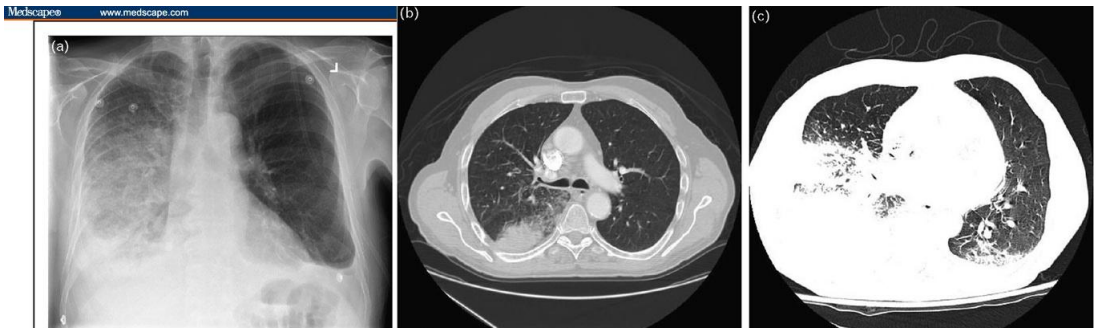
Quand une pneumonie ne guérit pas…

Benoit Lechartier
18.2.16



Nonresolving (or nonresponding) pneumonia (NRP)

« slow resolution of radiographic infiltrates or clinical symptoms despite adequate therapy»
Fein AM Postgrad Med 2003

« situation in which an inadequate clinical response is present despite antibiotic treatment»
IDSA/ ATS Guidelines for CAP management in adults 2007

En chiffres… problème fréquent en pneumologie (hospitalière)

10-25 % des **pneumonies acquises en communauté (CAP)** en intra-hosp
incidence en ambulatoire inconnue
8 % des motifs de **bronchoscopie**

jusqu'à **60 % des pneumonies nosocomiales** ont une réponse «inappropriée» au traitement empirique
->Mortalité élevée, jusqu'à **50 %**

Pour une pneumonie sévère aux **soins intensifs**, **40 %** de dégradation après stabilisation initiale

~**20 %** de **diagnostics autres** que CAP; agent étiologique identifié **46 %** ;
pneumonies **virales** dans **10-20 %**

cause indéterminée dans **27 - 44 %** des cas

Menendez *et al*, Thorax 2004
El-Solh et al. AJRCCM 2003
Arancibia F *et al*, AJRCCM 2000
Ruiz M *et al*, AJRCCM 1999

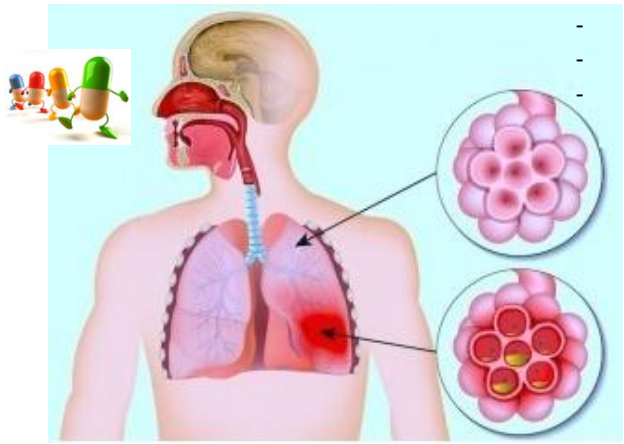
When should the chest radiograph be repeated during recovery?

