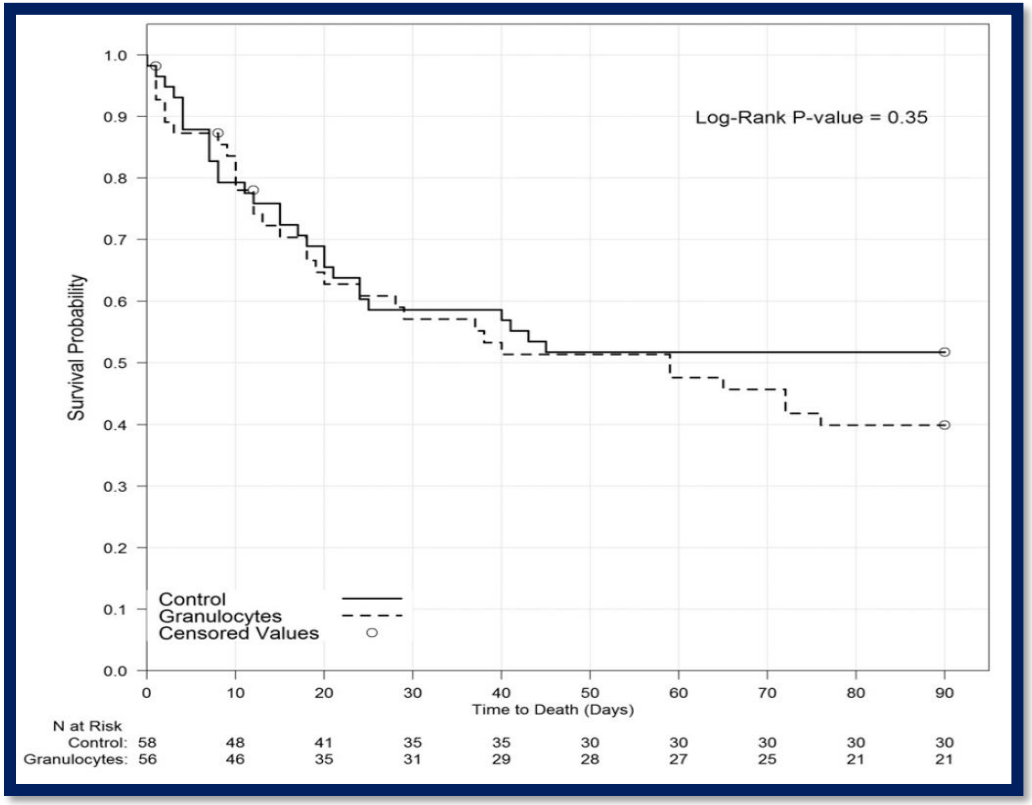
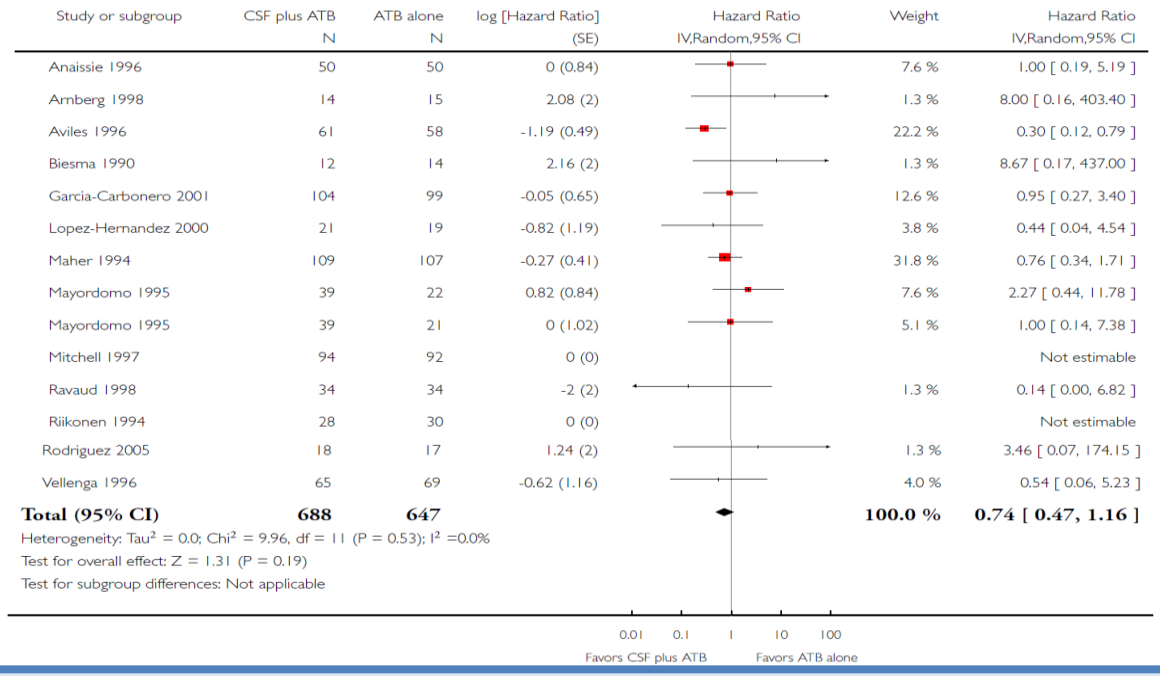
Efficacy of transfusion with granulocytes from G-CSF/dexamethasone–treated donors in neutropenic patients with infection

