



Hospices Civils de Lyon



Lyon  
**HemInf**  
study group

# Cas cliniques interactifs

## Virus respiratoires chez l'immunodéprimé

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**Pr. Florence ADER**

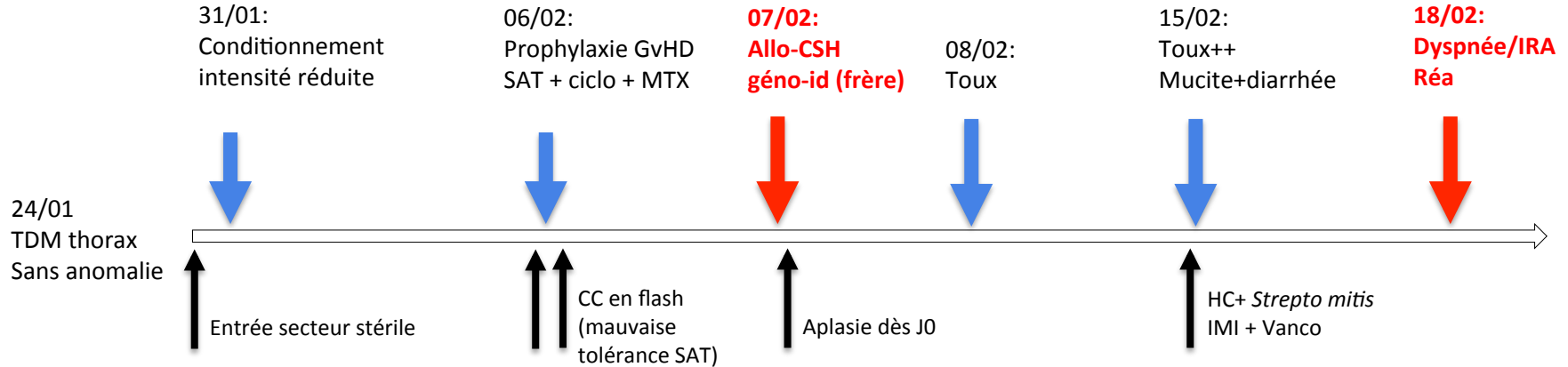
Maladies infectieuses et tropicales, CHU de Lyon  
Lyon HEMINF study group

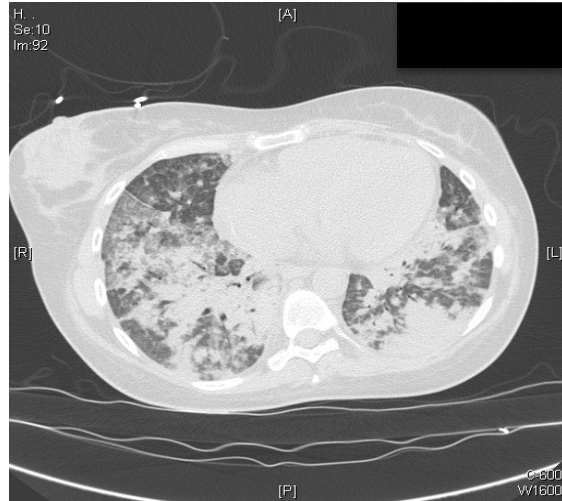
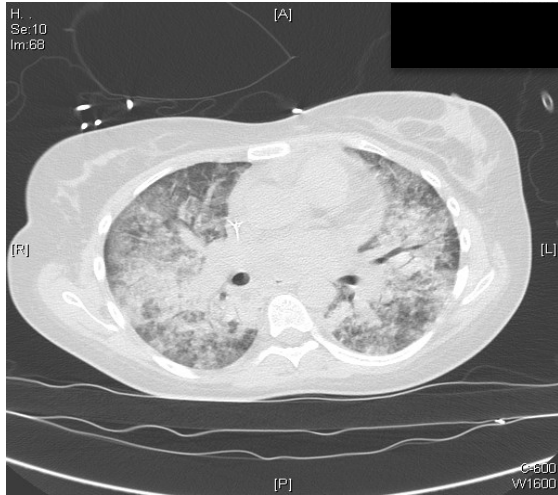
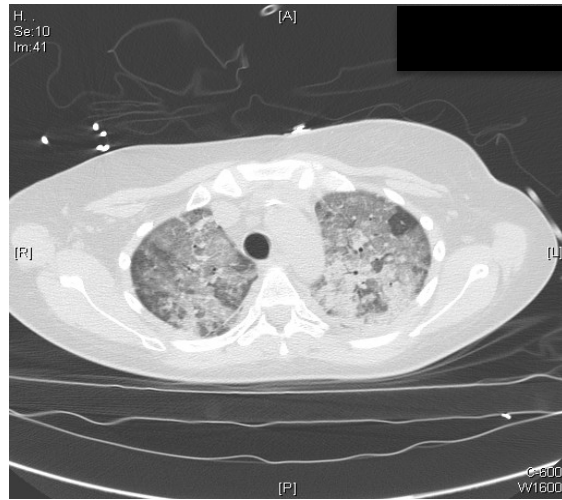
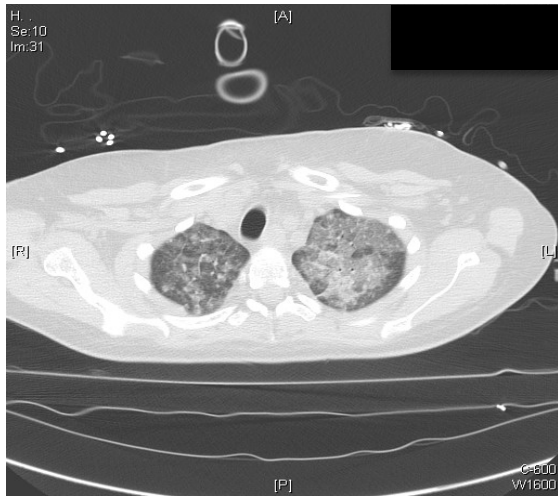
Inserm 1111, Centre International de Recherche en Infectiologie, Université Claude Bernard Lyon 1

[florence.ader@chu-lyon](mailto:florence.ader@chu-lyon)

# Histoire 1

Femme 32 ans  
Aplasia médullaire idiopathique progressive





Hypothèses étiologiques virales ?

Hors virus, hors bactéries, quelle(s) autre(s) hypothèse(s) microbienne(s) ?

Moyens diagnostiques ?

Avant intubation (non invasif)

