

Particularités diagnostiques et thérapeutiques des pneumonies chez le patient immunodéprimé

Dr V Lemiale

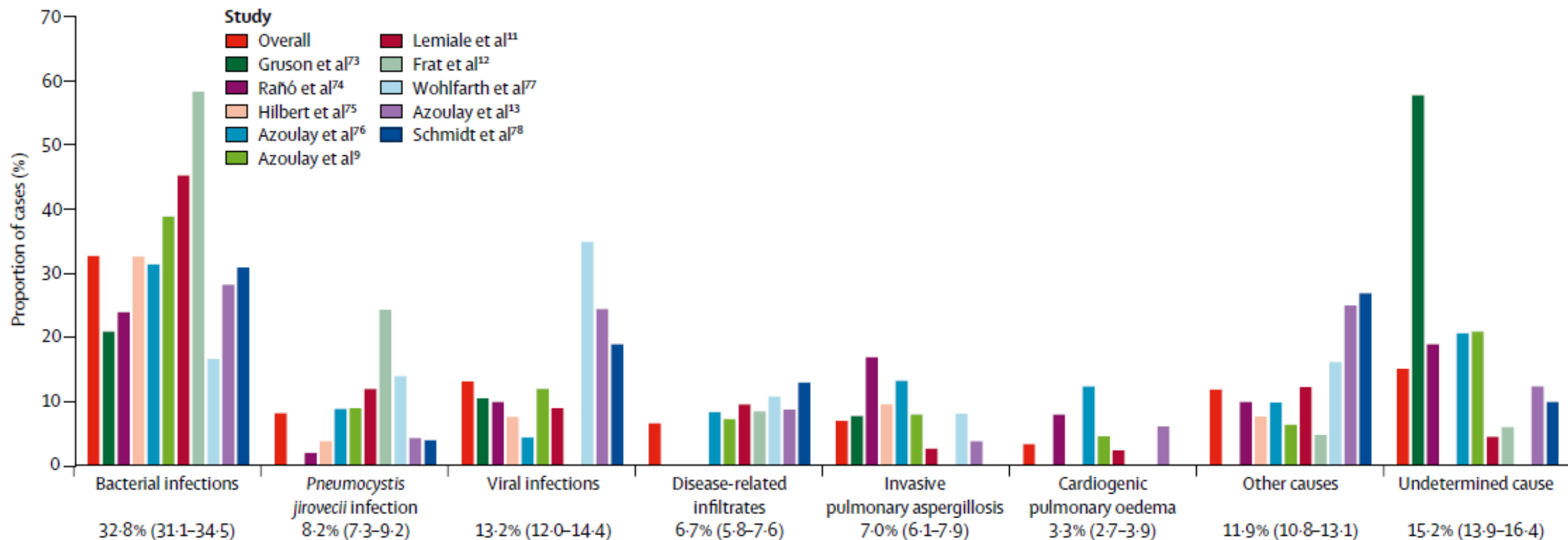
APHP Saint Louis

GrrrOH-Nine I






Liens d'intérêt

- GrrrOH :
 - GILEAD
 - MSD
 - ALEXION
 - FISHER and PAYKEL
 - SANOFI
 - CELGENE
 - FISHER -PAYKEL

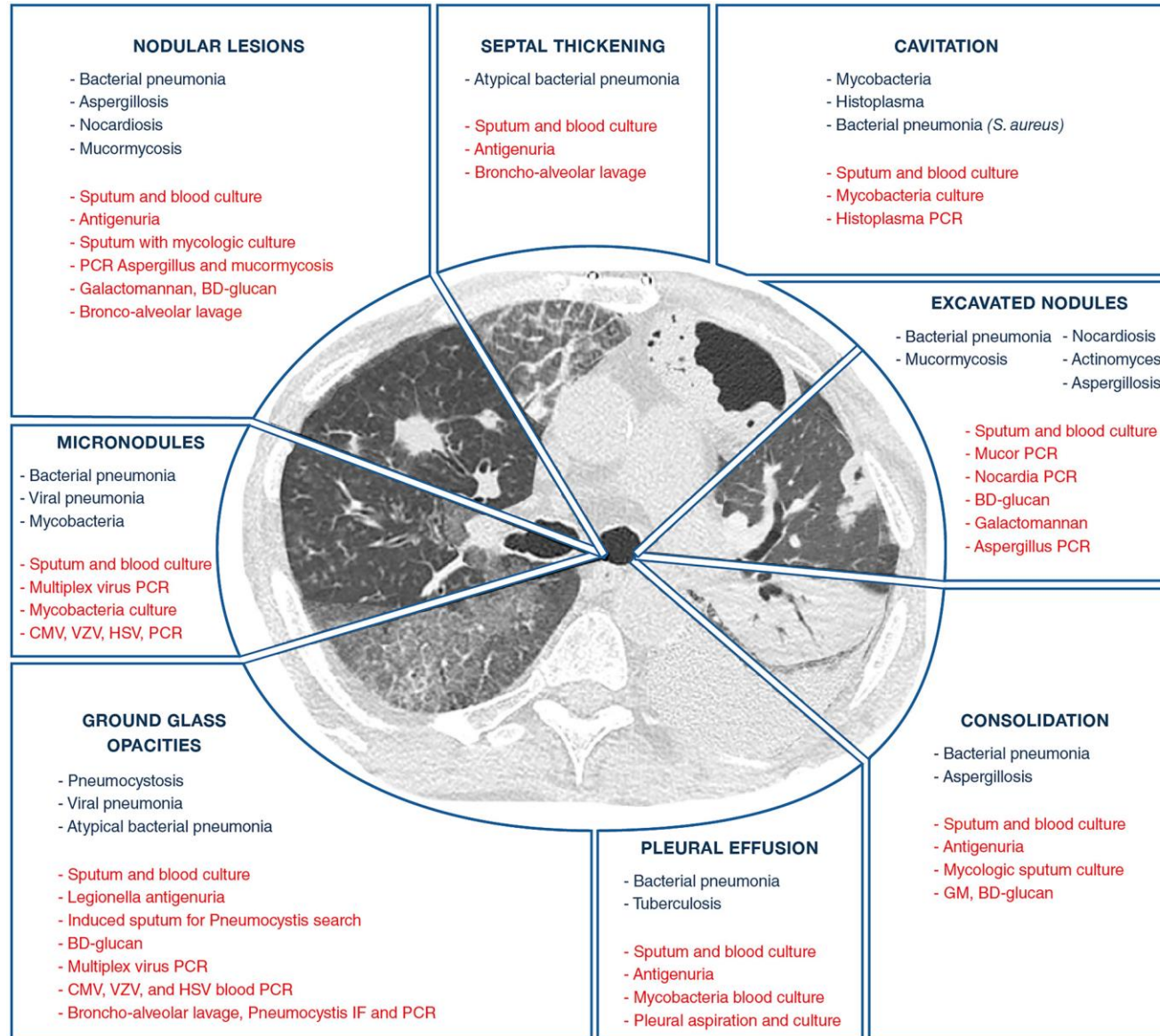
1-Diversité diagnostique

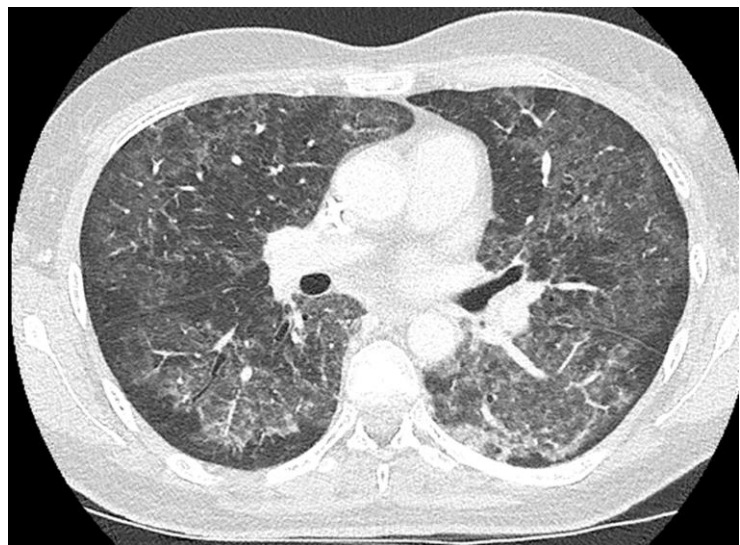
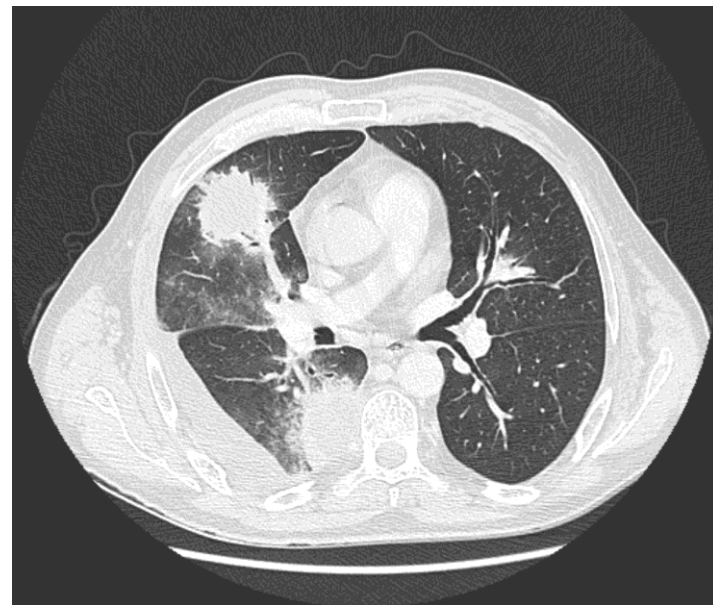