BLOOD, 29 OCTOBER 2015 • VOLUME 126, NUMBER 18

Thomas H. Price,[1,2] Michael Boeckh,[1,3] Ryan W. Harrison,[4] Jeffrey McCullough,[5] Paul M. Ness,[6] Ronald G. Strauss,[7] W. Garrett Nichols,[3,8] Taye H. Hamza,[4] Melissa M. Cushing,[9] Karen E. King,[6] Jo-Anne H. Young,[5] Eliot Williams,[10] Janice McFarland,[11] Jennifer Holter Chakrabarty,[12] Steven R. Sloan,[13] David Friedman,[14] Samir Parekh,[15] Bruce S. Sachais,[16,17] Joseph E. Kiss,[18,19] and Susan F. Assmann[4]



Does G(M)-CSF improve survival in febrile neutropenia?



Study or subgroup	CSF plus ATB N	ATB alone N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Anaissie 1996	50	50	0 (0.84)		7.6 %	1.00 [0.19, 5.19]
Arnberg 1998	14	15	2.08 (2)		1.3 %	8.00 [0.16, 403.40]
Aviles 1996	61	58	-1.19 (0.49)		22.2 %	0.30 [0.12, 0.79]
Biesma 1990	12	14	2.16 (2)		1.3 %	8.67 [0.17, 437.00]
Garcia-Carbonero 2001	104	99	-0.05 (0.65)		12.6 %	0.95 [0.27, 3.40]
Lopez-Hernandez 2000	21	19	-0.82 (1.19)		3.8 %	0.44 [0.04, 4.54]
Maher 1994	109	107	-0.27 (0.41)		31.8 %	0.76 [0.34, 1.71]
Mayordomo 1995	39	22	0.82 (0.84)		7.6 %	2.27 [0.44, 11.78]
Mayordomo 1995	39	21	0 (1.02)		5.1 %	1.00 [0.14, 7.38]
Mitchell 1997	94	92	0 (0)			Not estimable
Ravaud 1998	34	34	-2 (2)		1.3 %	0.14 [0.00, 6.82]
Riikonen 1994	28	30	0 (0)			Not estimable
Rodriguez 2005	18	17	1.24 (2)		1.3 %	3.46 [0.07, 174.15]
Vellenga 1996	65	69	-0.62 (1.16)		4.0 %	0.54 [0.06, 5.23]
Total (95% CI)	**688**	**647**			**100.0 %**	**0.74 [0.47, 1.16]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 9.96$, df = 11 (P = 0.53); $I^2 = 0.0\%$
Test for overall effect: Z = 1.31 (P = 0.19)
Test for subgroup differences: Not applicable

Overall mortality	**OR 0.74 [0.47-1.16]**
Infection-related mortality	**OR 0.75 [0.47-1.20]**

Cochrane Database Syst Rev. 2014 Oct 30

Michael Darmon
Elie Azoulay
Corinne Alberti
Fabienne Fieux
Delphine Moreau
Jean-Roger Le Gall
Benoît Schlemmer

Impact of neutropenia duration on short-term mortality in neutropenic critically ill cancer patients