Après intubation

What you need to know about RSV

**RSV** stands for **Respiratory Syncytial Virus**

RSV is a  
**Really  
Serious  
Virus**

### WHEN IS RSV SEASON?

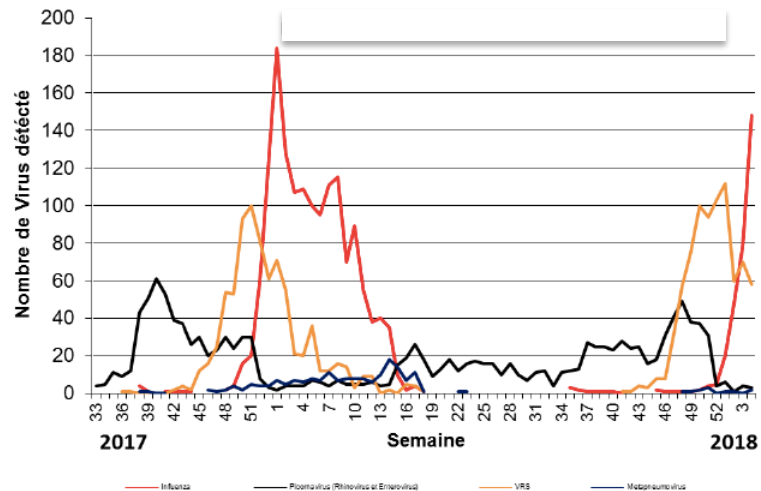
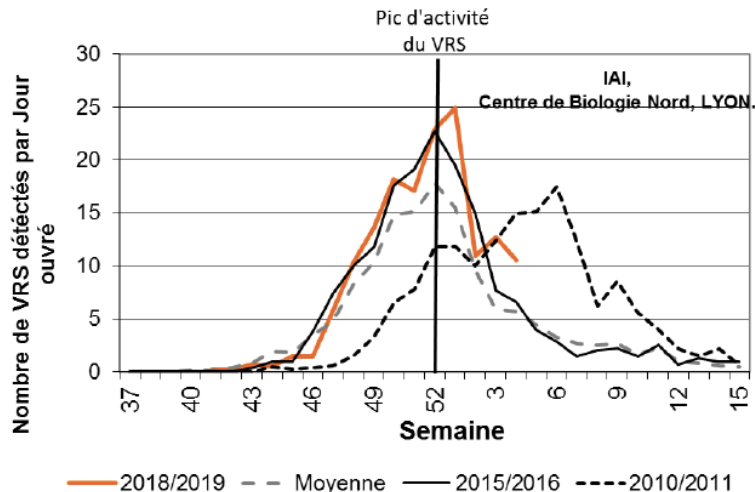
Typically RSV season runs from November - March. But it can begin as early as July in Florida and end as late as April in the West.

Protect babies and families this RSV season  
**Educate. Advocate. Integrate.**



Consult the CDC's RSV Census Regional Trends to learn more [www.cdc.gov/rsv/research/us-surveillance.html](http://www.cdc.gov/rsv/research/us-surveillance.html)

[www.nationalperinatal.org](http://www.nationalperinatal.org)



# Les familles de CARV (hors grippe)

## ARN

### **Paramyxovirus :**

Virus respiratoire syncytial (VRS),  
Parainfluenza humain (PIVh-1, -2, -3, and -4)  
Metapneumovirus (MPVh)

### **Rhinovirus humain (RoVh)**

3 groupes A, B, and C, plus de 100 serotypes

### **Coronavirus humain (CoVh)**

Group I-like (HCoV-229E and HCoV-NL63)  
Group II-like (HCoV-OC43 and HCoV-HKU1)

### **Picornaviruses**

### **Orthomyxovirus**

## ADN

### **Adenovirus**

Bocavirus  
Polyomavirus

Enfants < 5a  
Sujets âgés

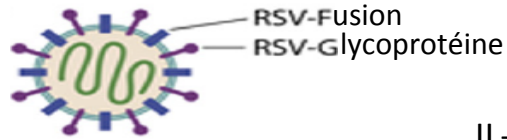
Maladies  
pulmonaires  
chroniques  
(TVO, DDB)

Transplantation  
organe solide  
(poumons++)