Diversité diagnostique

Immunological deficiency	Neutrophils 	Monocytes/dendritic cells/macrophages 	B lymphocytes 	T lymphocytes 	Humoral (antibody) immunity 
Diseases	Acute leukaemia; myelodysplastic syndrome; aplastic anaemia; chemotherapy and drug-related neutropenia	Hairy cell leukaemia; aplastic anaemia; allogeneic bone marrow transplant; malignant histiocytosis; acute myeloid leukaemia; chronic myeloid leukaemia; solid tumours; haemophagocytic lymphohistocytosis	Multiple myeloma; B-cell lymphoma; chronic lymphocytic leukaemia	T-cell leukaemia; T-cell lymphoma; Hodgkin disease	Multiple myeloma; chronic lymphoid leukaemia
Treatments	Chemotherapy-induced neutropenia	Steroids; basiliximab; antithymocyte globulin; tacrolimus; mycophenolate mofetil; belatacept	Chemotherapy; steroids; asplenia; rituximab	Steroids; fludarabine; cyclophosphamide; methotrexate; azathioprine; alemtuzumab; mycophenolate mofetil; cyclosporine; mTOR inhibitors (sirolimus); tacrolimus; 2-chlorodeoxyadenosine; daratumumab	Ibrutinib; rituximab; daratumumab; cyclophosphamide
Most frequently encountered infections	<ul style="list-style-type: none"> Gram-negative bacteria Gram-positive bacteria <i>Candida</i> <i>Aspergillus</i> <i>Nocardia</i> 	<ul style="list-style-type: none"> Non-tuberculous mycobacteria <i>Salmonella</i>, <i>Listeria</i>, <i>Legionella</i>, <i>Histoplasma</i>, <i>Brucella</i> Herpes simplex virus, varicella zoster virus, parainfluenza virus, respiratory syncytial virus <i>Candida parapsilosis</i> <i>Staphylococcus aureus</i>, <i>Enterococcus faecalis</i>, <i>Pseudomonas aeruginosa</i> 	<ul style="list-style-type: none"> Encapsulated bacteria (<i>Streptococcus pneumoniae</i>, <i>Streptococcus pyogenes</i>, <i>Haemophilus influenzae</i>) <i>Giardia lamblia</i>, <i>Campylobacter</i>, <i>Salmonella</i> <i>Mycoplasma</i> Enterovirus Recurrent infections 	<ul style="list-style-type: none"> Herpes simplex virus, cytomegalovirus, Epstein-Barr virus <i>Pneumocystis</i>, <i>Aspergillus</i>, <i>Cryptococcus</i> Mycobacterial infection Skin candidiasis Diarrhoea (rotaviruses, adenoviruses, <i>Cryptosporidium</i>, microsporidia, etc) John Cunningham virus 	<ul style="list-style-type: none"> Encapsulated bacteria (<i>S pneumoniae</i>, <i>S pyogenes</i>, <i>H influenzae</i>) <i>Mycoplasma</i>, <i>Ureaplasma urealyticum</i> Other infections related to associated T-cell defects