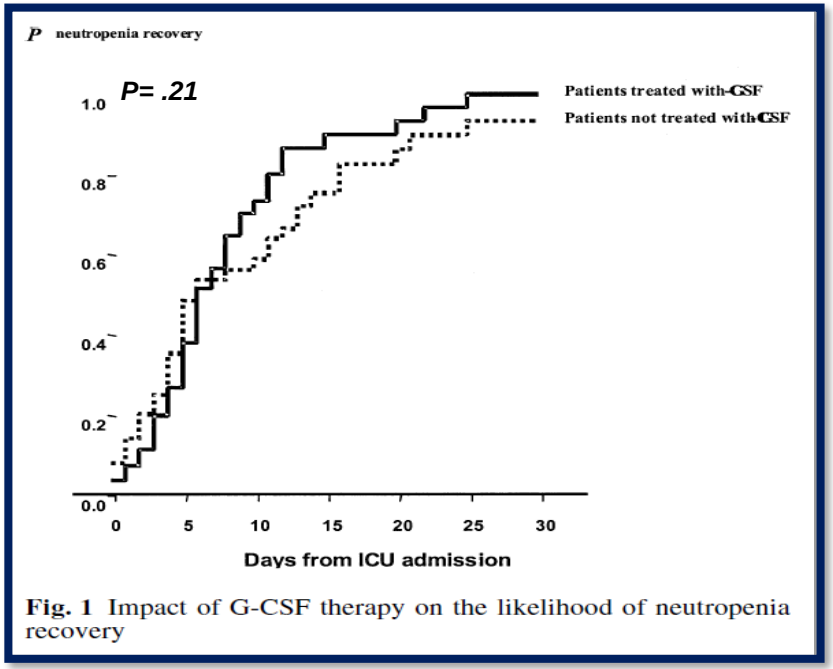
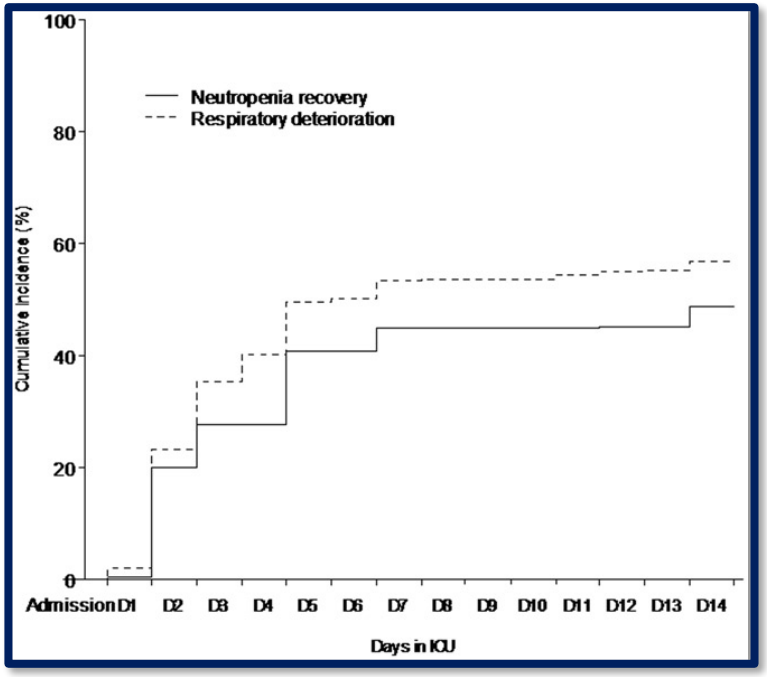


Fig. 1 Impact of G-CSF therapy on the likelihood of neutropenia recovery

Intensive Care Med 2002

Granulocyte colony-stimulating factor and respiratory status of critically ill neutropenic patients with hematologic malignancies

Xavier Mignard[a], Lucie Biard[b], Virginie Lemiale[a], Djamel Mokart[c], Frédéric Pène[d], Achille Kouatchet[e], Julien Mayaux[f], François Vincent[g], Martine Nyunga[h], Fabrice Bruneel[i], Antoine Rabbat[jt], Christine Lebert[k], Pierre Perez[l], Anne-Pascale Meert[m], Dominique Benoit[n], Rebecca Hamidfar[o], Michael Darmon[p], Elie Azoulay[a] and Lara Zafrani[a]

