DES Infectiologie 2023

Module Infections des immunodéprimés

Infections à virus saisonniers pneumotropes chez les immunodéprimés : focus VRS, grippe et SARS COV2

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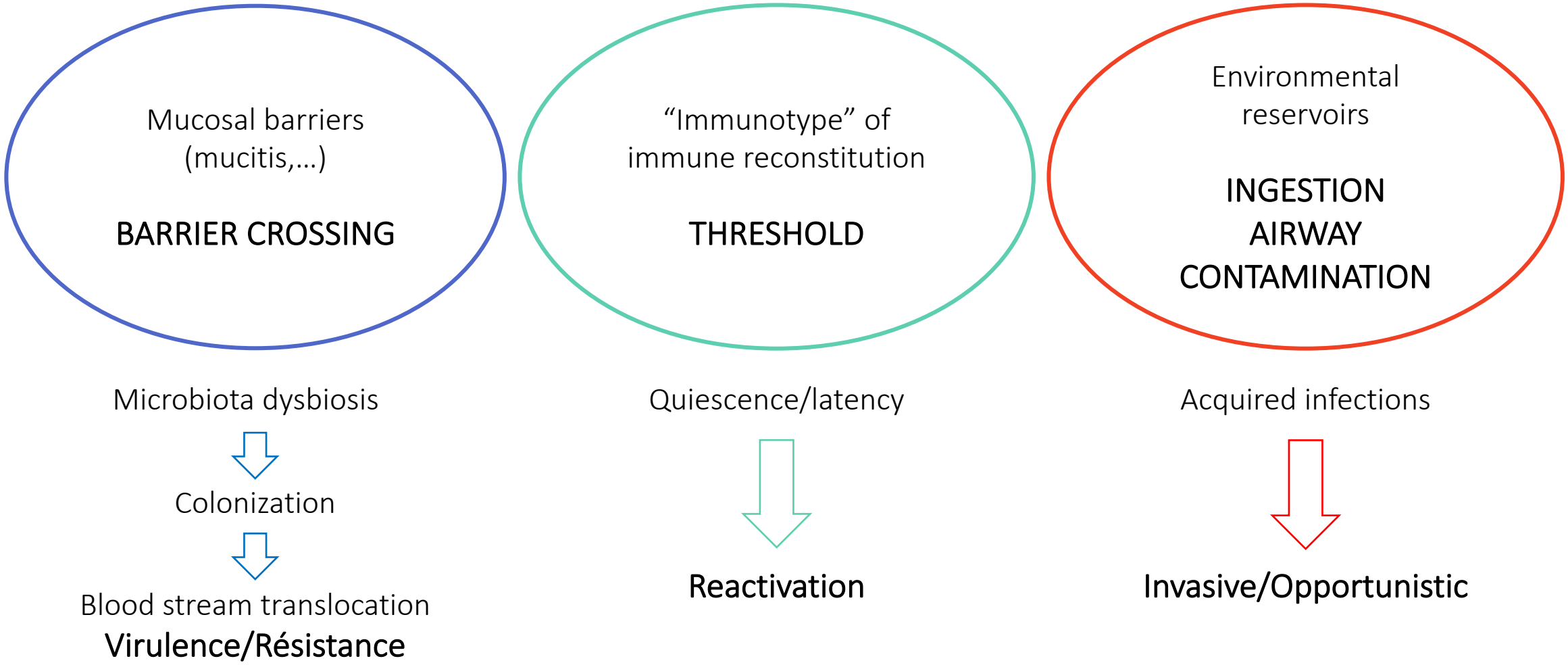
Université Lyon 1 – Inserm 1111 Centre International de Recherche en Infectiologie


Mucosal barriers
(mucitis,…)
BARRIER CROSSING
“Immunotype” of
immune reconstitution
THRESHOLD
Environmental
reservoirs
INGESTION
AIRWAY
CONTAMINATION
Microbiota dysbiosis
Colonization
Blood stream translocation
Virulence/Résistance
Quiescence/latency
Reactivation
Acquired infections
Invasive/Opportunistic

Virulence/Resistance

Bacteria

Enterobacteria

Strepto/enterococcus

Staph aureus/coag nég

Non-fermenting GNB

Yeasts

Candida spp.