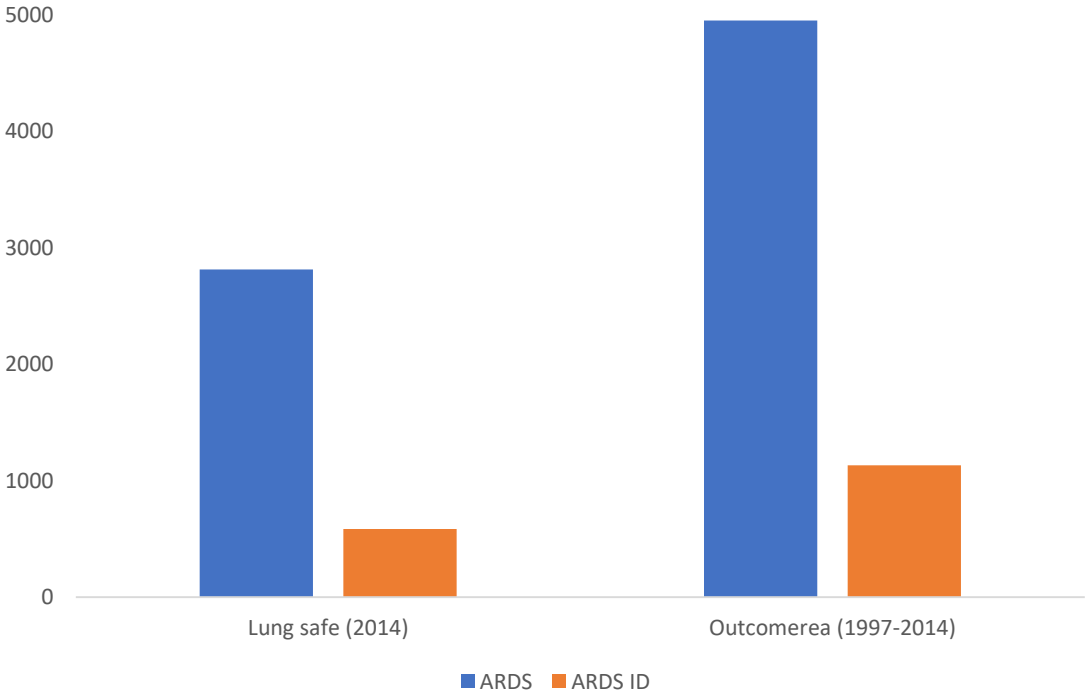
2-Intérêt de l'imagerie



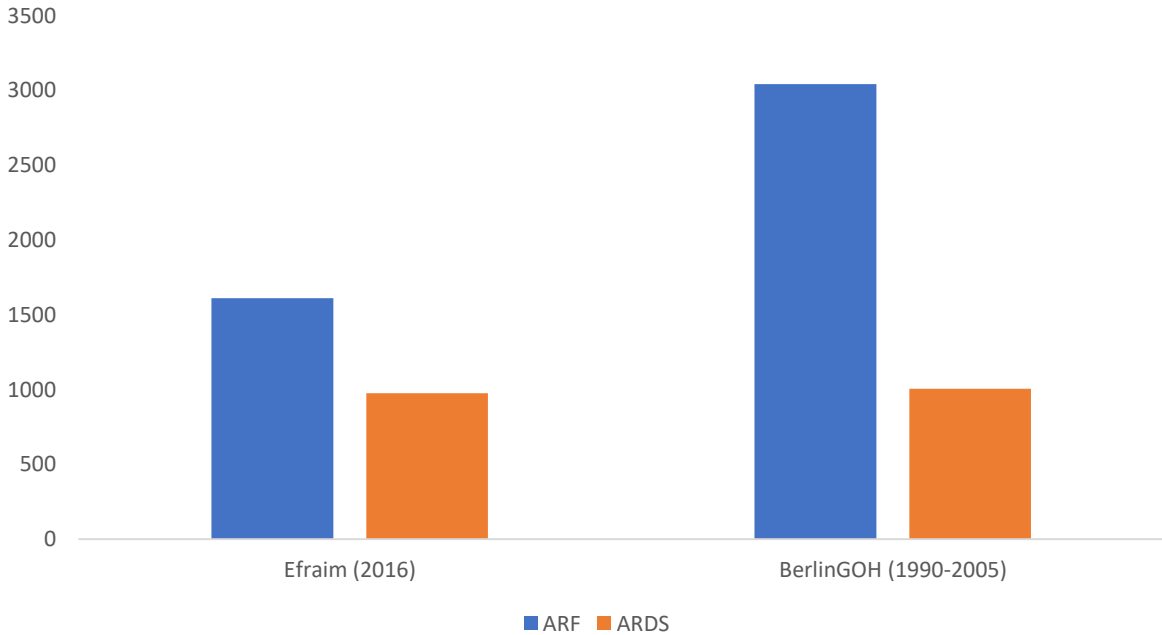


3- Sévérité

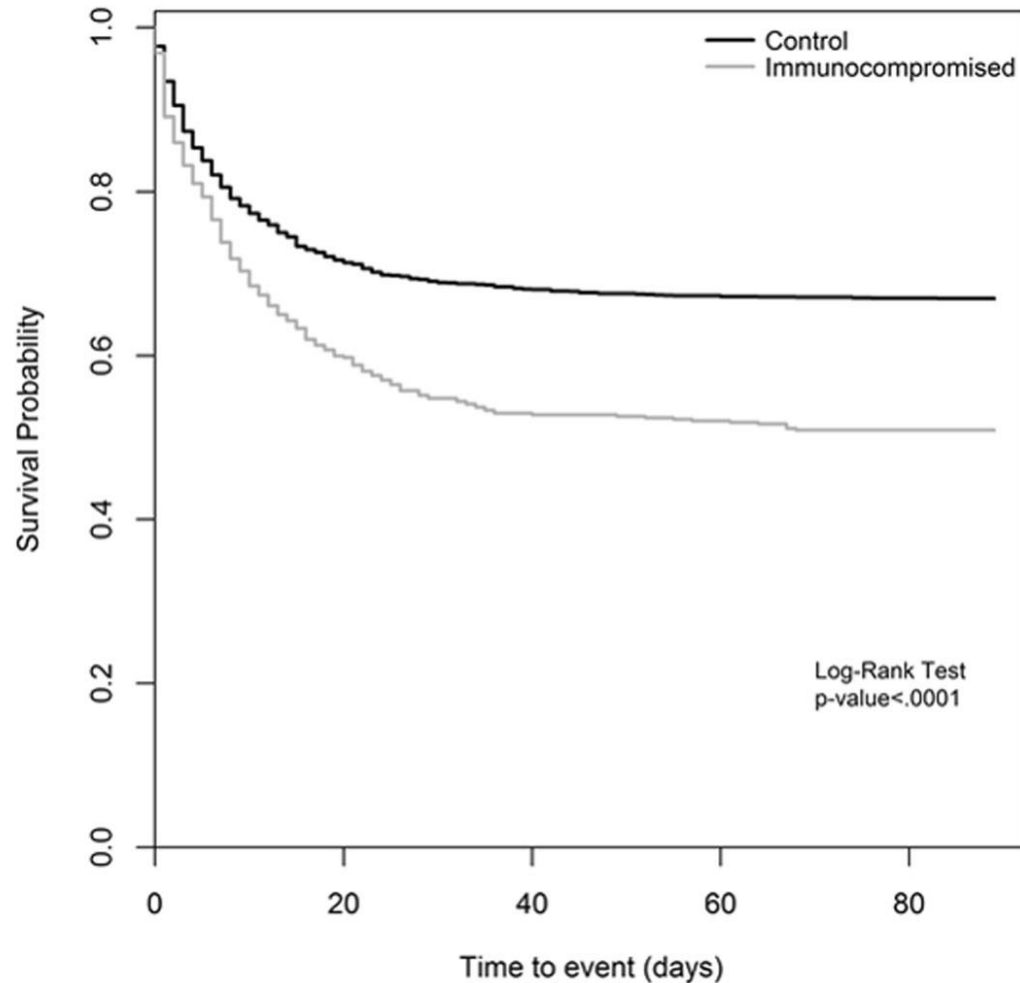
20% des SDRA sont des patients ID



30 to 50 % des patients ID avec IRA ont un SDRA



Sévérité du SDRA



# at risk					
Control	2111	1512	1437	1420	1414
Immunocompromised	542	325	287	282	276

Moins de comorbidités

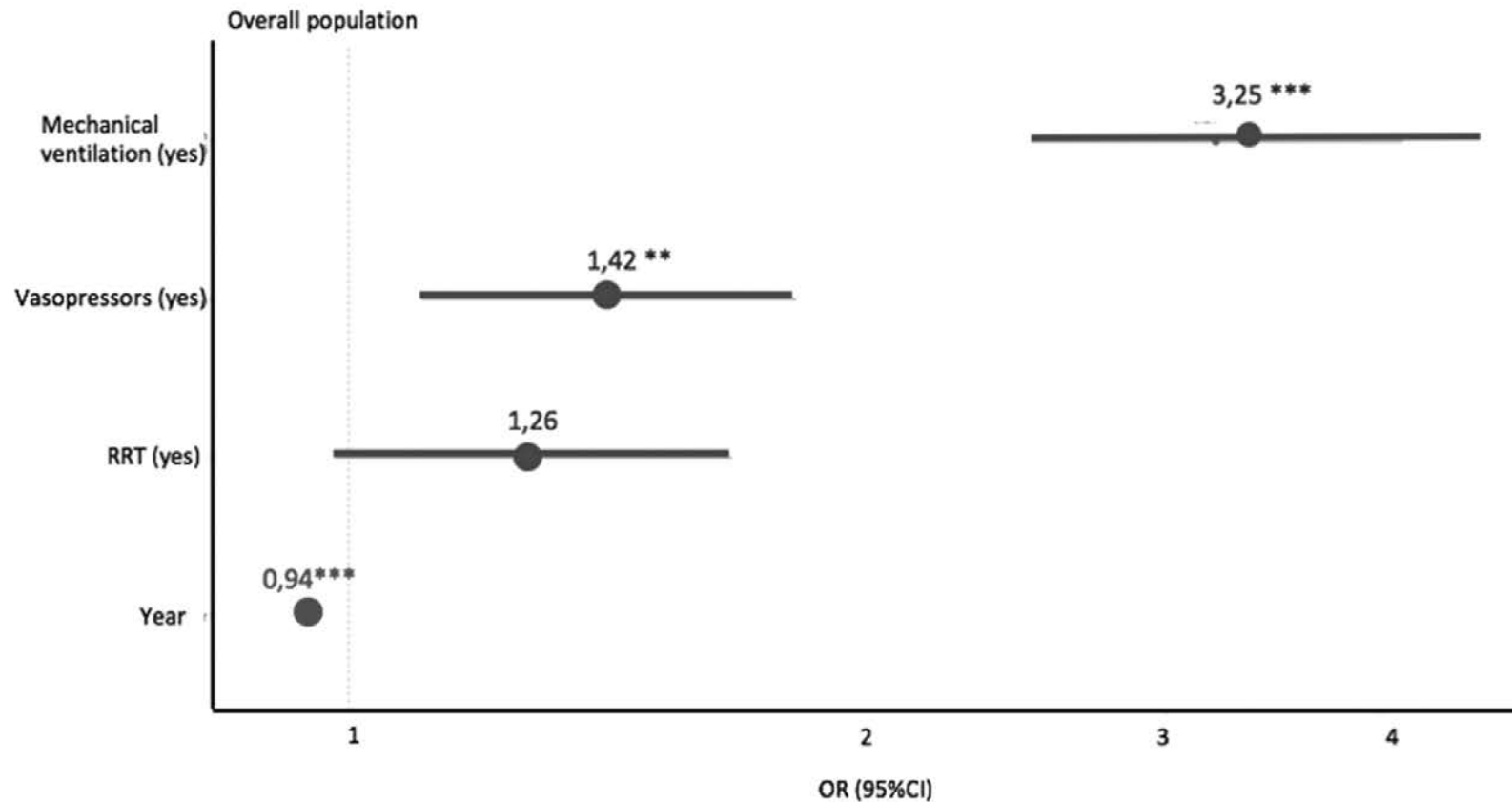
Pneumonie : étiologie la plus fréquente

Plus de VNI (20.9 vs 15.9,9%, p=0,004)

Plus d'échec de VNI (10.4% vs 6,1%, p=,002)

Plus de décision de fin de vie

Impact des défaillances d'organes



2000 patients avec choc septique (57%) ou sepsis
Neutropénie 31%
Mortalité 40%

4-Impact du retard d'admission

218 patients

Hématologie 80%, oncologie 20%

Pneumonie et choc septique

TABLE 3. Multivariate analysis of in-hospital mortality risk factors

Variable	OR (CI 95%)	P
Age >60 years	3.26 (1.55 – 6.82)	0.0019
Poor performance status	1.28 (0.53 – 3.1)	0.58
Allogeneic HSCT	3.74 (1 – 14.06)	0.051
Delay from first symptom onset (per day)	1.07 (1 – 1.15)	0.049
Ventilation strategy		
Use of O ₂ only	1	
Use of NIV only	0.87 (0.2 – 3.85)	0.86
Use of MV only	6.53 (2.31 – 18.5)	<0.001
Use of MV after NIV	7.51 (2.60 – 21.73)	<0.001
Glasgow Coma Scale score (per point)	0.84 (0.73 – 0.98)	0.023
Inclusion period 2004 – 2009	0.31 (0.12 – 0.75)	0.01

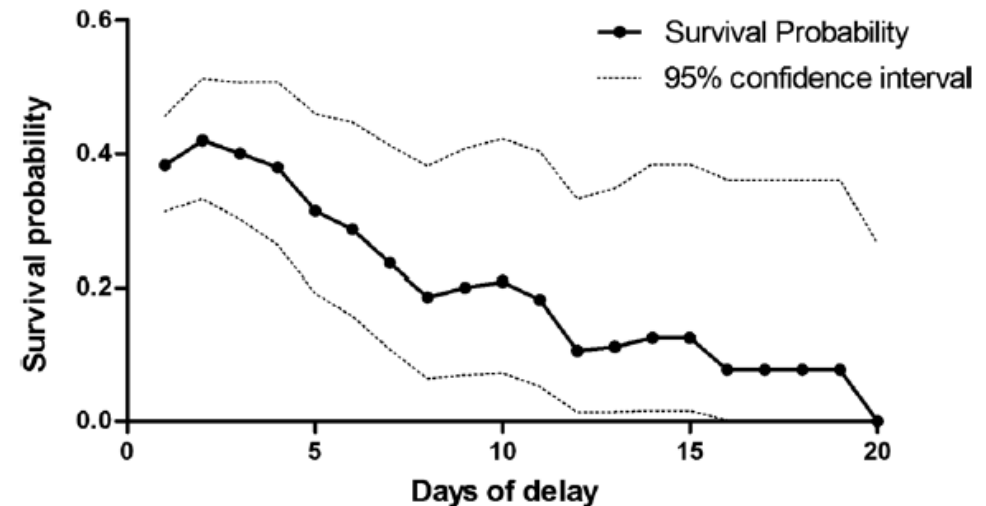
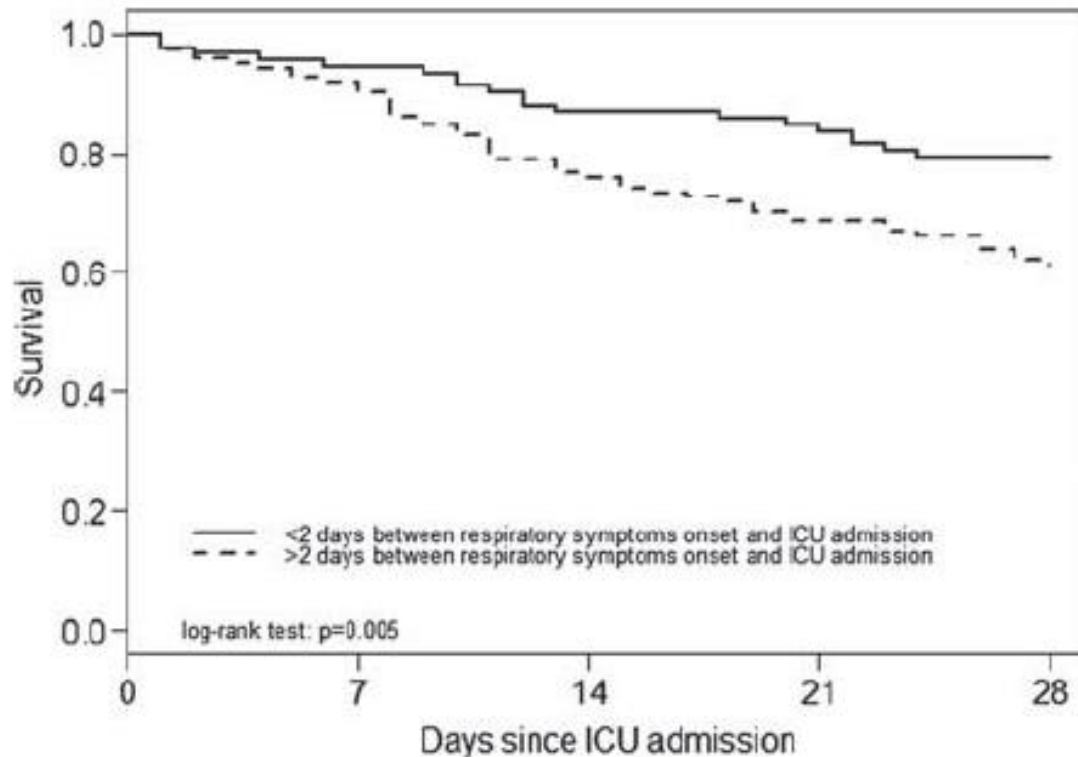
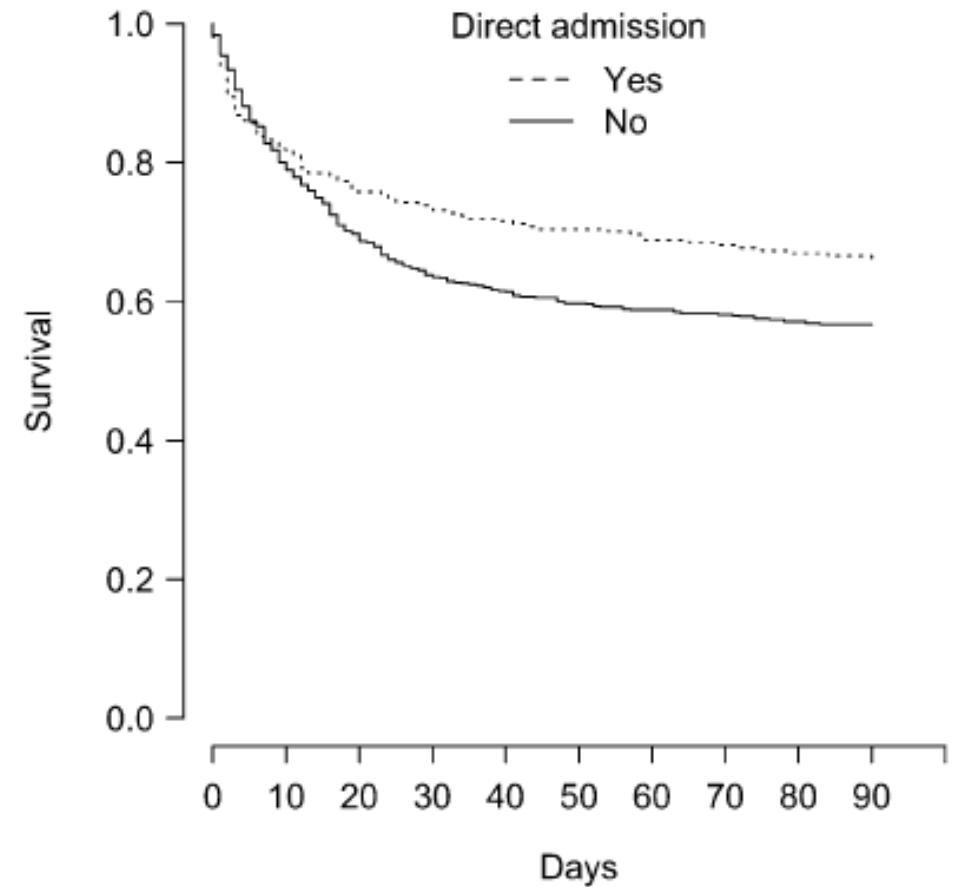


FIG. 1. Survival probability depending on the time between first symptoms and ICU admission.