Transplantations  
de CSH

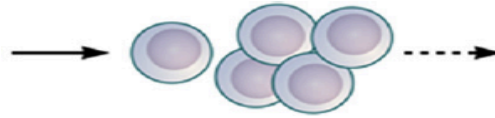


## VRS type A et B



Voies  
aériennes

IL-33



C lymphoïdes  
innées gp 2

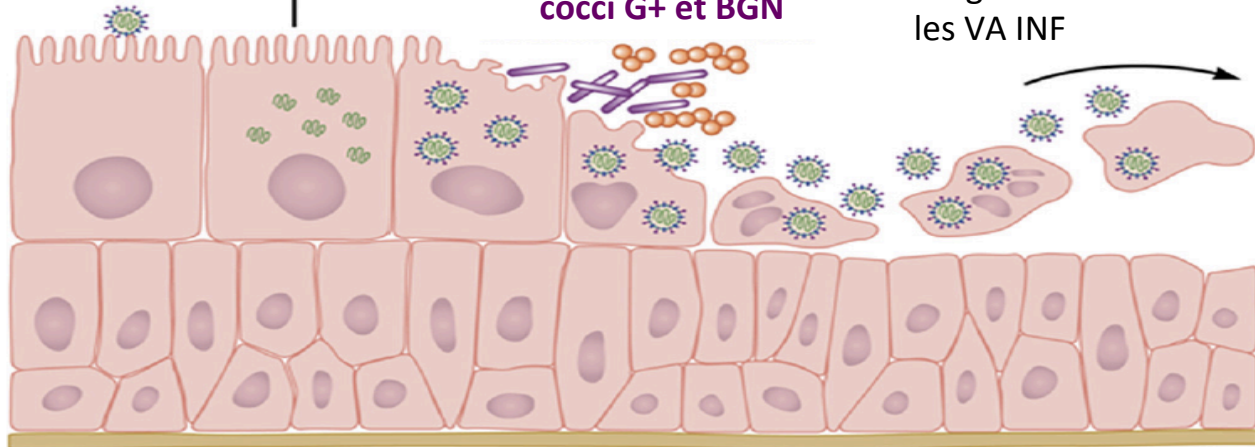
Co-infections par  
cocci G+ et BGN

IL-13, IL-4, IL-5

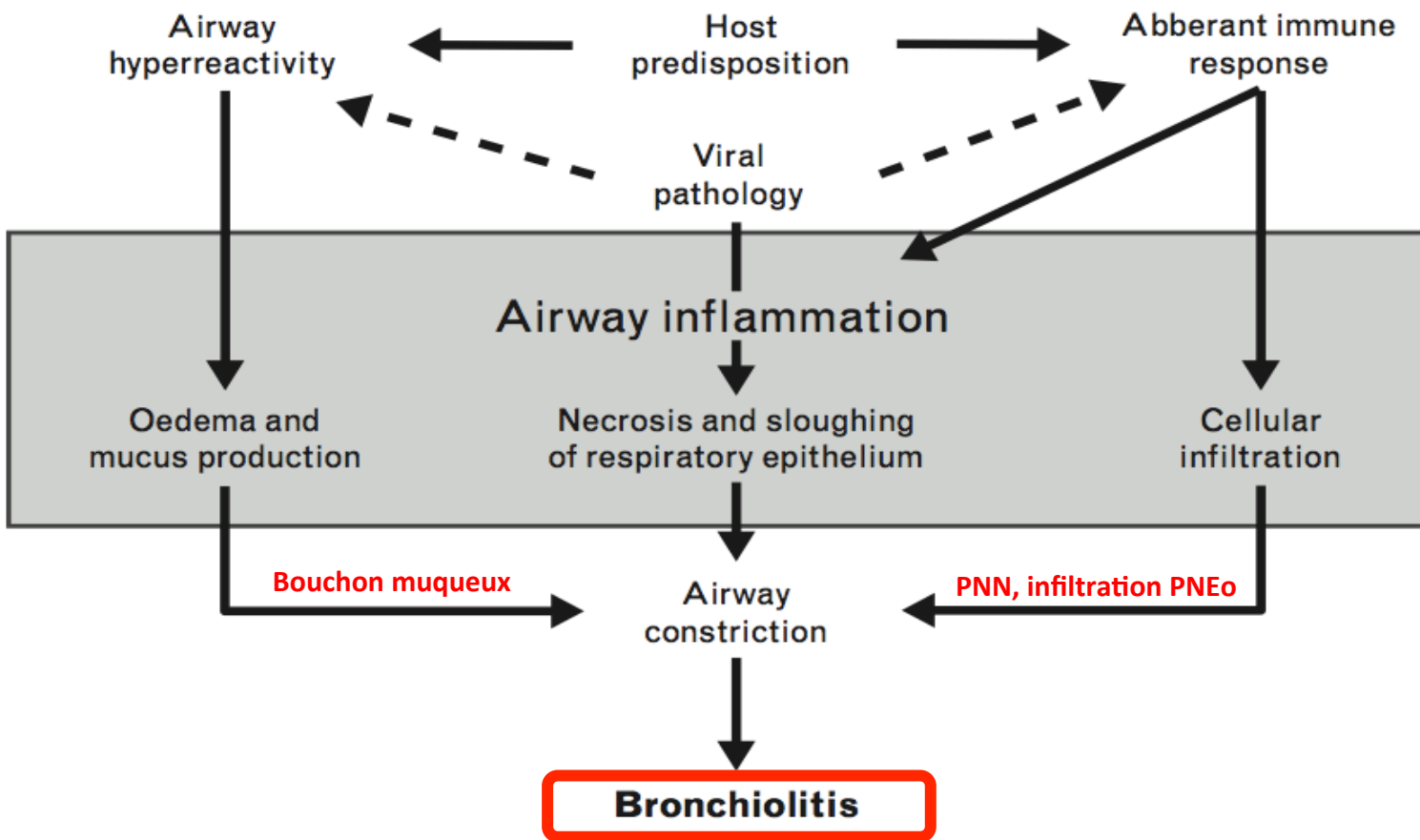
Manifestations asthmatiformes

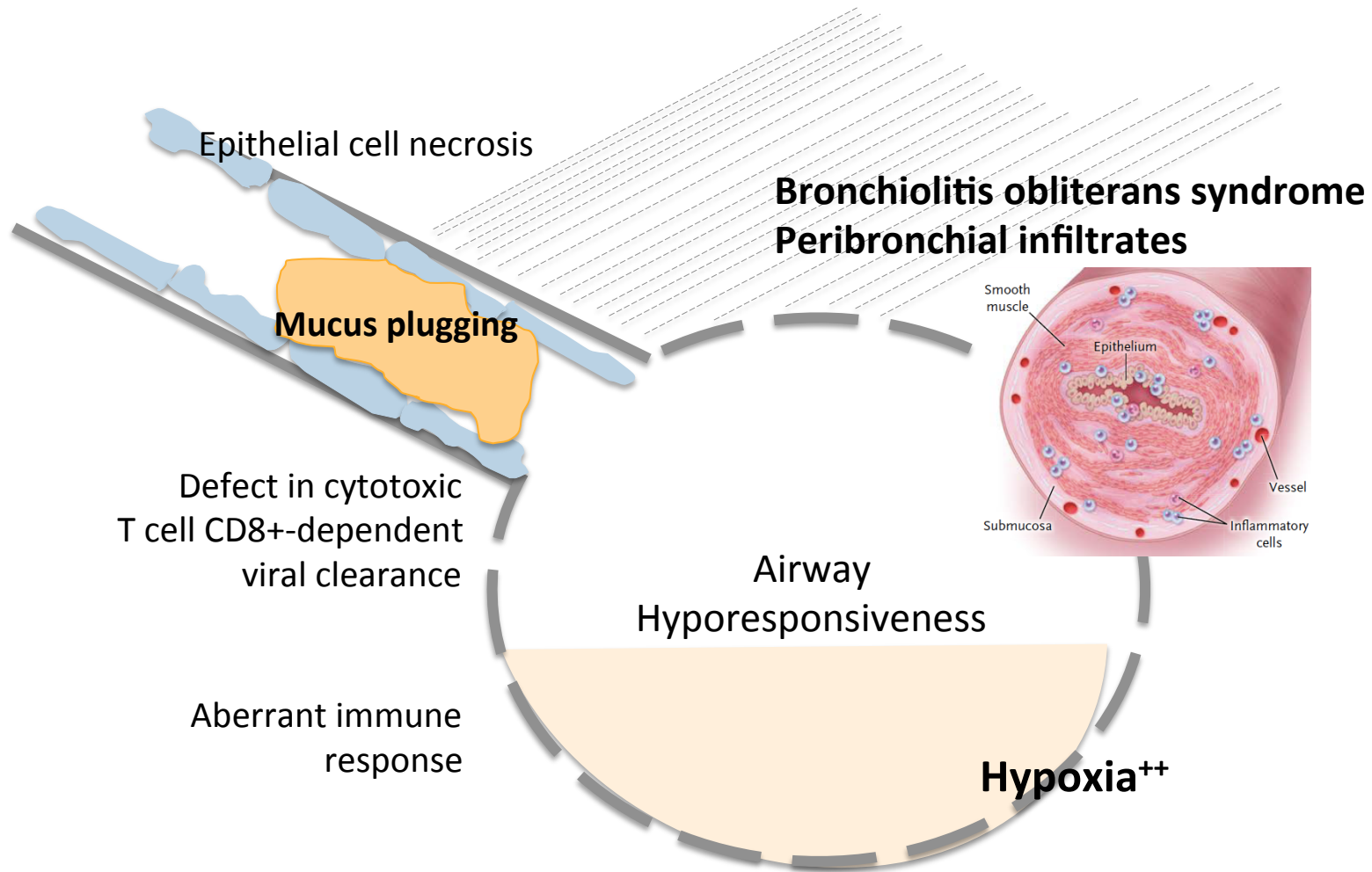
Decollement cellules  
épithéliales infectées (NS-2)