Reactivation

Virus

HSV1/2

VZV

EBV

CMV

HHV-6/7/8

Adenovirus

BK virus

Parvovirus B19

Parasites

Toxoplasma

Bacteria

Mycobacterium TB complex

NTM

Invasive/Opportunistic

Bacteria

Streptococcus pneumoniae

Legionella spp.

Nocardia spp.

Fungi

Pneumocystis jirovecii

Aspergillus spp.

Mucorales

Fusarium spp.

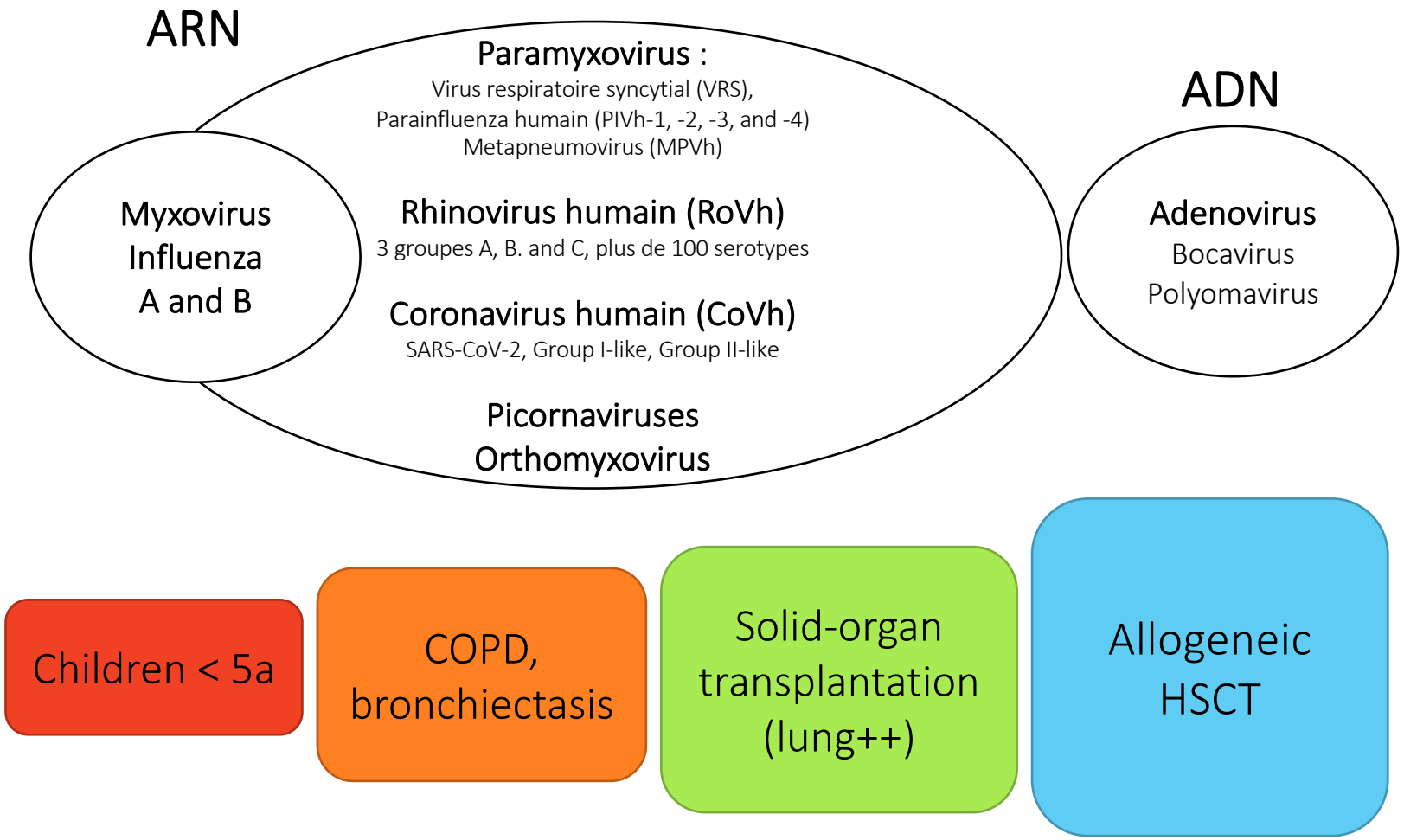
Scedosporium spp.