Impact du retard d'admission



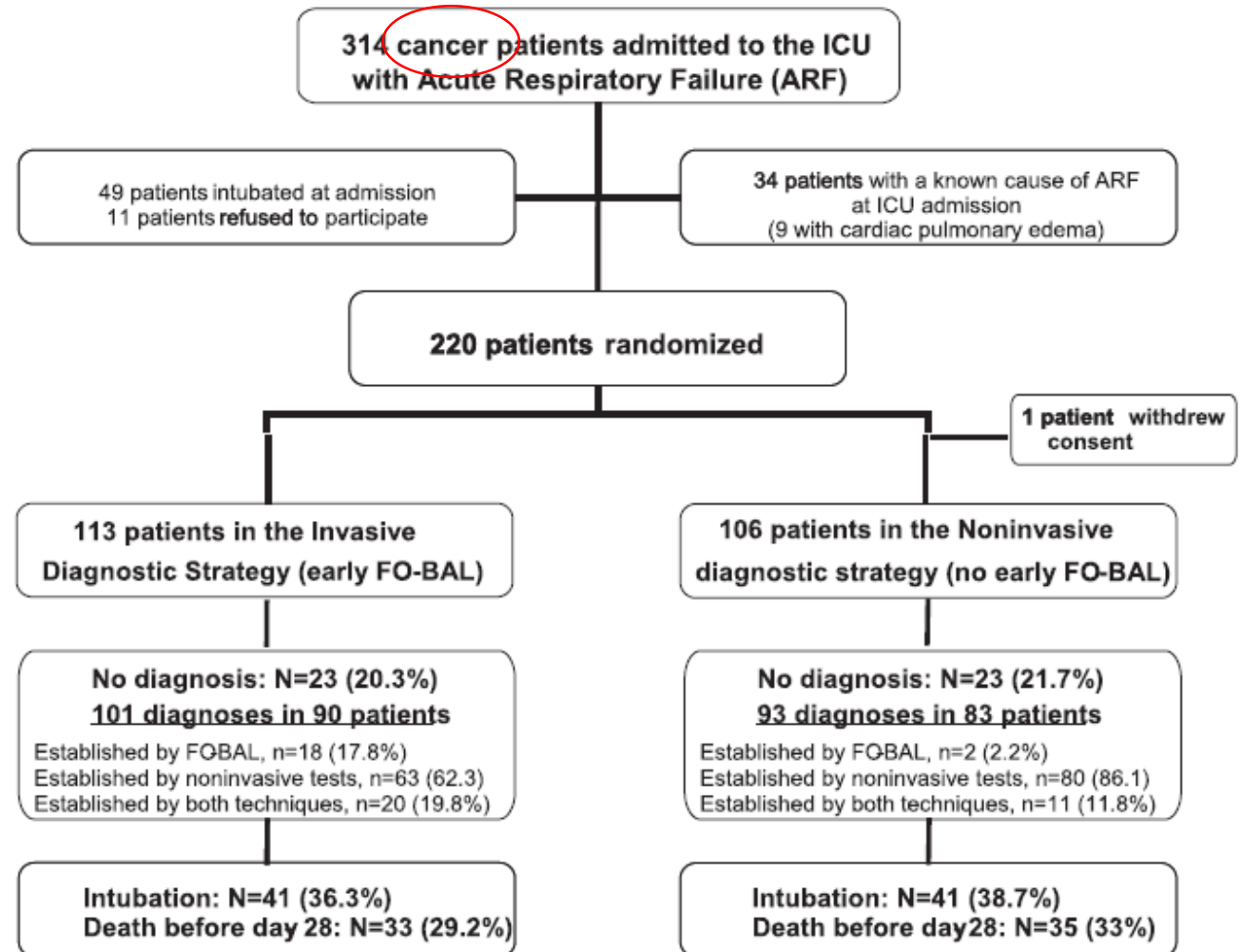
219 patients issus de minimax



Patients admis des urgences vs passage en salle initial

5- stratégie diagnostique

- Examen non invasifs
 - ECBC
 - Hémocultures
 - Ag Legionelle
 - Expectoration induite (PCP)
 - PCR virale NP
 - PCR sanguin
 - Ag gactomannan
 - PCR panfongique
 - BD glucan
 - PCT (intérêt à valider)



Quels examens disponibles en 2022?

Comparison of Respiratory Pathogen Detection in Upper versus Lower Respiratory Tract Samples Using the BioFire FilmArray Respiratory Panel in the Immunocompromised Host

Natalya Azadeh
Canadian Respiratory Journal

Metagenomic Next-Generation Sequencing for Infectious Disease Diagnosis: A Review of the Literature With a Focus on Pediatrics

Priya Edward¹ Journal of the Pediatric Infectious Diseases Society 2021;10(S4):S71–7

Transfer transcriptomic signatures for infectious diseases

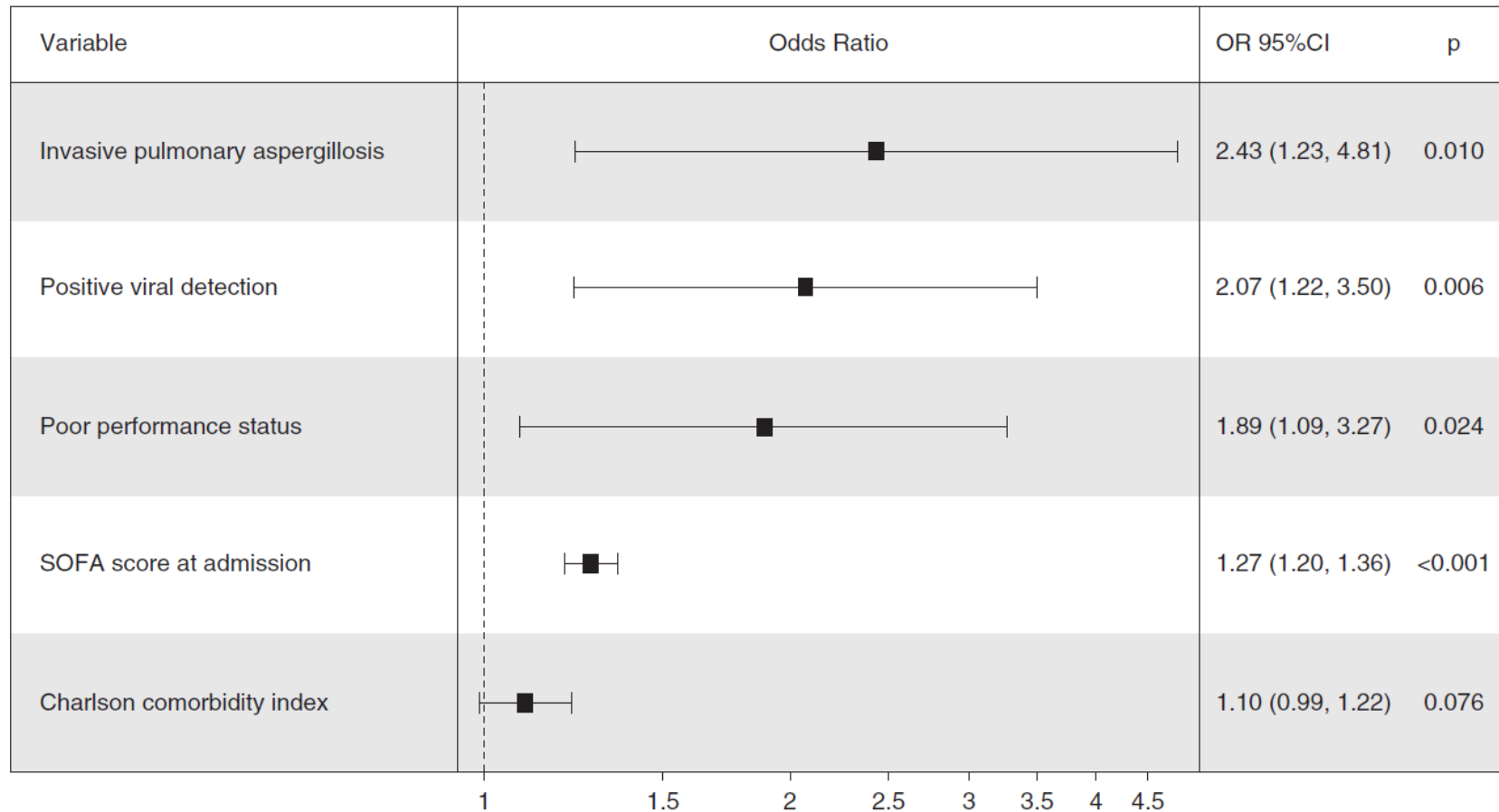
[Julia di Iulio](#) PNAS, May 24, 2021; 118 (22) e2022486118

Impact de détection d'un virus

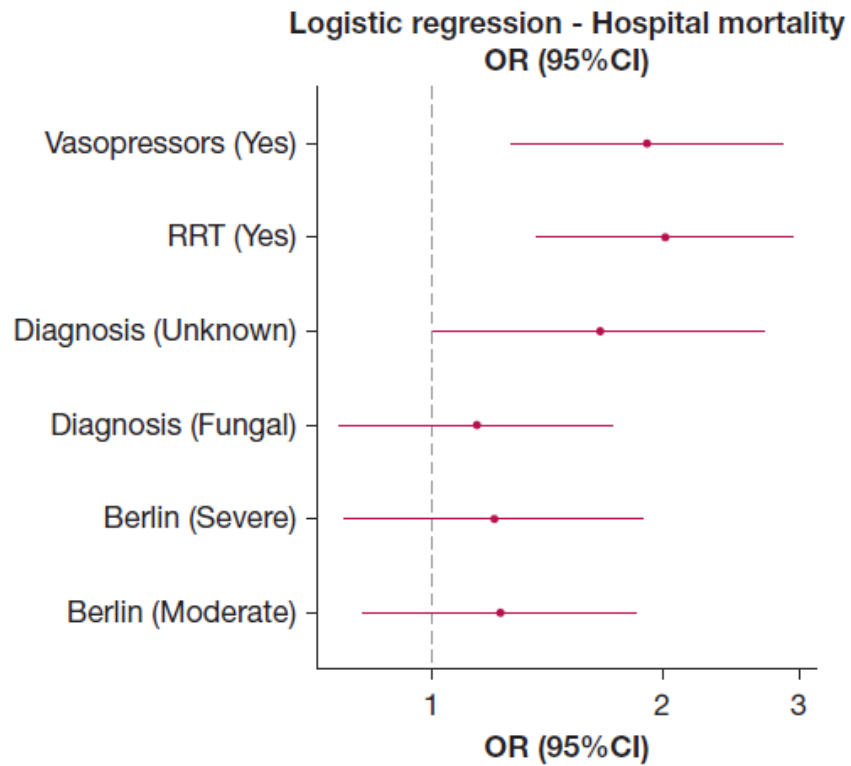
747 patients avec aspiration naso-pharyngée (21% positive)