Progression de l'infection vers  
les VA INF



Mb basale





Message 1  
Algorithme  
diagnostique

**Patient immunodéprimé  
symptômes ORL et/ou respiratoire ±  
fébrile, période automno-hivernale**

écouvillon bilatéral naso-pharyngé poolé avec  
écouvillon oropharynx postérieur

**Rx thorax**  
**TDM thorax SPC**



**Kit multiplex virus pneumotropes**

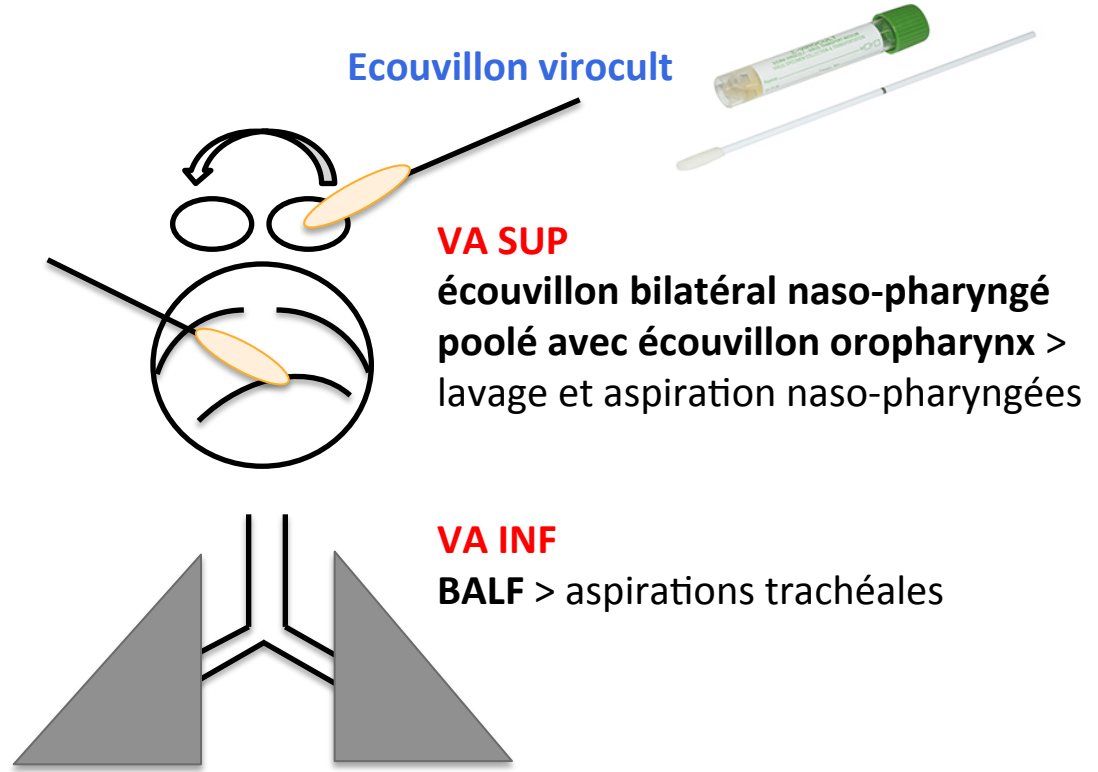


**Grippe, VRS et autre(s) selon  
saison, épidémio**

Cycle threshold (?)

# Techniques et indications de prélèvements

1. Aspiration naso-pharyngée
2. Lavage naso-pharyngé
3. Ecouvillon naso-pharyngé
4. Aspiration trachéale
5. LBA



## Message 2 : qui traiter ?

Les data poolées publiées sur les patients d'hématologie exhortent à (BIII) :

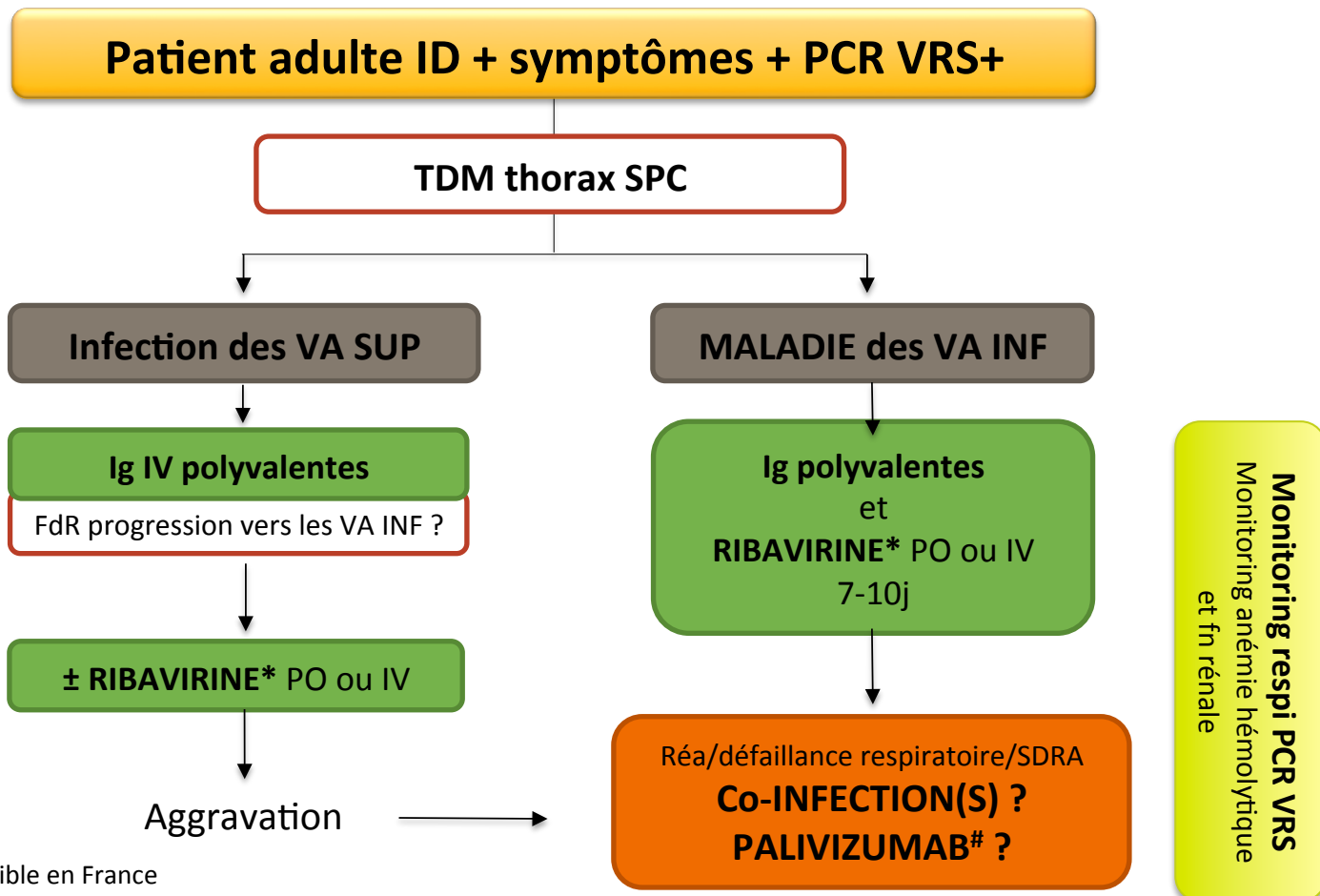
Traiter les maladies à VRS des VA SUP à **haut risque de progresser vers les VA INF**

Traiter les **maladies à VRS des VA INF**



**Optimisation pronostique**

Message 3  
Algorithme  
thérapeutique



\* forme aérosol non disponible en France

# ATU nominative ANSM

# Ribavirine (RBV)

Biodisponibilité orale **45-65%** (après effet 1<sup>er</sup> passage hptq)

Ingestion **repas: graisse** optimisation biodisponibilité 1.46

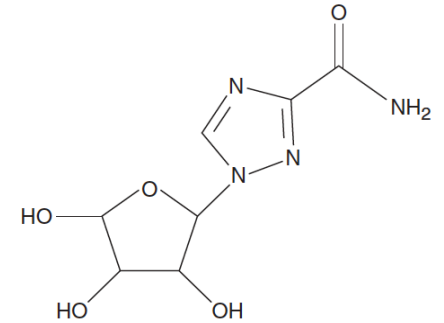
Diffusion tissulaire (Vd) **lente mais importante**, SNC inclus

½ vie LONGUE = **150h** (1 dose) jusqu'à **300h** (doses cumulées)

Pas de métabolisation hptq = pas d'adaptation de dose hépatopathie chnq

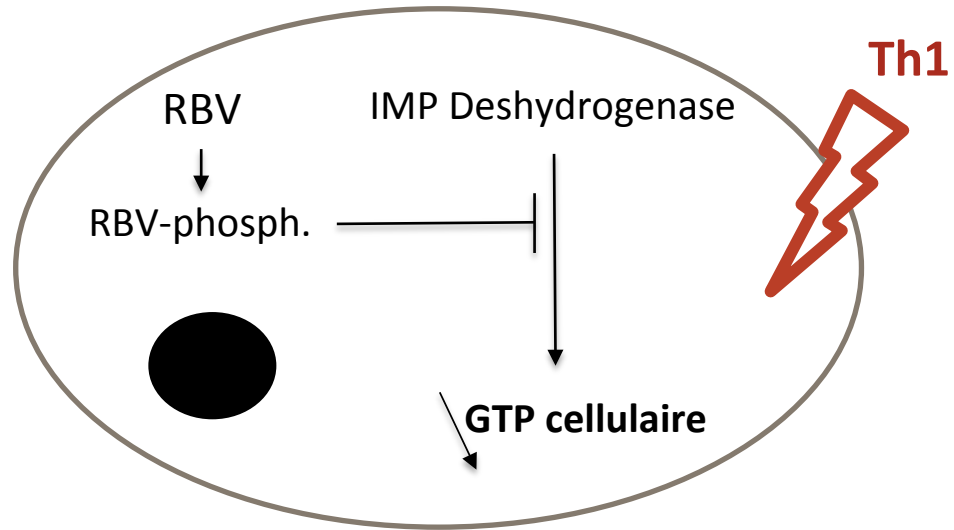
Clairance dpdte du :