Virus

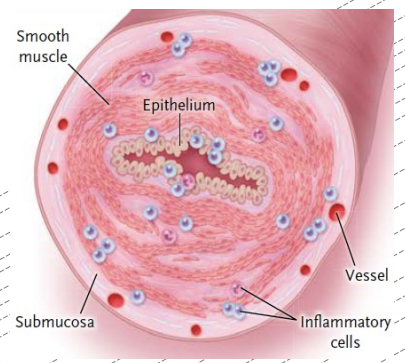
Influenza/VRS/Parainfluenza

Metapneumovirus

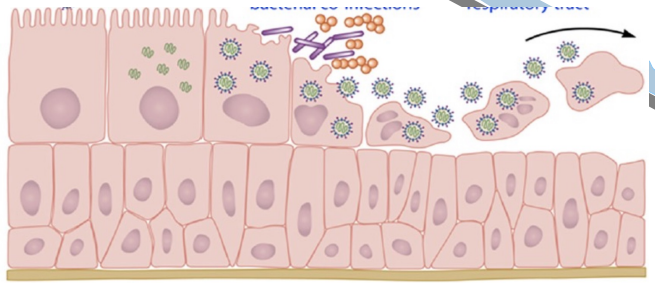
Community-acquired respiratory infections (CARV)



VRS chez l’adulte immunodéprimé



Epithelial cell necrosis



Mucus plugging

Bronchiolitis obliterans syndrome
Peribronchial infiltrates

Defect in cytotoxic
T cell CD8+-dependent viral clearance

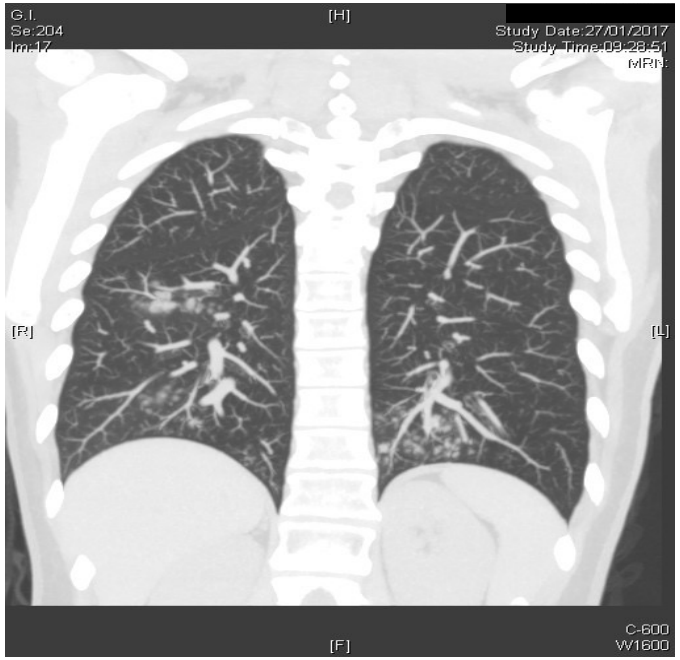
Airway
Hyporesponsiveness

Aberrant immune
response

Hypoxia^{++}

According to Griffiths C, Drews SJ, Marchant DJ. Clin Microbiol Rev 2017: 30:277–319