3. The chest radiograph need not be repeated prior to hospital discharge in those who have made a satisfactory clinical recovery from CAP. [D]
4. A chest radiograph should be arranged after about 6 weeks for all those patients who have persistence of symptoms or physical signs or who are at higher risk of underlying malignancy (especially smokers and those aged >50 years) whether or not they have been admitted to hospital. [D]
5. Further investigations which may include bronchoscopy should be considered in patients with persisting signs, symptoms and radiological abnormalities at around 6 weeks after completing treatment. [D]

Lim *et al.*, BTS guidelines Thorax 2009

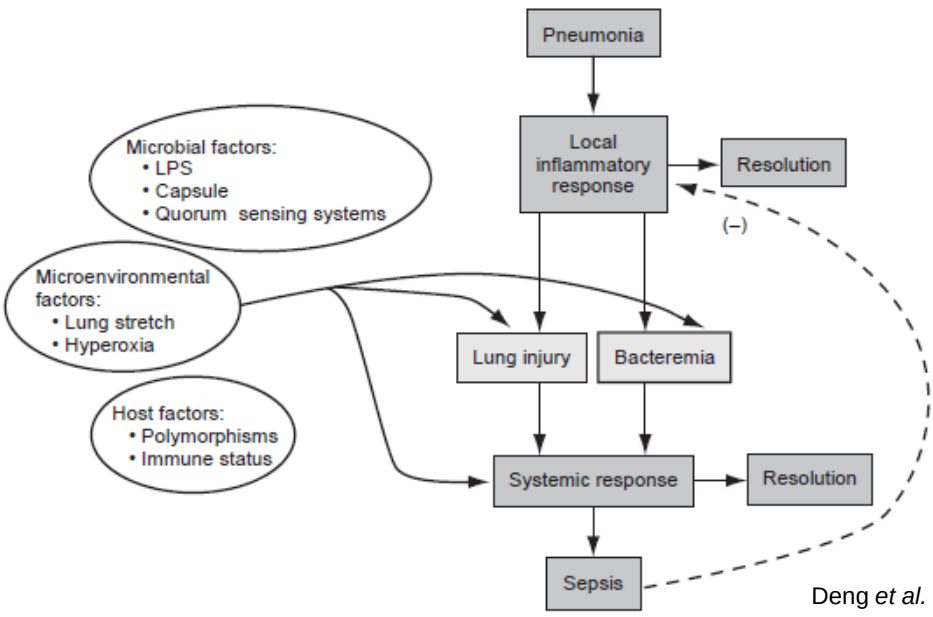
A qui la faute?

Hôte
- Réponse immunitaire
- Comorbidités
- Pneumopathie sous-jacente



Traitement
- Antibiothérapie adéquate (spectre, durée, posologie)

«Pneumonie» *per se*
- Germes résistants
- Complications infectieuses
- Causes non-infectieuses



Deng *et al.* Clin Chest Med 2005

Fig. 1. Systemic inflammatory response and factors that modulate this response in pneumonia.

Résolution attendue d'une pneumonie?

Abnormality	Duration (days)
Tachycardia and hypotension	2
Fever, tachypnea, and hypoxia	3
Cough	14
Fatigue	14
Infiltrates on chest radiograph	30

Recommandations BTS 2009:

RxT et **hospitalisation** si pas d'amélioration sous ttt après **48h**

En **intrahosp**. Délai pour réponse clinique **72h**

Résolution lente sur RxT: persistence d'une anomalie radiographique **>1 mois**
malgré une amelioration clinique

Lim WS *et al.* Thorax 2009

Fein *et al.* Respiratory infections in the elderly, 1991

Sensibilité à l'antibiothérapie empirique ?

	S. pneumoniae	*Haemophilus influenzae*	*Legionella pneumophila*
Co-amoxicilline	82-84%	88%	0
Macrolide	85-88 %	95%	99%
Quinolone	99%	>80%	>80%
Ceftriaxone	96%	99%	0

Source: CHUV - 2014

Failure of initial empirical therapy

108. When a change in empirical antibiotic therapy is considered necessary, a macrolide could be substituted for or added to the treatment for those with low severity pneumonia treated with amoxicillin monotherapy in the community or in hospital. [D]
109. For those with moderate severity pneumonia in hospital on combination therapy, changing to doxycycline or a fluoroquinolone with effective pneumococcal cover are alternative options. [D]
110. Adding a fluoroquinolone is an option for those with high severity pneumonia not responding to a β-lactam/macrolide combination antibiotic regimen. [D]