- **poids** (adapter dose/poids)
- **fn rénale**





## RBV: analogue guanosine



# Maniement de la RBV orale ou IV reco ECIL-4

Oral or intravenous ribavirin maximal dosing 10 mg/kg body weight every 8 h for adults

Day 1: Start with 600 mg loading dose, then 200 mg every 8 h

Day 2: 400 mg every 8 h

Day 3: Increase the dose to a maximum of 10 mg/kg body weight every 8 h

**30 mg/kg/jour max**

**Doses progressivement croissantes sur 3j**



In case of adverse events:

Decrease dose or discontinue ribavirin

Creatinine clearance:

Oral or intravenous administration

30–50 mL/min

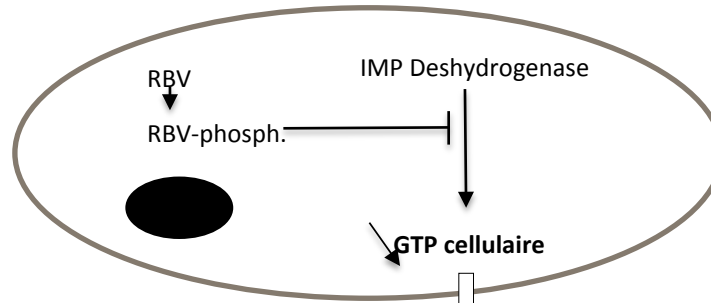
Maximal 200 mg every 8 h

10–30 mL/min

No recommendation can be given<sup>b</sup>

**Adaptation fn rénale**

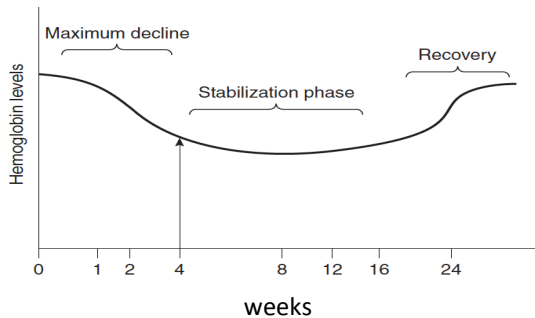
<sup>b</sup> Some experts use 200 mg once daily under close clinical and laboratory monitoring.



**Anémie hémolytique dose-dépendante et réversible**



Déplétion GTP et ATP  
Acidose lactique

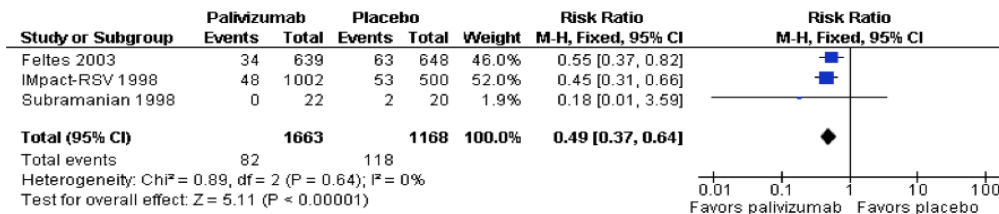


Difficulté pop<sup>o</sup> avec hémopathies  
 Considérée sévère si perte Hb > 2g/dL  
 RBV PO 14% (54/375 patients)  
 RBV IV 36% (405/1112 patients)  
 Transfusion

# Palivizumab: Ac monoclonal humanisé recombinant prophylactique de l'infection à VRS de l'enfant

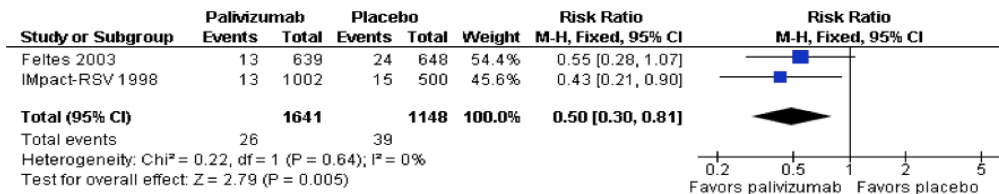
## Hospitalisation

Figure 1. Forest plot of comparison: I Palivizumab versus placebo, outcome: I.1 Hospitalisation for RSV infection.



## Admission réa

Figure 2. Forest plot of comparison: I Palivizumab versus placebo, outcome: I.4 Admission to ICU.



Andabaka et al., Cochrane Data Base 2013

**ATU ANSM – 15 mg/kg de poids corporel (nb de cures ?)**

# Indications et positionnement du Palivizumab chez l'adulte immunodéprimé

En aigu: pneumopathie à VRS sous RBV en état critique ?

**Probablement**

En prophylaxie post-exposition sur les patients immunodéprimés à haut risque ?

- Comment déterminer l'exposition
- Délai de post-exposition
- Coût/efficacité ?????