Pas grave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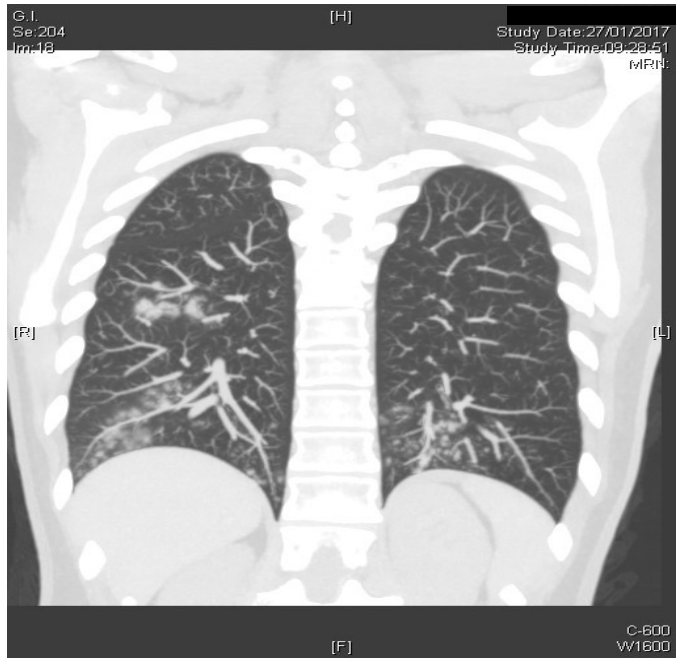
[H]
Study Date:27/01/2017
Study Time:09:28:51
MRN:
[R]
[L]
[F]
C-600
W1600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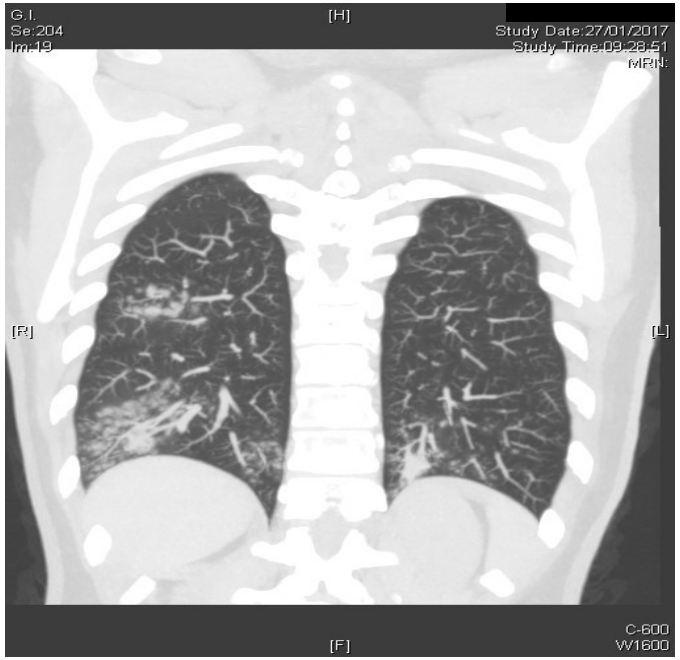