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Lim WS *et al.* BTS guidelines,Thorax 2009

Annals of Internal Medicine REVIEW

Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia

A Systematic Review and Meta-analysis

Reed A.C. Siemieniuk, MD; Maureen O. Meade, MD; Pablo Alonso-Coello, MD, PhD; Matthias Briel, MD, MSc; Nathan Evaniew, MD; Manya Prasad, MBBS; Paul E. Alexander, MSc, PhD; Yutong Fei, MD, PhD; Per O. Vandvik, MD, PhD; Mark Loeb, MD, MSc; and Gordon H. Guyatt, MD, MSc

Background: Community-acquired pneumonia (CAP) is common and often severe.

Purpose: To examine the effect of adjunctive corticosteroid therapy on mortality, morbidity, and duration of hospitalization in patients with CAP.

Data Sources: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials through 24 May 2015.

Study Selection: Randomized trials of systemic corticosteroids in hospitalized adults with CAP.

Data Extraction: Two reviewers independently extracted study data and assessed risk of bias. Quality of evidence was assessed with the Grading of Recommendations Assessment, Development, and Evaluation system by consensus among the authors.

Data Synthesis: The median age was typically in the 60s, and approximately 60% of patients were male. Adjunctive corticosteroids were associated with possible reductions in all-cause mor-

distress syndrome (4 trials; 945 patients; RR, 0.24 [CI, 0.10 to 0.56]; RD, 6.2%; moderate certainty). They also decreased time to clinical stability (5 trials; 1180 patients; mean difference, −1.22 days [CI, −2.08 to −0.35 days]; high certainty) and duration of hospitalization (6 trials; 1499 patients; mean difference, −1.00 day [CI, −1.79 to −0.21 days]; high certainty). Adjunctive corticosteroids increased frequency of hyperglycemia requiring treatment (6 trials; 1534 patients; RR, 1.49 [CI, 1.01 to 2.19]; RD, 3.5%; high certainty) but did not increase frequency of gastrointestinal hemorrhage.

Limitations: There were few events and trials for many outcomes. Trials often excluded patients at high risk for adverse events.

Conclusion: For hospitalized adults with CAP, systemic corticosteroid therapy may reduce mortality by approximately 3%, need for mechanical ventilation by approximately 5%, and hospital stay by approximately 1 day.

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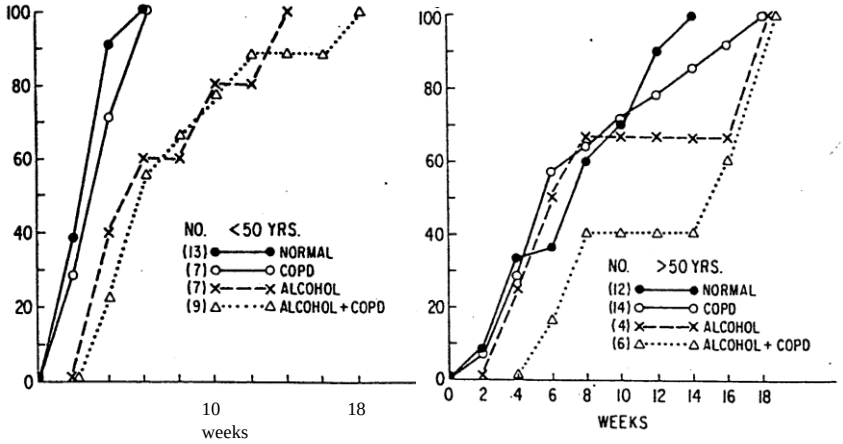
Evolution radiologique selon le germe identifié