# Histoire 2

Homme 40 ans  
Transplanté rénal  
Inh calc. + CC

Fièvre 39°C  
Conjonctivite  
Toux



J+2  
Rash maculo-  
papuleux  
torse/dos



J+4  
H°



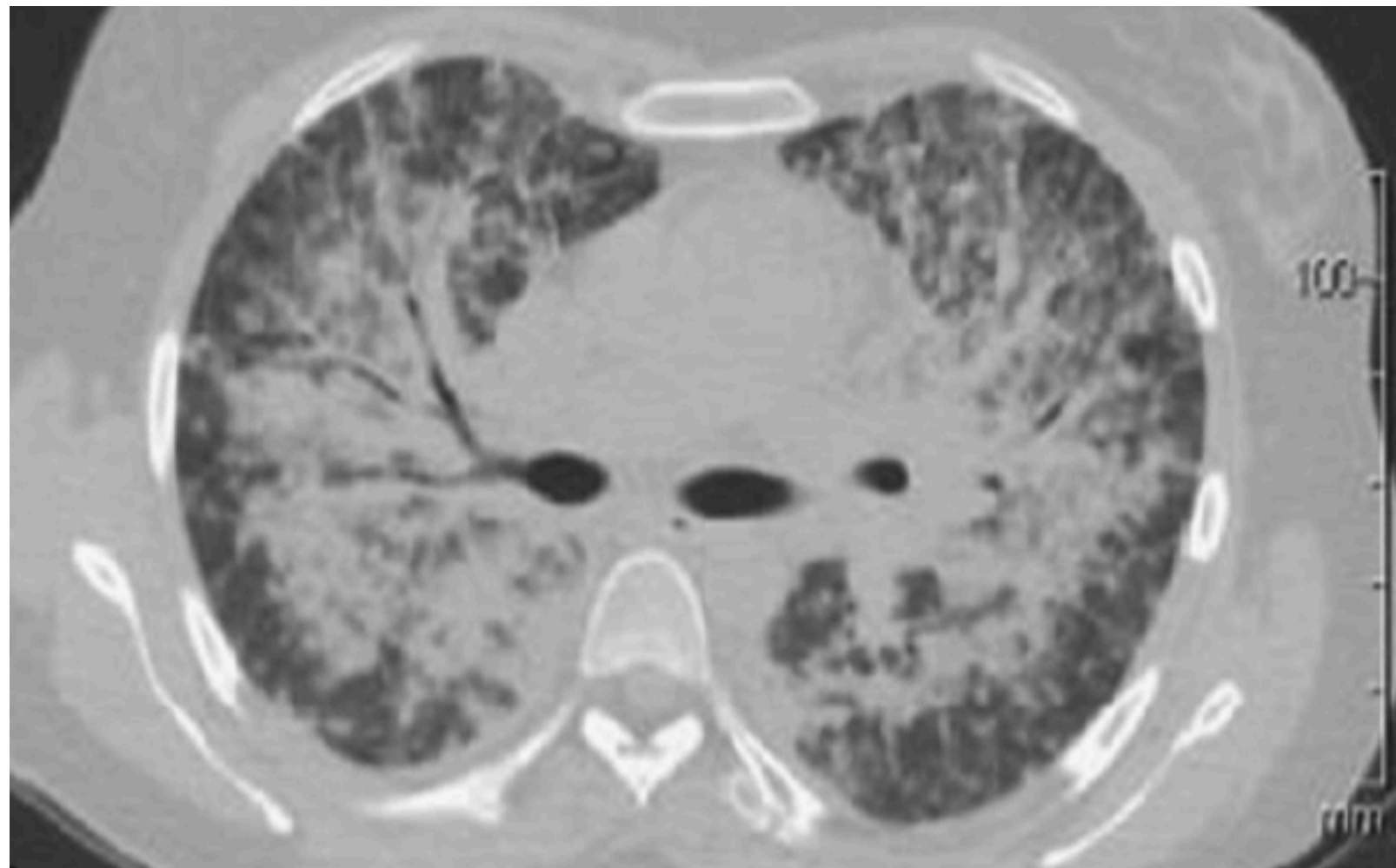
J+5  
ACV et C3G IV  
40°C  
Toux++  
Méningisme



J+6  
Dyspnée/IRA  
Réa



↑  
HC+ *Strepto pyogenes*





Hypothèses étiologiques virales ?

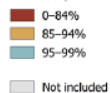
Paramyxovirus  
**Rougeole**

Moyens diagnostiques ?

Avant intubation (non invasif)

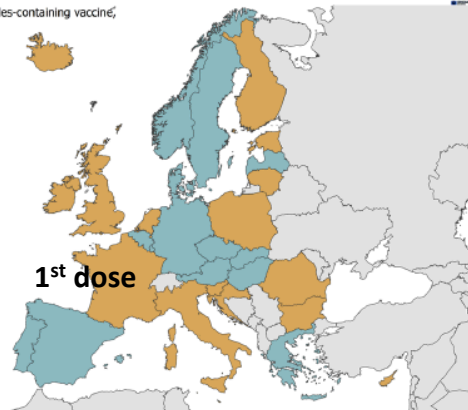
Après intubation

Vaccination coverage of measles-containing vaccine,  
first dose\*, 2017

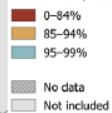


\* Estimates reported to WHO

1<sup>st</sup> dose

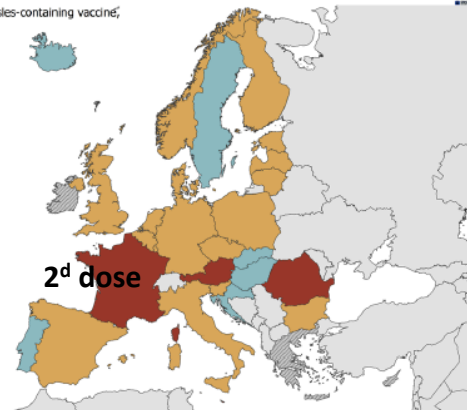


Vaccination coverage of measles-containing vaccine,  
second dose\*, 2017

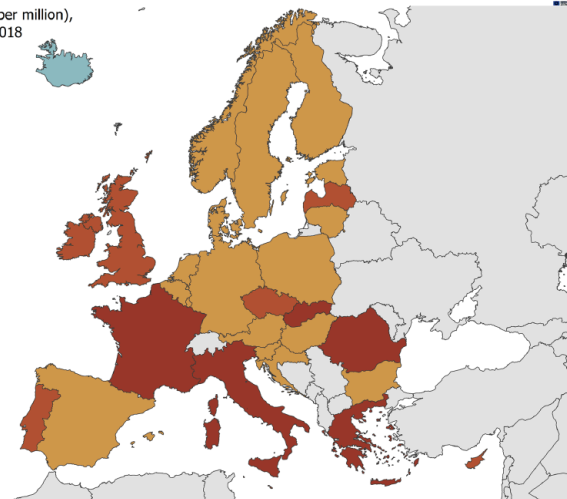
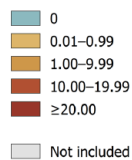


\* Estimates reported to WHO

2<sup>d</sup> dose



Notification rate of measles (per million),  
December 2017–November 2018





Contagiosity++,  $R_0 \approx 15$

Incubation 8-12

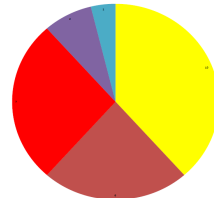
3 C's

Cough/coryza/conjunctivitis

Koplik (inconstant, specific)

Rash

Laryngitis  
tracheo-bronchitis  
interstitial pneumonitis  
post-measle pneumonia  
ARDS



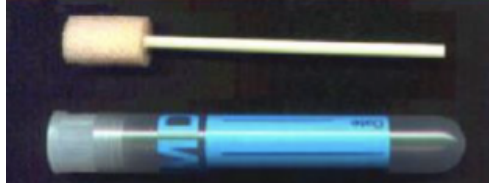
■ *S. pneumoniae*    ■ *S. pyogenes*  
■ *S. aureus*        ■ *S. mitis*  
■ *H. influenzae*    + *Moraxella catarrhalis*

acute encephalitis  
seizures  
post-infectious encephalomyelitis  
measles inclusion body encephalitis

Lymphopenia + Hypovitaminosis A



1



Ecouvillon de mousse – 1 min le long des gencives

2

**Salive**      IgM ou RT-PCR

3



Ecouvillon naso-pharyngé RT-PCR

# Grossesse et rougeole: 6-10% pneumopathie

Prévention vaccinale **ROUGEOLE++** (projet grossesse)



Haut Conseil de la santé publique

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## AVIS

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relatif à la problématique de la rougeole  
chez la femme enceinte

23 mai 2011

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Contage

**6 jours**

**Ig polyvalentes IV**

1 dose

200 à 400 mg/kg

**RIBAVIRINE** (*Cf Hirsch HH, Clin Infect Dis 2013*)

+

**Vitamin A 200 000 UI/j – IM – 4j**

Vitamine A pommade ophtalmique

±

Ig IV polyvalentes (hypogamma G)