447 patients avec une détresse respiratoire aigue (25% positive)

300 patients sans détresse respiratoire(16% positive)



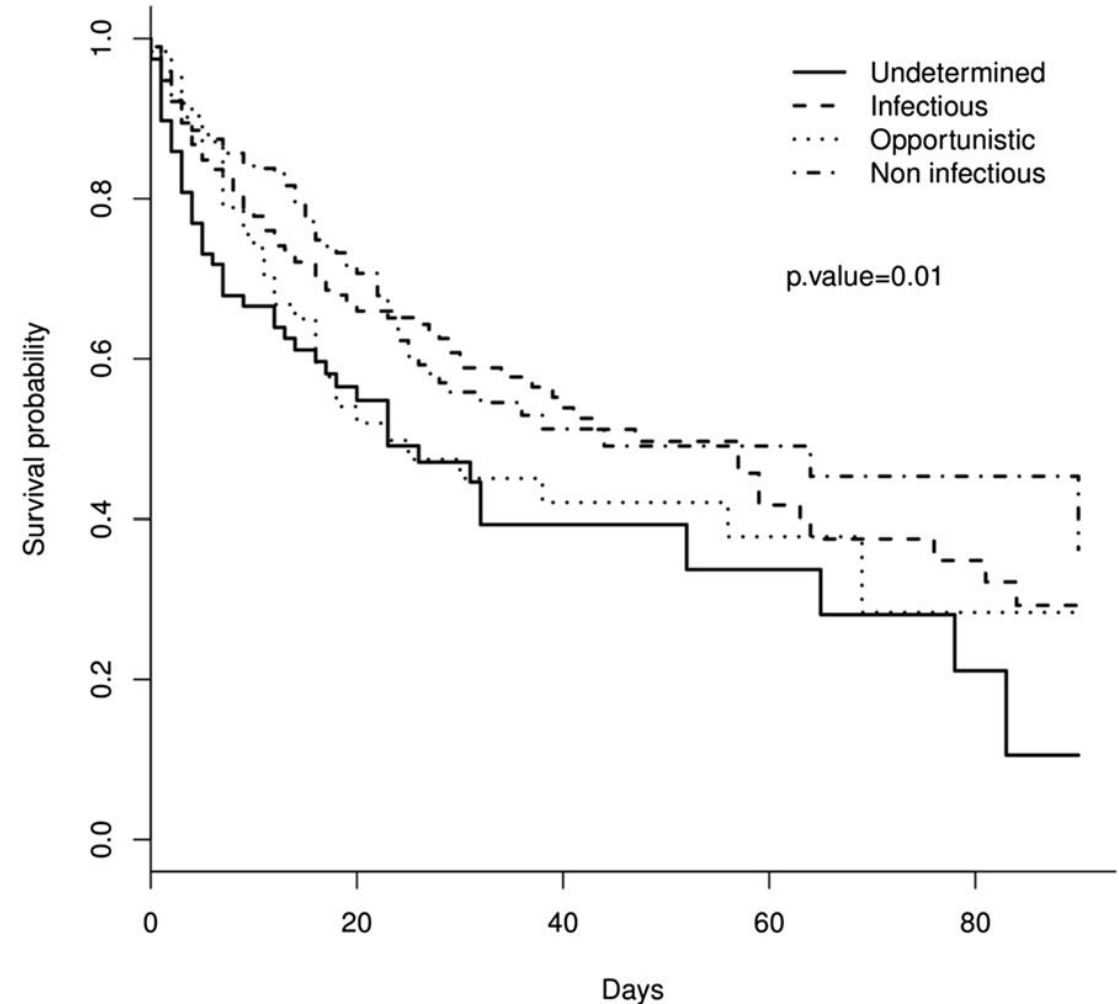
6- impact de l'absence de diagnostic



789 ID with ARDS

13 % undetermined diagnosis

Demoule et al, Chest (2020) :1947-1957



604 hematological patients with ARF

12,9 % undetermined diagnosis

Contejean et al. Ann. Intensive Care (2016) 6:102

7-Particularité du traitement antibiotique

- La durée de l'antibiothérapie dépend de la neutropénie. En l'absence de neutropénie durée habituelle d'antibiothérapie
- Adaptée au BGN en cas de neutropénie (recommandation ASCO 2018)
- Associations fréquentes
 - Pneumocoque / myélome
 - Listeria/ Leucémie tricholeucocytes
- Désescalade possible : étude rétrospective positive
étude prospective en cours

Particularités du patient neutropénique

Table 3 Bacterial infectious diagnoses

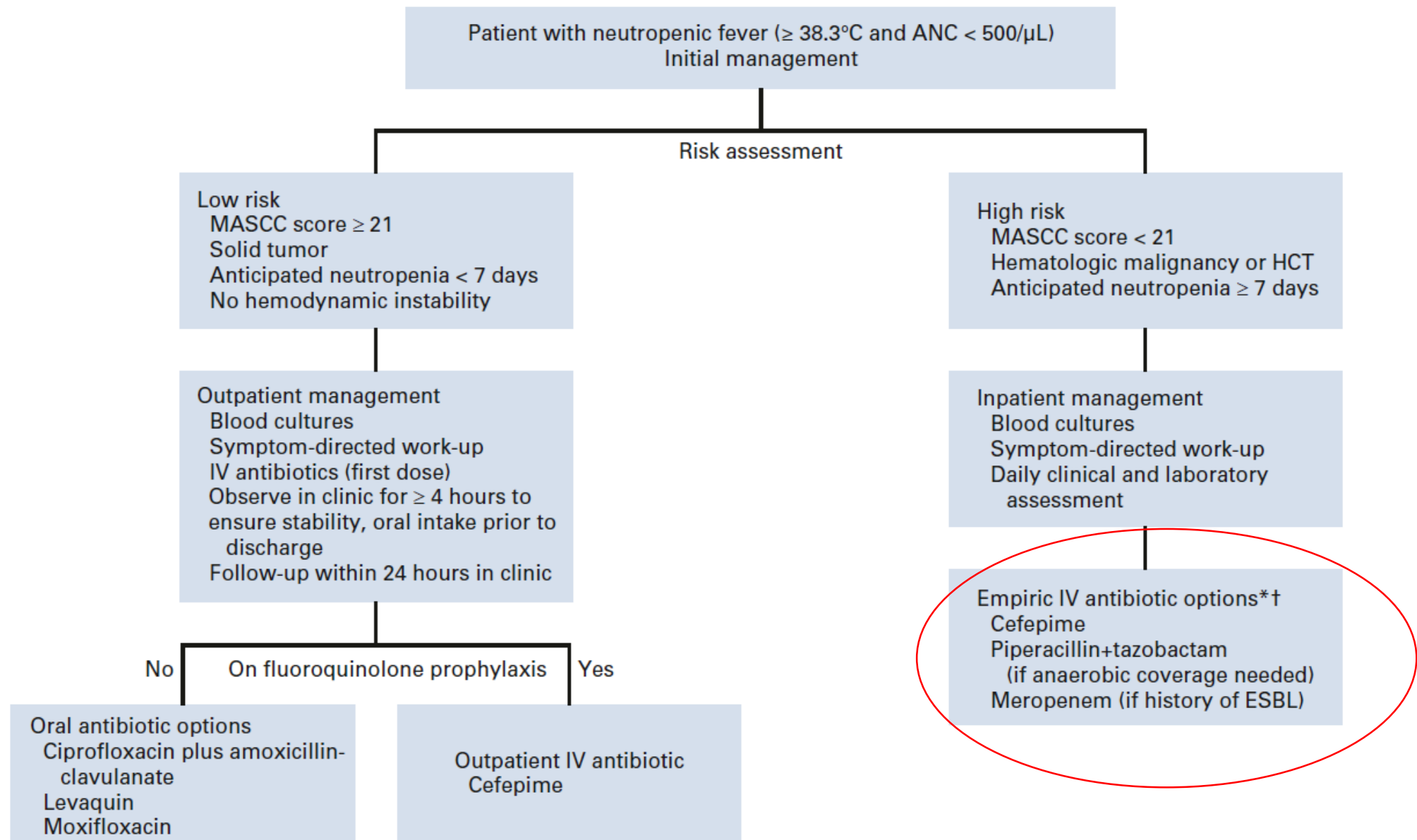
	Non-neutropenic (n = 356)	Neutropenic (n = 79)	p value
			0.044
Gram-negative bacteria			
<i>Pseudomonas</i>	31 (9%)	14 (18%)	
<i>Klebsiella</i>	33 (9%)	14 (18%)	
<i>Escherichia coli</i>	40 (11%)	14 (18%)	
<i>Enterobacter</i>	18 (5%)	3 (4%)	
<i>Stenotrophomonas</i>	3 (1%)	3 (4%)	
<i>Legionella</i>	4 (1%)	2 (3%)	
<i>Branhamella catarrhalis</i>	6 (2%)	2 (3%)	
<i>Acinetobacter</i>	7 (2%)	1 (1%)	
<i>Haemophilus influenzae</i>	13 (4%)	1 (1%)	
<i>Campylobacter jejuni</i>	0 (0%)	1 (1%)	
<i>Citrobacter</i>	1 (0.5%)	1 (1%)	
<i>Proteus</i>	4 (1%)	0	
<i>Hafnia alvei</i>	3 (1%)	0	
<i>Morganella</i>	3 (1%)	0	
<i>Serratia</i>	3 (1%)	0	
<i>Salmonella</i>	2 (0.5%)	0	
<i>Neisseria meningitidis</i>	2 (0.5%)	0	
<i>Bacteroides</i>	1 (0.5%)	0	
<i>Bordetella hinzii</i>	1 (0.5%)	0	
Gram-positive bacteria			
<i>Coagulase-negative staphylococci</i>	49 (14%)	9 (11%)	
<i>Enterococcus</i>	31 (9%)	6 (8%)	
<i>Staphylococcus aureus</i>	49 (14%)	4 (5%)	
<i>Streptococcus</i>	11 (3%)	2 (3%)	
<i>Streptococcus pneumoniae</i>	34 (10%)	1 (1%)	
<i>Actinomyces</i>	3 (1%)	0	
<i>Clostridium</i>	1 (0.5%)	0	
Others			
<i>Mycoplasma</i>	3 (1%)	0	