Infectious Agent	Frequency of transient radiographic deterioration	Time until full radiographic resolution	Residual radiographic abnormalities
Legionella species	Majority	2 to 6 months	25 percent
Staphylococcus aureus	Majority	3 to 5 months	Common
Streptococcus pneumoniae with sepsis	Majority	3 to 5 months	25 to 35 percent
Streptococcus pneumoniae (nonbacteremic)	Occasional	1 to 3 months	Rare
Gram-negative	Occasional	3 to 5 months	10 to 20 percent
Haemophilus influenzae	Occasional	1 to 5 months	Occasional
Chlamydia species	Rare	1 to 3 months	10 to 20 percent
Mycoplasma pneumoniae	Rare	2 to 4 weeks	Rare
Moraxella catarrhalis	Rare	1 to 3 months	Unusual

Macfarlane JT *et al.* Thorax, 1984
Fein AM *et al.* Clin Infect Dis 1999
Rodrigues J *et al.* Am J Med 1992

Normalisation des RxT après une pneumonie avec bactériémie à pneumocoque



Jay SJ *et al.* NEJM 1978

Facteurs de l'hôte liés à une évolution lente

Condition	Effects
Chronic obstructive pulmonary disease	Impaired cough and mucociliary clearance
Alcoholism	Aspiration, malnutrition, impaired neutrophil function
Neurologic disease	Aspiration, impaired clearance of secretions and cough
Heart failure	Edema fluid, impaired lymphatic drainage
Chronic kidney disease	Hypocomplementemia, impaired macrophage and neutrophil function, reduced humoral immunity
Malignancy	Impaired immune function, altered colonization, effects of chemotherapy
Human immunodeficiency virus	Impaired cell-mediated and humoral immunity
Diabetes mellitus	Impaired neutrophil function and cell-mediated immunity

Fein *et al.* Clin Infect Dis, 1999

Table 2. Genetic Polymorphisms Associated with Lung Infection Outcomes.*

Gene Product	Association	References
Initiating and amplifying mechanisms		
TLRs (toll-like receptors)		
TLR4	Legionella pneumonia, severe respiratory syncytial virus infection	Tal et al.,[109] Hawn et al.[110]
TLR5	Legionella pneumonia	Hawn et al.[111]
CD14	Respiratory syncytial virus bronchiolitis	Inoue et al.[112]
IRAK-4 (interleukin-1 receptor–associated kinase 4)	Bacterial infections, particularly pneumococcal infection	Ku et al.[113]
NEMO — NF-κB activation	Recurrent invasive pneumococcal disease	Ku et al.[114]
Mal (MyD88 adaptor-like protein) — toll-like receptor signaling	Invasive pneumococcal disease	Khor et al.[115]
MBL (mannose-binding lectin)	Invasive pneumococcal disease, recurrent respiratory infections, acute lung injury	Roy et al.,[116] Gomi et al.,[117] Gong et al.[118]
Complement C2	Invasive pneumococcal disease and recurrent pneumonias	Jönsson et al.[119]
SP-A, SP-D (surfactant proteins A and D)	Severe respiratory syncytial virus infection	Lahti et al.,[120] Löfgren et al.[121]
Regulating mechanisms		
NF-κB p50	Acute lung injury	Adamzik et al.[122]
IκB-α	Invasive pneumococcal disease, acute lung injury	Chapman et al.,[123] Zhai et al.[124]
Interleukins		
Interleukin-6	Invasive pneumococcal disease	Schaaf et al.[125]
Interleukin-10	Pneumonia outcomes and acute lung injury	Wattanathum et al.,[126] Gong et al.[127]
HO-1 (heme oxygenase-1)	Pneumonia susceptibility	Yasuda et al.[128]
STAT3 (signal transducer and activator of transcription 3)	Hyper-IgE syndrome — recurrent severe lung infections	Holland et al.[88]

* NEMO denotes NF-κB essential modulator, and NF-κB nuclear factor κB.