*Forni AL, Schluger NW, Roberts RB. Clin Infect Dis 1994;19:454–62*

*Rafat C, et al. medicine 2013;92(5):257*

*Bichon et al. Medicine (2017) 96:50 Medicine*

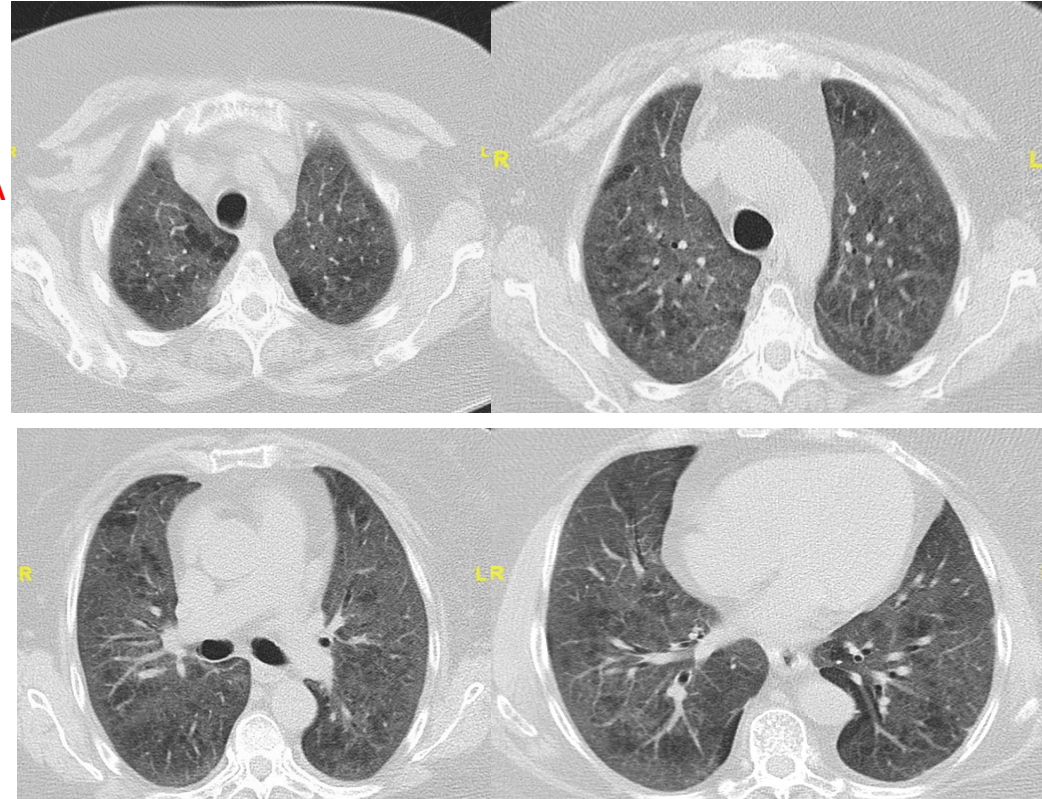
# Histoire 3

Femme 65 a  
MM IgG lambda (7<sup>e</sup> ligne de ttmt)  
POMALIDOMIDE + EDX + DXM  
Hypogamma + lymphopénie

Juillet 2018  
Consultation de routine  
Toux sèche  
Depuis 10j



**Dyspnée/IRA**  
**Hypxémie**  
**Réa**





## Hypothèses étiologiques infectieuses ?

Bio sang:

PCR ADENOVIRUS

$5.8 \times 10^6$  copies/mL

PCR CMV

$3.3 \times 10^4$  copies/mL

1-3 B-D-Glucanes

795 pg/mL

Que proposez-vous ?

Enfant > adulte  
Maladie à **ADENOVIRUS (ADV)**

Ig IV polyvalentes

Virémie  $\geq 1\ 000$  copies/mL  
**BRONCHO-PNEUMOPATHIE**

**CIDOFOVIR + Probenicid**  
5 mg/kg/sem  
2 à 3 sem  
Réévaluation

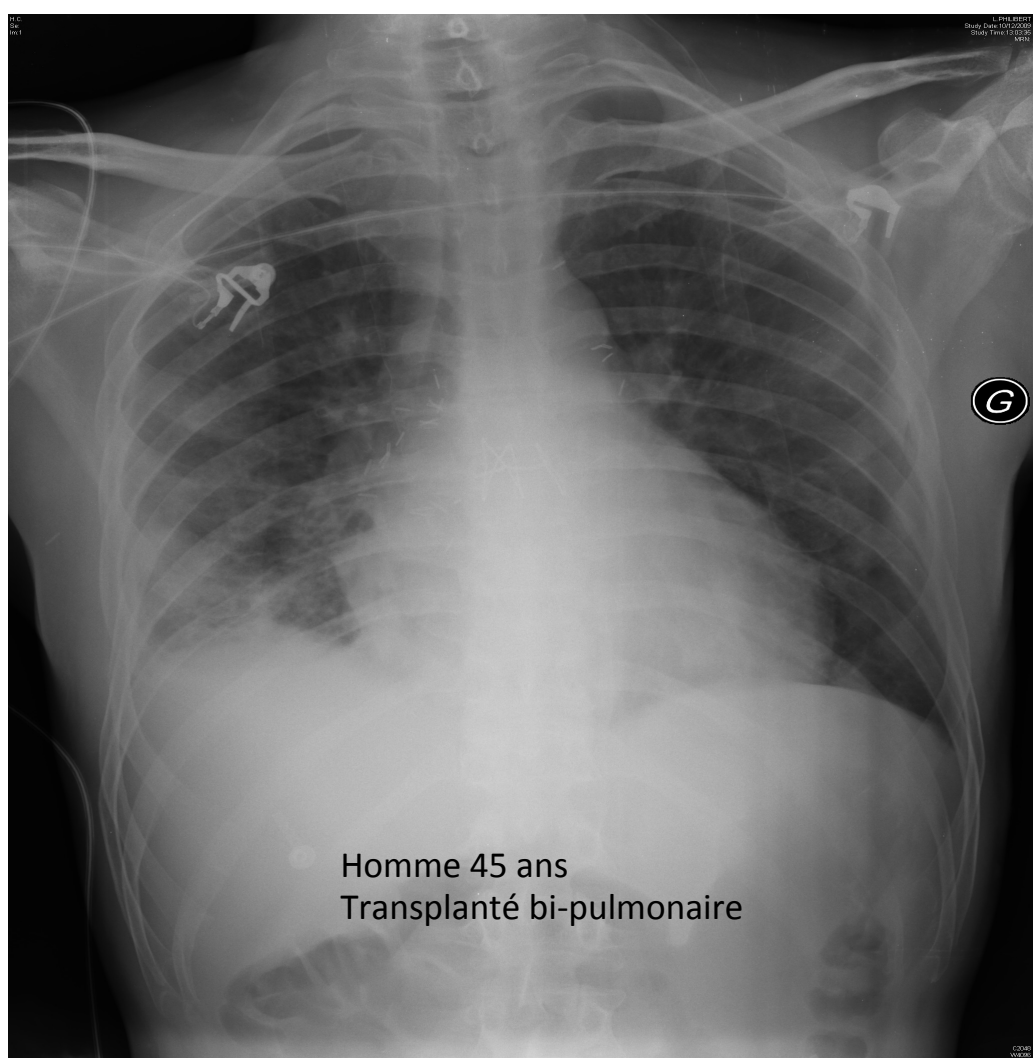
Cidofovir en formulation liposomale **BRINCIDOFOVIR** ?

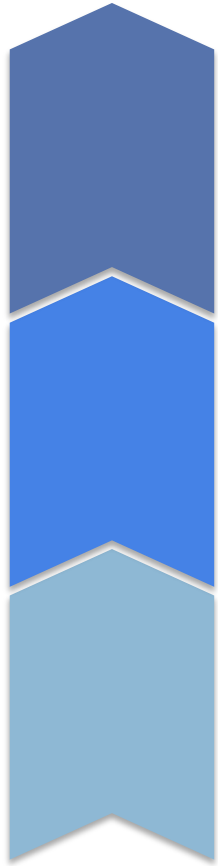
Sauvetage:  
**transfert adoptif de CTL**



Certaines souches (sérotypes  
espèce C) sont sb à la RBV  
→ Labo viro

Et la grippe...?