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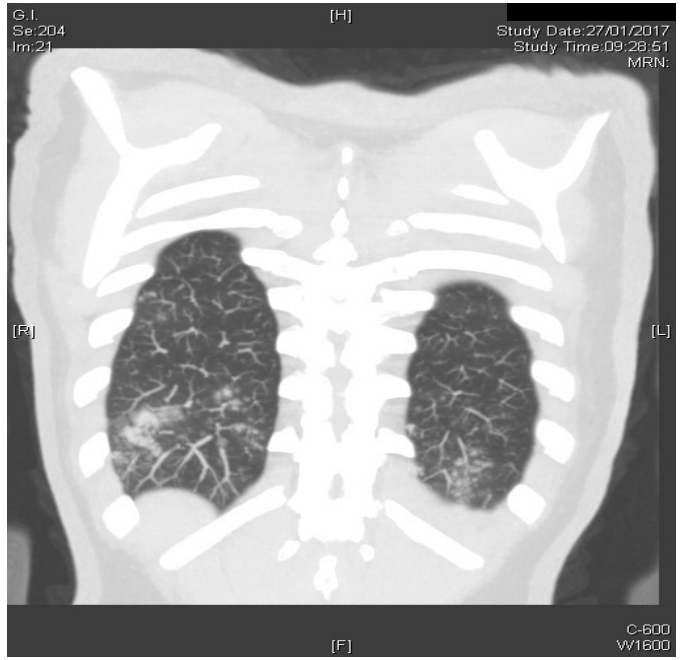
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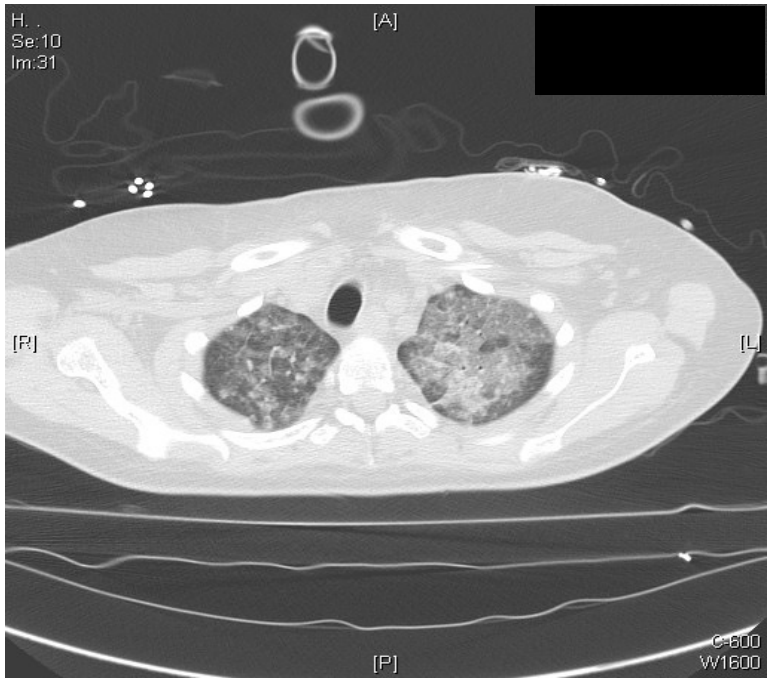
C-600
W1600