Metzgerd, NEJM 2008

Pathogènes spécifiques selon anamnèse ou antécédents (1)

Condition	Commonly encountered pathogen(s)
Alcoholism	*Streptococcus pneumoniae,* oral anaerobes, *Klebsiella pneumoniae, Acinetobacter* species, *Mycobacterium tuberculosis*
COPD and/or smoking	*Haemophilus influenzae, Pseudomonas aeruginosa, Legionella* species, *S. pneumoniae, Moraxella carar-rhalis, Chlamydophila pneumoniae*
Aspiration	Gram-negative enteric pathogens, oral anaerobes
Lung abscess	CA-MRSA, oral anaerobes, endemic fungal pneumonia, *M. tuberculosis*, atypical mycobacteria
Exposure to bat or bird droppings	*Histoplasma capsulatum*
Exposure to birds	*Chlamydophila psittaci* (if poultry: avian influenza)
Exposure to rabbits	*Francisella tularensis*
Exposure to farm animals or parturient cats	*Coxiella burnetti* (Q fever)

IDSA/ATS guidelines 2007

Pathogènes spécifiques selon anamnèse ou antécédents (2)

HIV infection (early)	*S. pneumoniae, H. influenzae, M. tuberculosis*
HIV infection (late)	The pathogens listed for early infection plus *Pneumocys-tis jirovecii, Cryptococcus, Histoplasma, Aspergillus,* atypical mycobacteria (especially *Mycobacterium kansasii*), *P. aeruginosa, H. influenzae*
Hotel or cruise ship stay in previous 2 weeks	*Legionella* species
Travel to or residence in southwestern United States	*Coccidioides* species, *Hantavirus*
Travel to or residence in Southeast and East Asia	*Burkholderia pseudomallei,* avian influenza, SARS
Influenza active in community	Influenza, *S. pneumoniae, Staphylococcus aureus, H. influenzae*
Cough >2 weeks with whoop or posttussive vomiting	*Bordetella pertussis*
Structural lung disease (e.g., bronchiectasis)	*Pseudomonas aeruginosa, Burkholderia cepacia, S. aureus*
Injection drug use	*S. aureus*, anaerobes, *M. tuberculosis, S. pneumoniae*
Endobronchial obstruction	Anaerobes, *S. pneumoniae, H. influenzae, S. aureus*
In context of bioterrorism	*Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), *Francisella tularensis* (tularemia)

IDSA/ATS guidelines 2007

Causes infectieuses de NRP

Complications de pneumonies

- Foyer infectieux compromettant l'efficacité de l'antibiothérapie

- épanchement parapneumonique/ empyème

-> drainage de tout épanchement parapneumonique en cas de NRP

non compliqué: jusqu'à 40 % des pneumonies bactériennes
compliqué /empyème: 5-15% des pneumonies bactériennes

- pneumonie nécrosante ou abcédante (anaérobes; polymicrobiennes...)

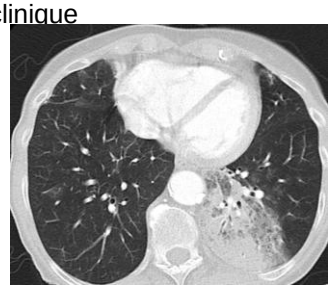
- infections métastatiques (endocardite, méningite, arthrite)

Lim WS *et al.* BTS guidelines,Thorax 2009

Causes non-infectieuses de NRP: Néoplasies

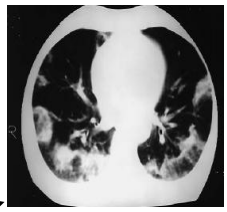
- obstruction endoluminale; pneumonie secondaire ou abcès post-obstruction
- erreur diagnostique

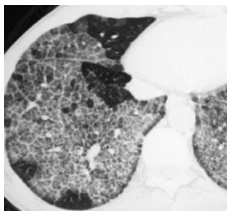
- **Carcinome bronchique**: développement endobronchique ou compression extrinsèque
- **Tumeur carcinoïde**: à rechercher chez un jeune ou non-fumeur
- **Adénocarcinome de type lépidique** (bronchiolo-alvéolaire): condensation focale; +-bronchogrammes aériques. Fréquente discrépance entre taille et clinique