Faut-il **augmenter la dose vaccinale antigrippale** chez certaines sous-populations à haut risque de grippe grave ?

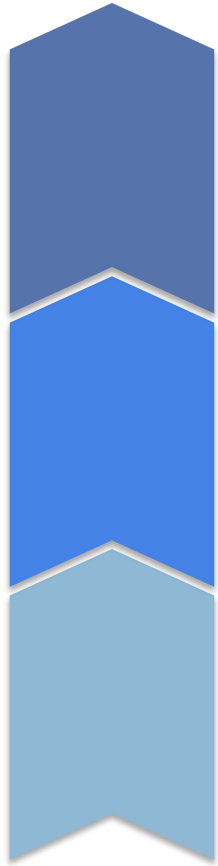
# Plutôt **oui**, mais...

Inactivated vaccine

Standard dose **15 µg** HA/strain vs. high-dose (HD) **60 µg** HA/strain  
3 HA/vaccine for 3 or 4 circulating strains

## Examples of trials

Target population	Design	Safety	Immunogenicity	Efficacy	References
Elderly	2 flu season 2011-2013 > 65 y Double-blind Multi-center (Canada/US) Randomized 15,998 SD vs. 15,991 HD <b>!/ Sanofi-Pasteur trial</b>	SAE 9% SD vs. 8.3% HD	Higher seroprotection (HAI titers)	D+14, lab-confirmed. Overall yes, but strain-dpdt	Efficacy of HD vs. SD Influenza vaccine in older adults DiazGranados CA et <i>al.</i> N Engl J Med 2014;371:635-45.
Solid-organ transplantation	Flu season 2016-2017 Double-blind Randomized 77 SD vs. 84 HD	No difference in SAE	Significantly increased Higher seroconversion Higher GMT fold increase	<b>No data</b>	High-Dose Flu vaccine in SOT Natori Y et <i>al.</i> Clin Infect Dis 2018; 66: 1699

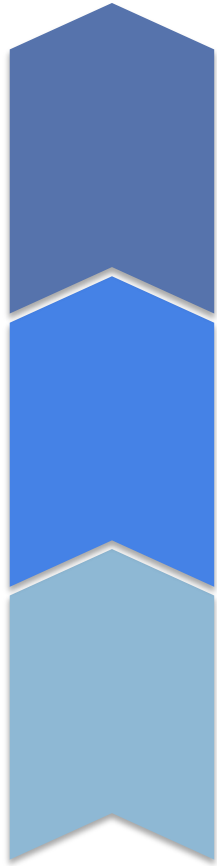


Faut-il **augmenter la dose curative d'oseltamivir** dans certaines sous-populations présentant une grippe grave ?

Faut-il augmenter la dose vaccinale antigrippale chez certaines sous-populations à haut risque de grippe grave ?

# Plutôt non, mais...

	Main result	References
CDC	2009 H1N1, Severe influenza in critically ill, 300 mg/d	Prevention Centers for Disease Control and Prevention. Morb Mortal Wkly Rep 2011 60:1–25
Hospitalized patients Elderly > 65 y	1. Primary end-point: viral clearance day+5 <b>No benefit on primary end-point except for Influenza B + no overall difference in clinical outcome (O2, H°, ICU)</b>	1. Lee N, et <i>al.</i> A prospective intervention study on higher-dose oseltamivir treatment in adults hospitalized with Influenza A and B infections. <i>Clin Infect Dis</i> 2013; 57:1511–1519 2. South East Asia Infectious Disease Clinical Research Network. Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomised controlled trial. <i>BMJ</i> 2013;346:f3039
Critically ill patients	Primary end-point: difference in ICU-free days <b>No benefit</b>	Welch SC et <i>al.</i> High-dose versus standard dose oseltamivir for treatment of severe influenza in adult intensive care unit patients. <i>Int Care Med</i> 2015; 41:1365–1366
PK/PD	Average plasma [oseltamivir] with a renally equivalent dosing regimen of 75 mg twice daily have been reported to be <b>2000- to 4000-fold higher</b> than the 50 % MIC for H1N1 isolates	Ariano RE et <i>al.</i> Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza. <i>CMAJ</i> 2010;182:357–363



Y-a-t-il une place pour une **multithérapie antivirale** dans certaines sous-populations à haut risque présentant une grippe grave ?

Faut-il augmenter la dose curative d'oseltamivir dans certaines sous-populations présentant une grippe grave ?

Faut-il augmenter la dose vaccinale antigrippale chez certaines sous-populations à haut risque de grippe grave ?



# Bof, mais...

## **A Randomized Double-Blind Phase 2 Study of Combination Antivirals for the Treatment of Influenza**

*Beigel JH et al. Lancet Infect Dis 2017; 17(12): 1255-1265*

AMT (100 mg), OSL (50 mg) and RBV (200 mg) x2/day for 5 days  
Significant decrease of viral shedding at day+3  
No clinical improvement of symptoms

## **Combination therapy with amantadine, oseltamivir and ribavirin for influenza A infection: safety and pharmacokinetics**

*Seo S et al. Antivir Ther. 2013 ; 18(3): 377-386*

HV, AMT (75 mg), OSL (50 mg) and RBV (200 mg) x3/day for 10 days = no PK interaction  
6 immunocompromized patients, 1 SAE

Dans la période d'overlap VRS/Influenza, une bithérapie OSL/RBV de couverture peut être envisagée chez l'immunodéprimé avec atteinte sévère dans l'attente de la documentation

# Alternative typology : influenza-associated IPA in critically ill patients

Invasive Aspergillosis Complicating  
Pandemic Influenza A (H1N1)  
Infection in Severely  
Immunocompromised Patients

*Garcia-Vidal C et al., Clin Infect Dis 2011*

**Influenza-associated Aspergillosis in Critically Ill  
Patients**

*van de Veerdonk FL et al., Am J Respir Crit Care Med 2017*

Invasive aspergillosis in patients admitted to the intensive  
care unit with severe influenza: a retrospective cohort study

*Schauwvlieghe AF et al., Lancet Respir Dis 2018*



**Invasive pulmonary aspergillosis complicating  
severe influenza: epidemiology, diagnosis  
and treatment**

*Vanderbeke L et al., Curr Op Infect Dis 2018*

**Influenza-associated invasive  
pulmonary aspergillosis, Europe**

30 November 2018



**RAPID RISK ASSESSMENT**

Key points:

- H1N1 2009 strain
- GM BALF
- CC
- High mortality-rate (55-70%), especially when no underlying disease.

## Take home messages

CARV (community-acquired respiratory viruses)

Facteur saisonnier

Prélèvement par écouvillon type Virocult®

RT-PCR multiplex virus pneumotropes + PCR ADV (enfant<sup>++</sup>)

Grippe

VRS

Rougeole !!!

Mesures préventives<sup>++</sup>: vaccination antigrippale, éviter contagé

Grippe = Oseltamivir oral, Zanamivir IV

VRS = ribavirine (RBV) ± possibilité Ig IV spécifiques Pavilizumab (enfants<sup>++</sup>)

ADV = cidofovir, brincidofovir

Ig polyvalentes IV ?

Pneumopathie bactérienne post-virale

Syndrome de bronchiolite oblitérante (SBO)

Transplantation: dysfn du greffon, rejet aigu et chronique