Grave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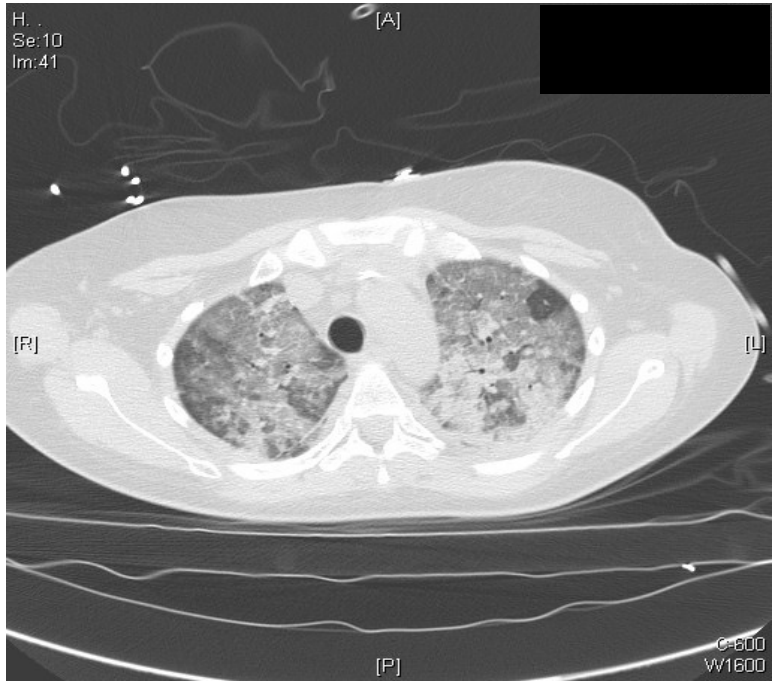
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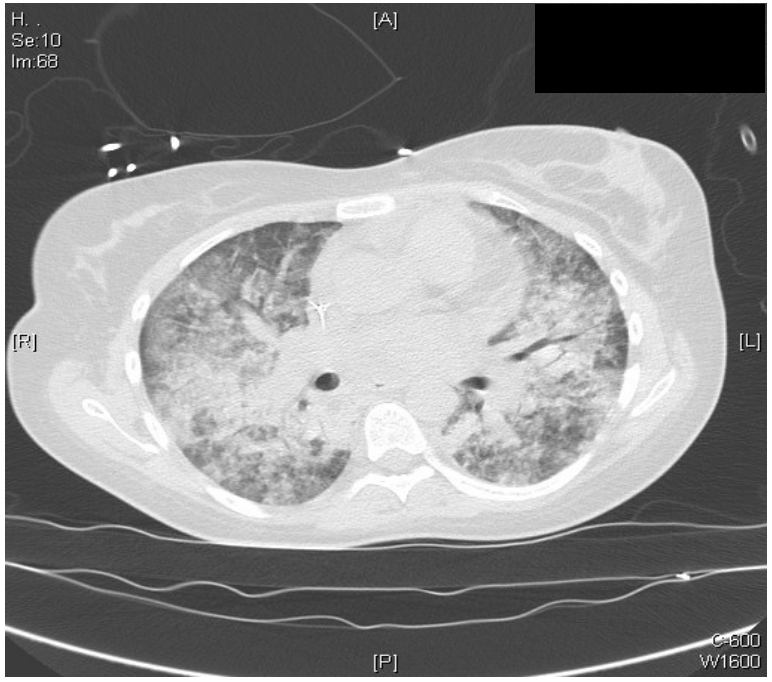
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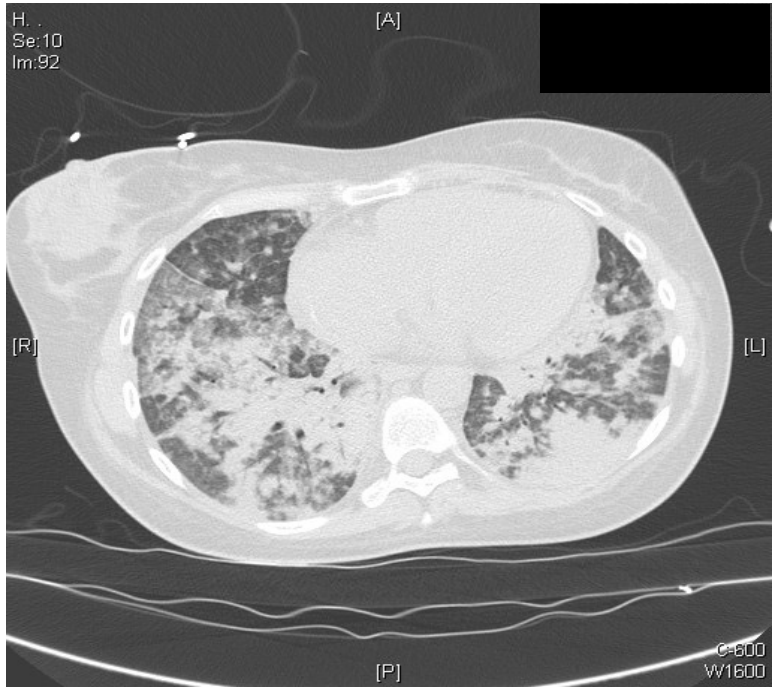
H. .
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[R]
[L]
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C=600
W1600