Table 1 Characteristics of neutropenic vs non-neutropenic patients

	Non-neutropenic (n = 1316)	Neutropenic (n = 165)	p value
Acute respiratory failure diagnosis (%)			<0.001
Bacterial	356 (27.1)	79 (47.9)	
Fungal	74 (5.6)	17 (10.3)	
Other	691 (52.5)	53 (32.1)	
Pneumocystis	48 (3.6)	3 (1.8)	
Unknown	147 (11.2)	13 (7.9)	

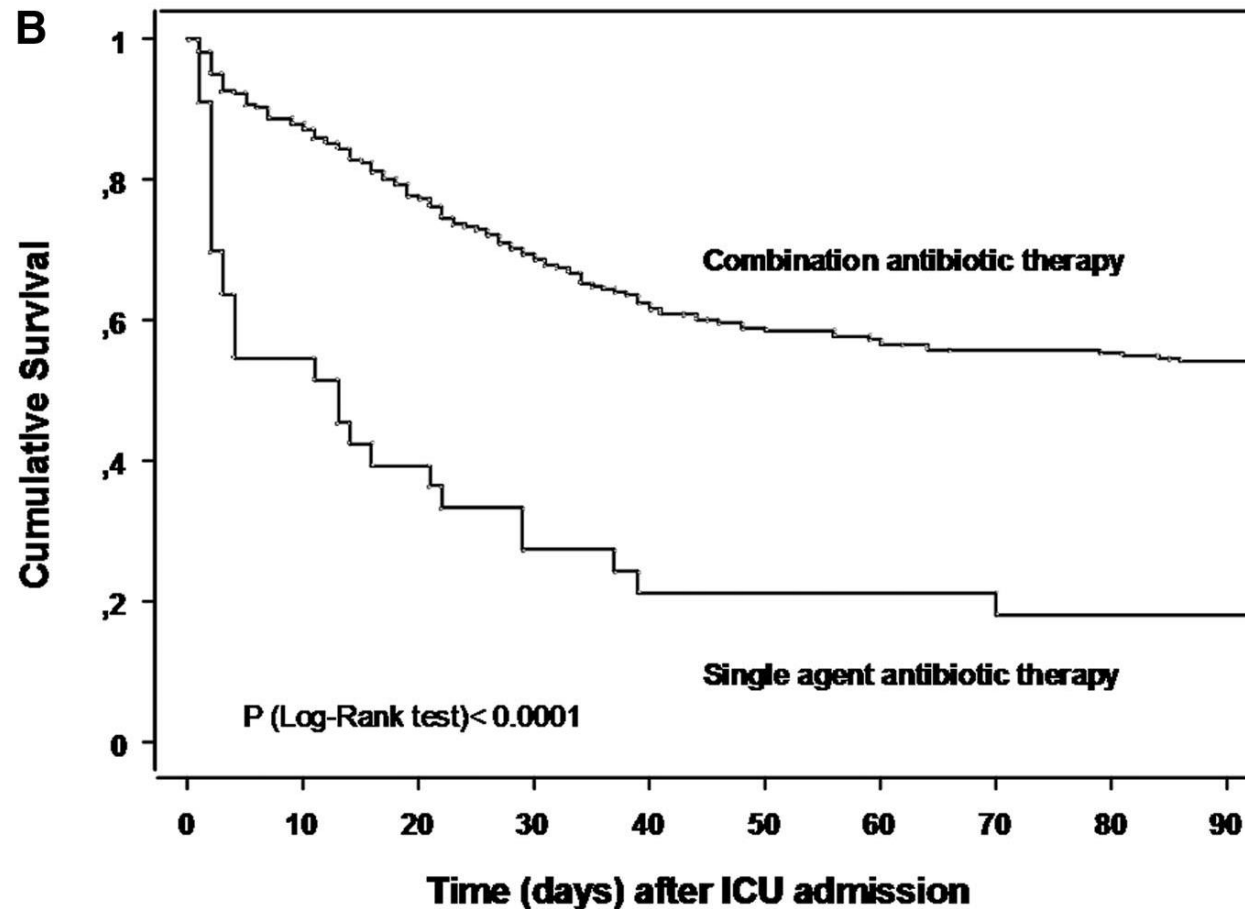
Infection bactérienne avant tout

Bactérie gram négatif ++++



Antibiothérapie associée ?

- Aminoglycosides



Peu de données

Analyse rétrospective

Etude en cours

Plutôt choc septique et peu efficace pour les pneumonies

Fièvre persistante chez un patient neutropénique

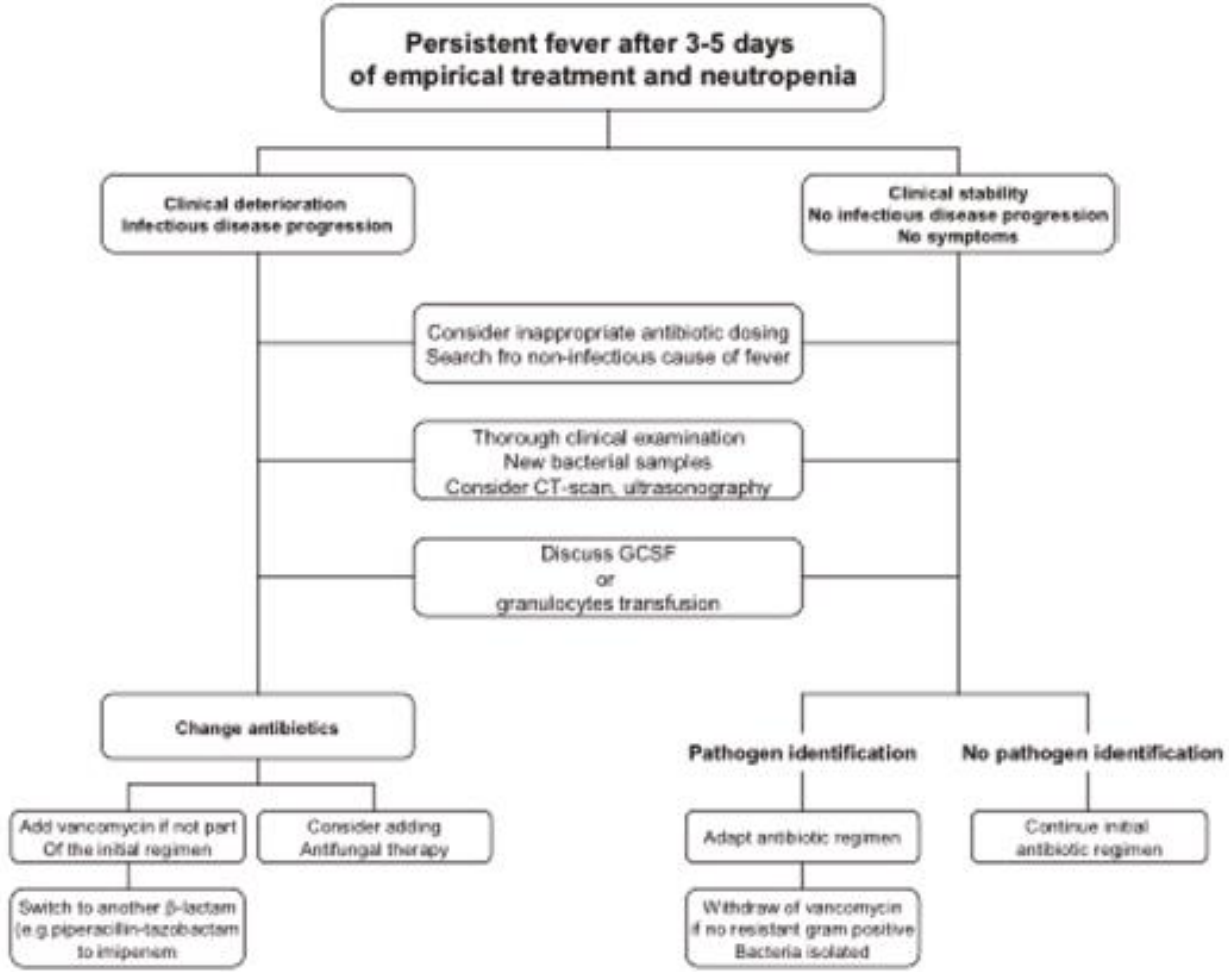
Table 4 Causes of fever persistence after initial empirical antibiotic in neutropenic patients

Infectious causes of persistent fever

- Inappropriate antibiotic dosing and concentration
- Clostridium difficile*-induced diarrhea
- Antibiotic-resistant pathogen
 - Multidrug-resistant bacteria,
 - Mycobacteria,
 - Fastidious pathogens (e.g., *Legionella*, *Mycoplasma*, *Chlamydia pneumoniae*, *Bartonella*)
- Fungal infection
 - Molds: *Aspergillus* and zygomycetes
 - Yeasts: *Candida* and *Cryptococcus*
- Parasitic infection
 - e.g., *Toxoplasma gondii*
- Viral infection
 - e.g., herpesviruses (cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, varicella-zoster virus, herpes simplex virus) parainfluenza virus, respiratory syncytial virus, influenza viruses.
- Persistent focus of infection (e.g., catheter)
- Uncontrolled infection (e.g., endocarditis or peritonitis)

Noninfectious causes of persistent fever

- Transfusion-related fever
- Hemophagocytic lymphohistiocytosis
- Venous thrombosis
- Drug- or transfusion-induced fever
- Graft-versus-host disease
- Underlying malignancy
- Pancreatitis



8-Place des facteurs de croissance

20 patients en sortie d'aplasie sous GSF

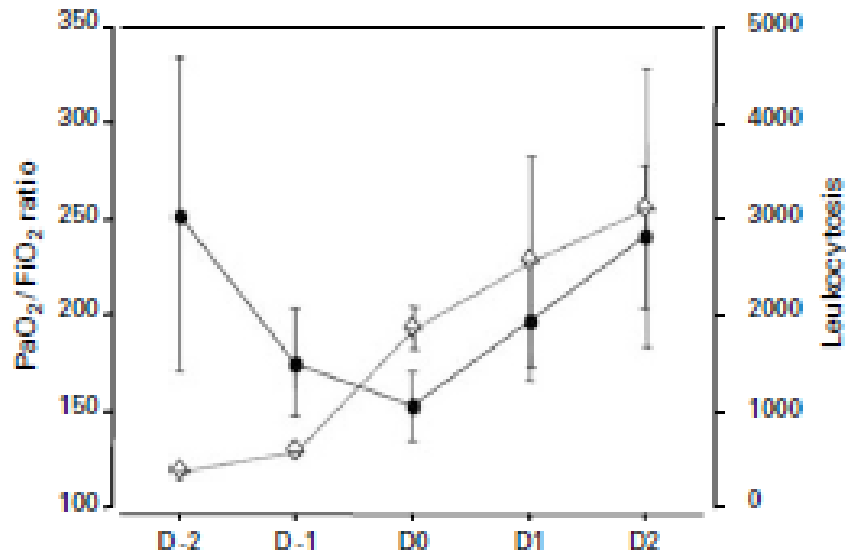


Figure 1 Time course of PaO₂/FiO₂ ratio (closed circles) and total leukocyte count (lozenges) during the 5-day period centered on the day of neutropenia recovery (D0).