- **Lymphome pulmonaire**: secondaire ou primaire (rare 4-10 %)
  MALT; Lymphome B de haut grade; granulomatose lymphoïde; PTLD

Causes non-infectieuses de NRP: maladies inflammatoires





Protéinose alvéolaire pulmonaire

Pneumonie organisée (cryptogénique) COP
- Infiltrats diffus à tendance migratrice

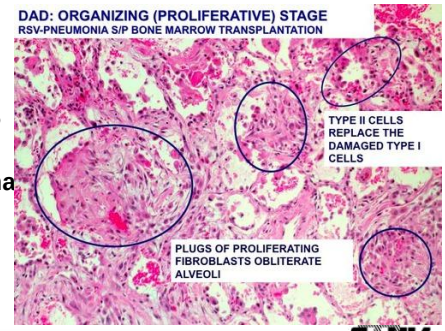
Vasculite systémique avec atteinte pulmonaire
- Wegener
- Syndromes hémorragiques alvéolaires

Pneumonie à éosinophiles (aiguë ou chronique)
- Infiltrats périphériques (chronique)
- Diffus (aiguë)

Sarcoïdose
- Confondue avec PAC en cas d'atteinte parenchymateuse sans ADP

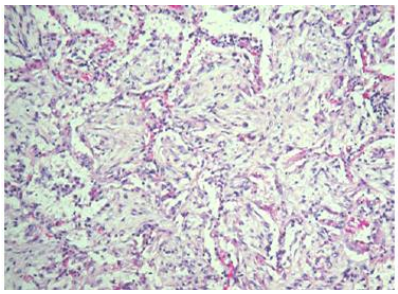
Pneumonie interstitielle aiguë – Diffuse alveolar damage „Hamma
- Verre dépoli patchy ou diffus – sombre pronostic

Protéinose alvéolaire pulmonaire
- Crazy paving – accumulation de substance lipoprotéinacée



Pneumopathie organisée (cryptogénique)

Prédominance **intra-alvéolaire**: remplissage des alvéoles et bronchioles terminales par du tissu conjonctif (fibroblastes et collagène)



Clinique de **pneumonies récidivantes**, réfractaires avec syndrome inflammatoire persistant et symptômes généraux malgré antibiothérapie

LBA: le plus souvent formule panachée

CT: opacités uni- ou bilatérales, sous-pleurales ou péribronchiques et **souvent migratrices, densités variables**

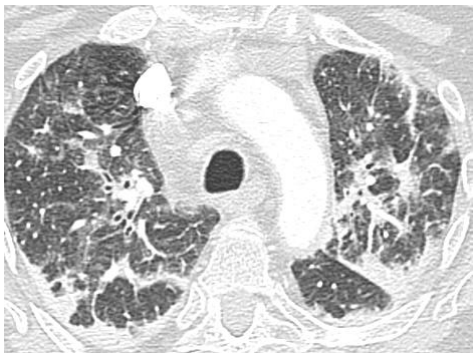
Dx après exclusion d'une cause infectieuse, idéalement par biopsie

Réponse souvent rapide à une **corticothérapie à haute dose** : 0.75 mg/kg/j pendant 4 sem puis schéma dégressif

Récidives fréquentes

Lebowitz *et al.* Rev Med Suisse 2013

Causes non-infectieuses de NRP: pneumopathies médicamenteuses



Amiodarone

Methotrexate

Nitrofurantoïne

Bléomycine

Nouvelles immunothérapies: TKI (erlotinib)…

Complications infectieuses des agents immunomodulateurs: antiTNFa (etanercept, infliximab, adalimumab), anti IL-1 (anakinra), Rituximab…

Everolimus

Causes non-infectieuses de NRP: causes cardiovasculaires

Embolie pulmonaire-> infarctus pulmonaire

+- épanchement pleural associé

Oedème pulmonaire cardiogène:

+- asymétrique en cas de BPCO avancée

NRP : démarche diagnostique

Facteurs de risque pour non-résolution/persistance:
Age
Comorbidités
Sévérité de la pneumonie
Pathogène spécifique

→ **Evoquer germes atypiques/inhabituels**
TBC, *Pneumocystis*…
-> Réévaluation microbiologique
Causes non-infectieuses

→ **CT thoracique**
Bilan biologique

→ **Bronchoscopie avec LBA**
+- Biopsie transbronchique
+- EBUS FNA si ADP

→ **Biopsie chirurgicale par thoracoscopie**

Prise en charge des complications infectieuses
Abcès /empyème

Compilation de plusieurs sources

LBA

Permet d'aboutir à un Dx dans 35-72 % des cas de NRP

Woodhead *et al.* Clin Microb Infect 2011

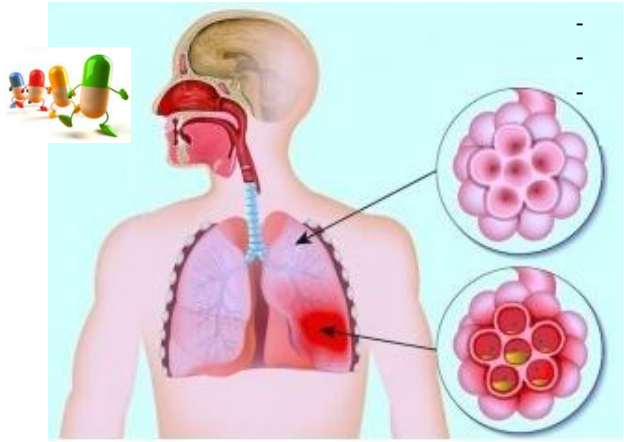
Tableau 1. Répartition alvéolaire: valeurs normales et pathologies suggérées lors d'anomalies
(Adapté de réf.[4]).

Types cellulaires	Norme	Anomalie	Diagnostics suggérés
Macrophage	85%		
Lymphocyte	10-15%	>25%	Sarcoïdose, béryllose, PHS, POC, PINS, pneumonie virale, pneumoconioses, collagénoses, pneumopathies médicamenteuses, pneumopathie radique, lymphome, pneumonie interstitielle lymphoïde
		>50%	PHS – PINS
Neutrophile	<3%	>3%	Dommage alvéolaire diffus, pneumonie bactérienne, collagénoses, FPI, bronchiolite oblitérante
		>50%	Dommage alvéolaire diffus, pneumonie bactérienne
Eosinophile	<1%	>1%	Pneumonie à éosinophiles, Churg-Strauss, syndrome hyperéosinophilique, ABPA
		>25%	Pneumonie à éosinophiles

Pasche *et al.* Rev Med Suisse 2012

A qui la faute?

Hôte
- Réponse immunitaire
- Comorbidités
- Pneumopathie sous-jacente



Traitement
- Antibiothérapie adéquate (spectre, durée, posologie)

«Pneumonie» *per se*
- Germes résistants
- Complications infectieuses
- Causes non-infectieuses

Pneumonies persistantes: résumé

- Situation clinique fréquente

Résolution «normale» varie selon l'étiologie, les comorbidités, la sévérité
-> la clinique prime durant les premiers jours de traitement

- Selon l'agent infectieux: évolution attendue + ou – longue
- Evoquer les **germes inattendus**: mycobactéries, *pneumocystis*, champignons
- Adapter l'antibiothérapie selon la possibilité de **germes résistants**
- Considérer les **comorbidités** de l'hôte: OH, âge, DM, BPCO
- Evaluer le **status immunitaire**: HIV, déficit en Ig…
- Exclure **complication infectieuse**: abcès et empyème
- Recherche de **causes non-infectieuses** d'infiltrats persistants: néoplasie, COP, vasculite, médicaments…
- Bilan à compléter par imagerie, bilan (micro)biologique, bronchoscopie (LBA) +- biopsies

Merci pour votre attention