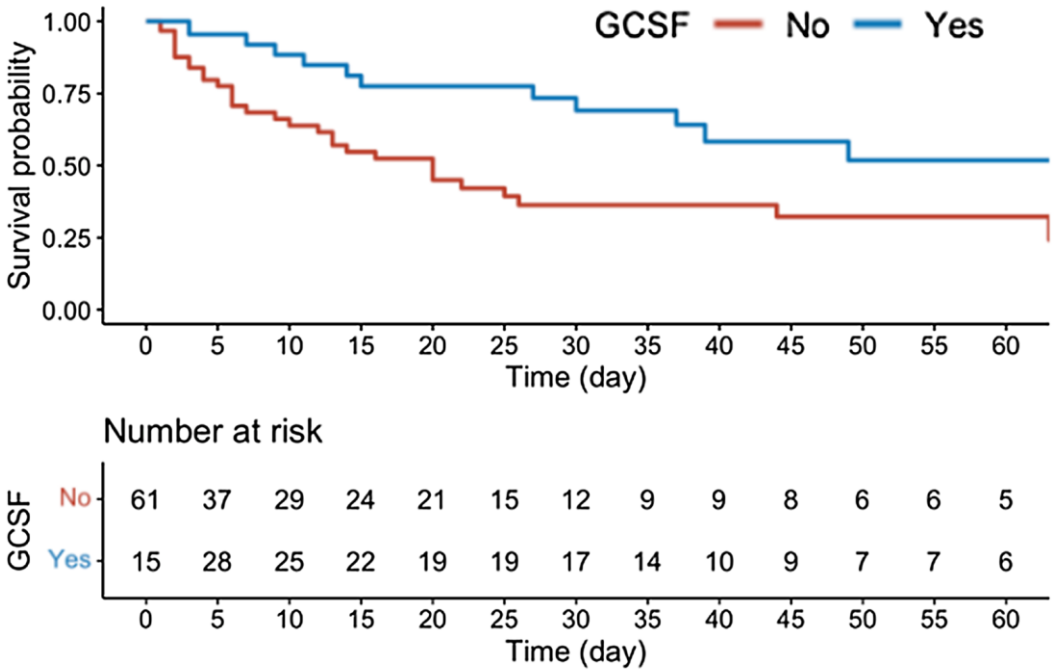


Leukemia Lymphoma 2019

RESEARCH Open Access

Necrotizing soft tissue infections in critically ill neutropenic patients: a French multicentre retrospective cohort study

Romain Arrestier[1,2,3*], Anis Chaba[4], Asma Mabrouki[5], Clément Saccheri[6], Emmanuel Canet[7], Marc Pineton de Chambrun[8], Annabelle Stoclin[9], Muriel Picard[10], Florent Wallet[11], François Perier[12], Matthieu Turpin[13], Laurent Argaud[14], Maxens Decavèle[15], Nahéma Issa[16], Cyril Cadoz[17], Kada Klouche[18], Johana Cohen[19], Djamel Mokart[20], Julien Grouille[21], Tomas Urbina[22], Camille Hua[23,24], Olivier Chosidow[23], Armand Mekontso-Dessap[1,2,3], Elie Azoulay[5] and Nicolas de Prost[1,2,3]



Arrestier *et al. Annals of Intensive Care* (2023) 13:34
https://doi.org/10.1186/s13613-023-01125-w

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Maîtrise de l'environnement

- **Isolement géographique: chambre individuelle**
- **Traitement de l'air: secteur à environnement maîtrisé**
  - **Filtration + renouvellement d'air**
- **Entretien des locaux**
  - **Technique de balayage humide**
- **Introduction d'objets extérieurs**
  - **Nettoyage avec détergent-désinfectant**
- **Contrôle de l'eau**
  - **Filtration des points d'eau**
  - **Ingestion d'eau embouteillée**

Recommandations SF2H, 2016

https://sf2h.net/wp-content/.../2016/12/BD-HY-XXIV-5-SF2H-immunodeprimes.pdf

Isolement de contact

Mesure	Haut risque	Bas risque
Coiffe	non	non
Masque chirurgical	oui	non
• Symptômes respiratoires chez soignants / visiteurs	oui	oui
• Période épidémique virale	oui	oui
Gants	non (hors PS)	non (hors PS)
Surblouse / tablier	possible	non
Surchaussures	non	non

Recommandations SF2H, 2016

https://sf2h.net/wp-content/.../2016/12/BD-HY-XXIV-5-SF2H-immunodeprimes.pdf

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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)

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Conclusions

- ❑ Résistance fréquente aux antimicrobiens
- ❑ Evaluation du risque fongique
- ❑ Optimisation de l'antibiothérapie
- ❑ Peu de place pour les traitements immunostimulants
- ❑ Mesures d'isolement ?

Etude COMBINATION-LOCK (Pr M Darmon): sepsis neutropénique
- **Amikacine vs. ∅**
- **Isolement standard vs. protecteur**