288 patients
70% sans GCSF
Score de propension

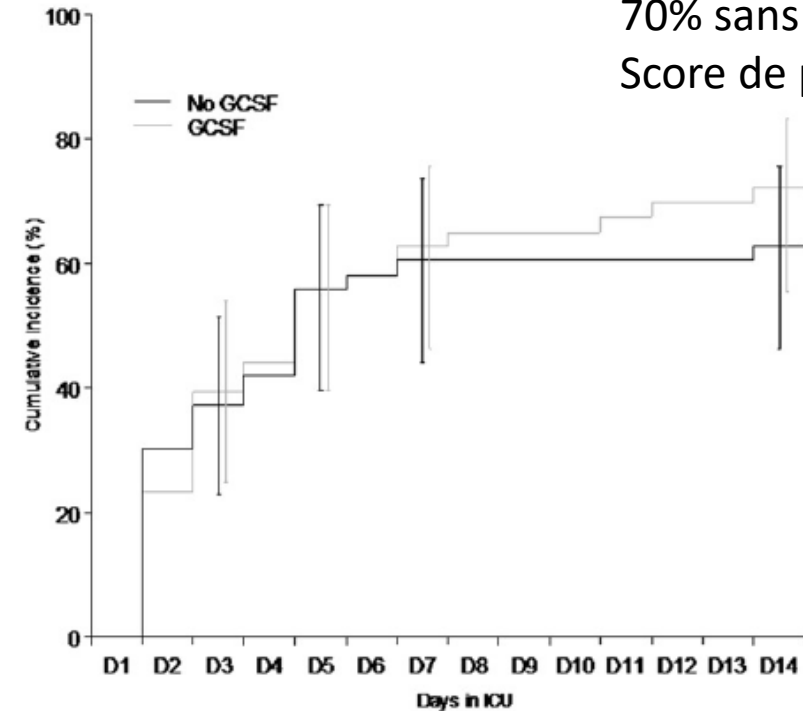
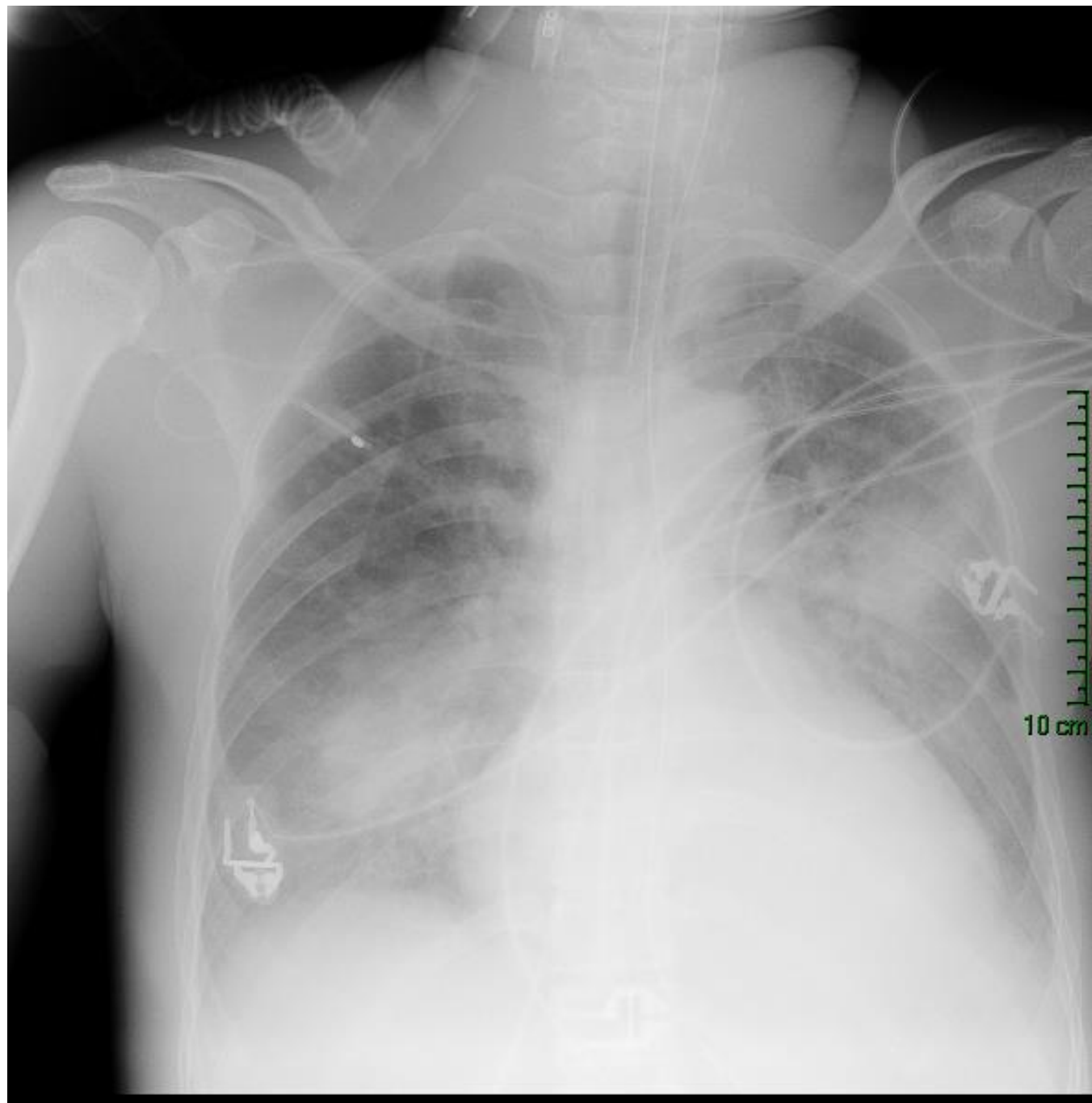


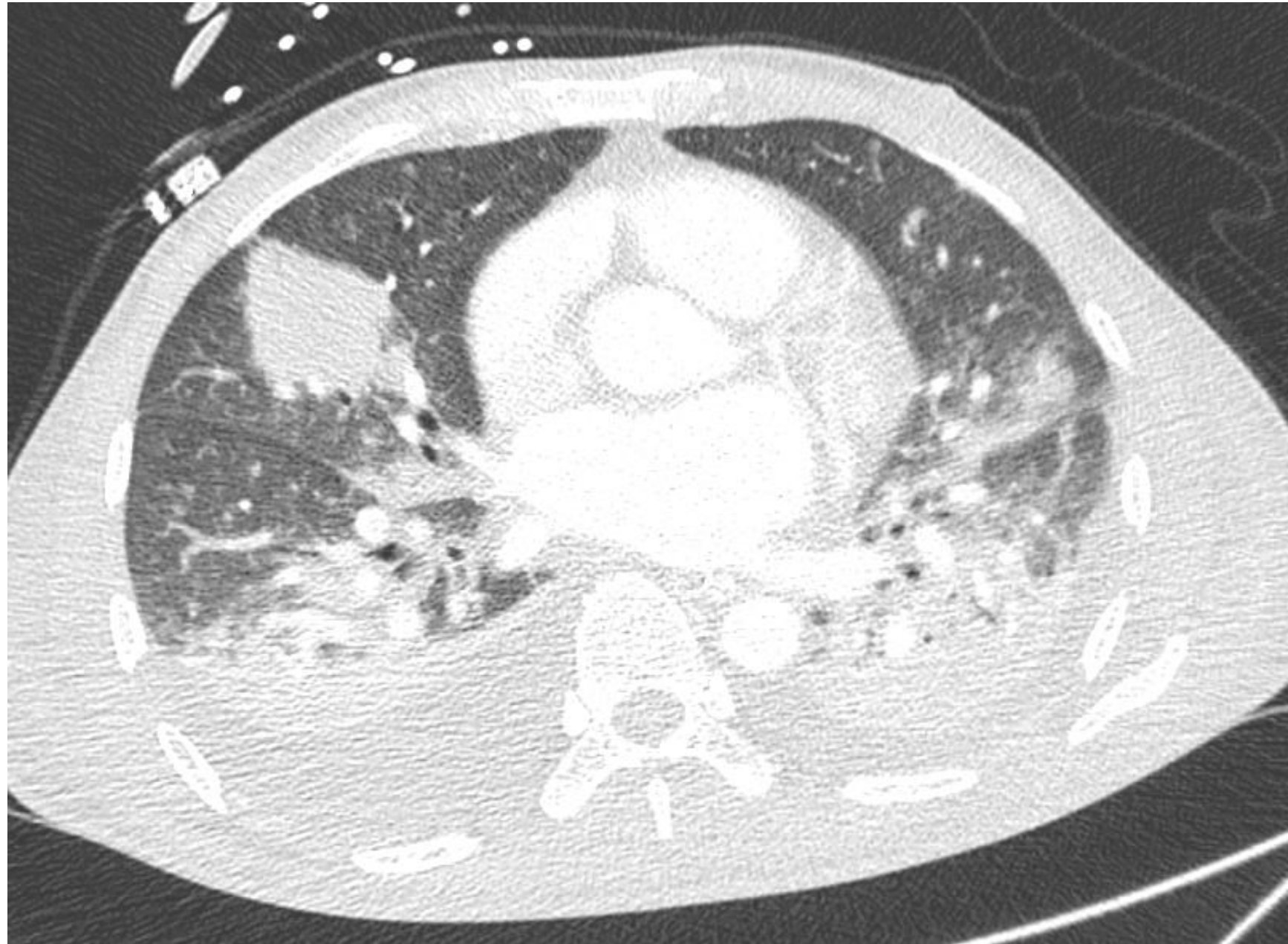
Figure 3. Cumulative incidence of respiratory deterioration and/or death according to administration or not of G-CSF in matched neutropenic patients with acute respiratory failure at admission (Vertical segments represent 95% confidence intervals of estimated cumulative incidences of events at days 3, 5, 7, and 14).

Quelques pneumonies à part

Mr P, 54 ans

- Découvert de LAM complexe en 09/2008
- Chimiothérapie : Anthracycline, Gemtuzumab ozogamicine
- Aplasie J10
- Multiples complications infectieuses :
 - Candidémie
 - Septicémie à bacteriodes fragilis
- J24 état de choc avec suspicion clinique de pneumonie; transfert en réanimation



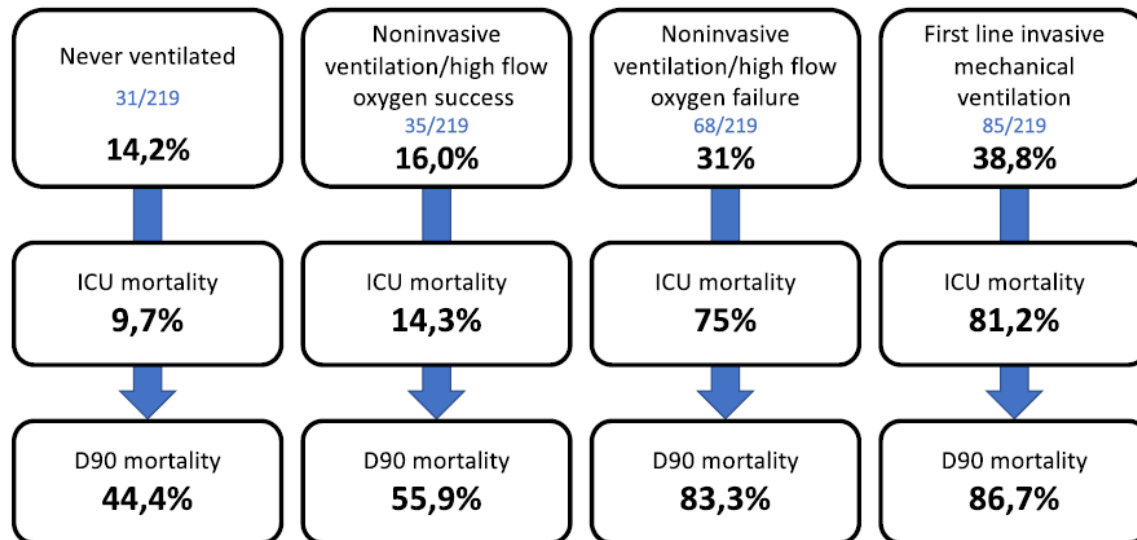


Diagnostic

- Fibroscopie bronchique : hémorragie intra alvéolaire
- Galactomanne + dans le LBA
- Galactomanne + en hématologie et en réanimation
- Défaillance multiviscérale
- Décès J4 de réanimation

Pronostic de l'aspergillose pulmonaire

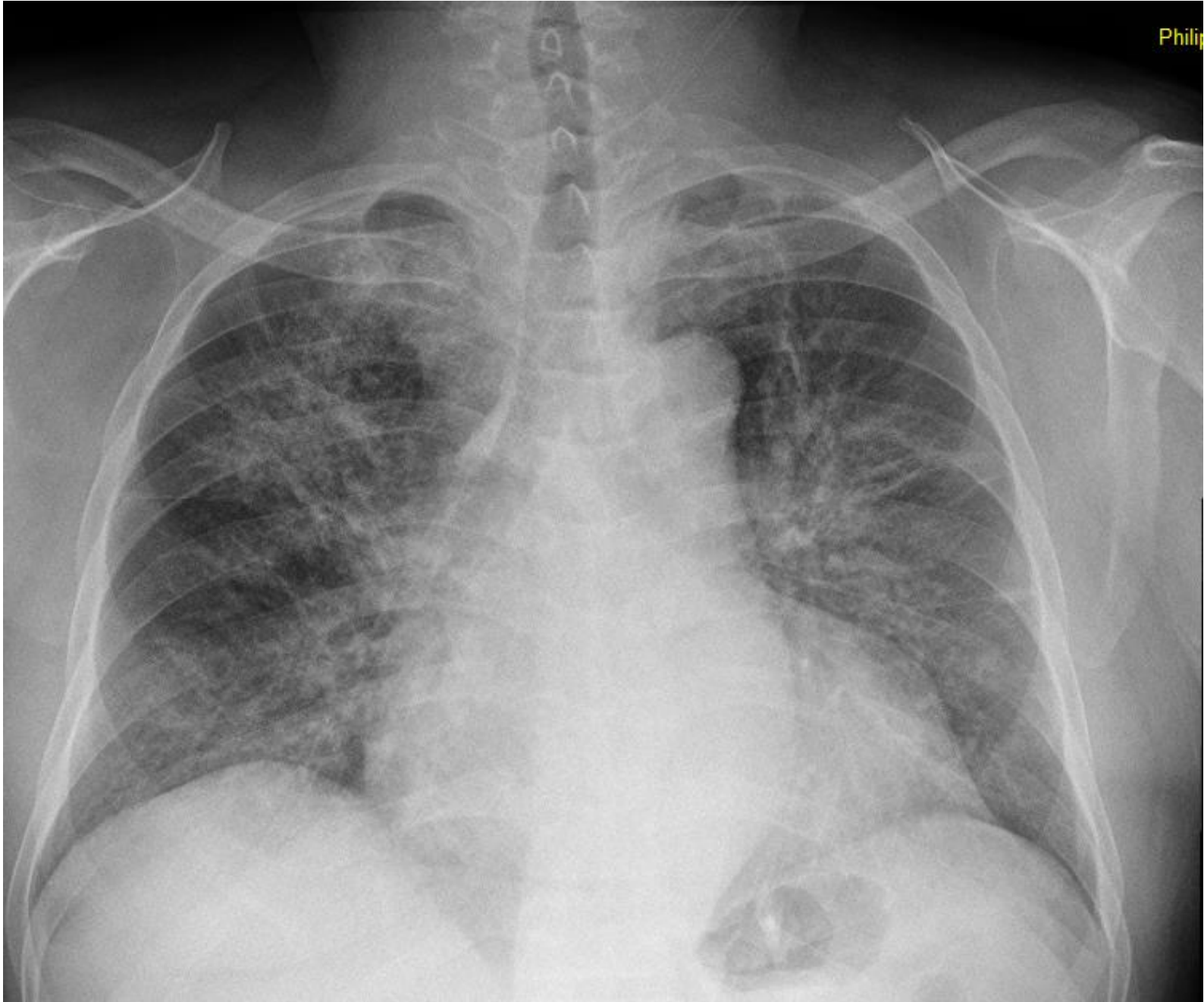
Rétrospectif
219 patients

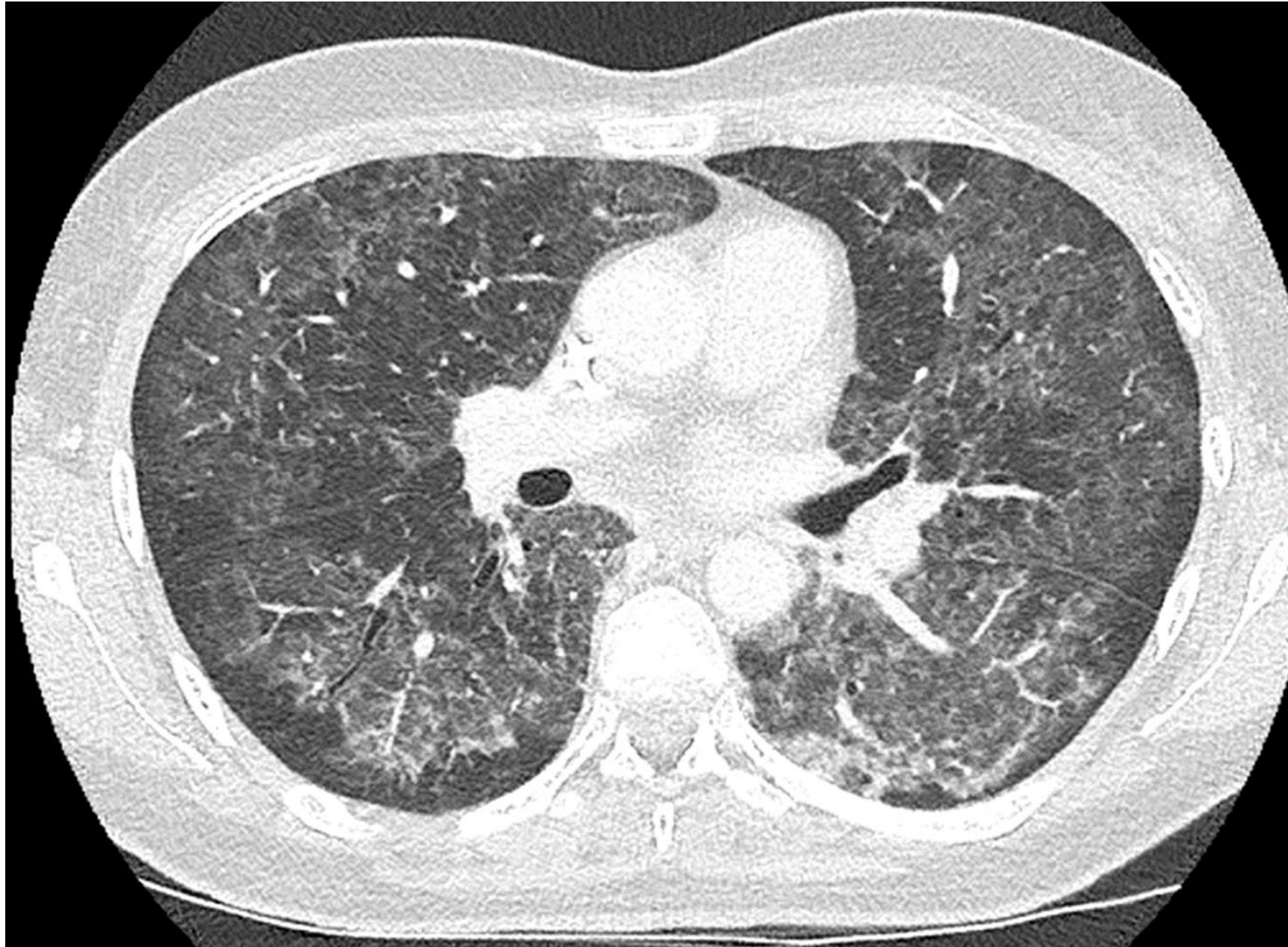


- Admission réanimation >5j
- Admission après 2010
- SOFA score (D1)
- Diffus vs localisé sur le TDM
- Nécessité de VNI
- Traitement par Voriconazole

HDM

- Mr X
- Transplantation rénale en 2008
- Février 2011: rejet aigue traité par IgIV, corticoïdes, ATG
- 12/08 consulte pour aggravation d'insuffisance rénale et dyspnée. Traitement antibiotique Clamoxyl/ Ciflox
- 17/08 transféré en néphrologie puis en réanimation pour dyspnée avec 6l/min d'O2





Diagnostic

- Expectoration induite : négatif
 - Hémoculture : négative
 - LBA : présence de pneumocystis jirovecii
 - PCR CMV 2 log/ml
-
- Pneumocytose pulmonaire
 - Traitement par BACTRIM forte dose

Conclusion

- La stratégie dépend des hypothèses diagnostiques
- Peu de particularité des examens complémentaires et de l'antibiothérapie
- Étiologie bactérienne la plus fréquente
- Sévérité de l'atteinte pulmonaire
- Impact important du retard thérapeutique