Diagnosis work up

Allo-HSCT

ENT symptoms/cough/fever

- Nasal swab 
  - **Multiplex kit pneumotropic viruses**
    - Influenza, RSV, CoV, others…

      [Cycle threshold (?)]
- **CT scan**

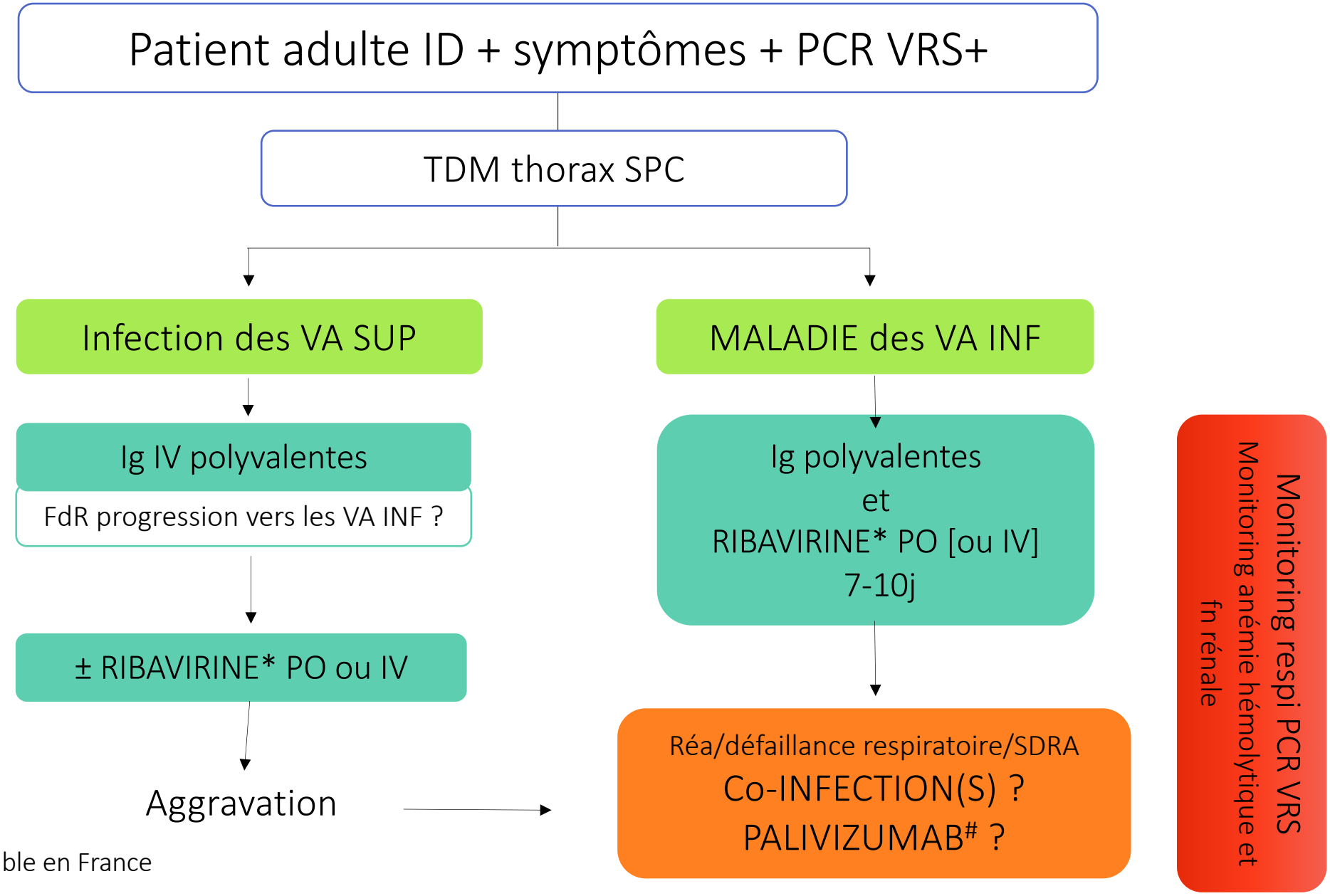
  (no injection)

Who to treat

Upper respiratory tract infection (RTI) at high-risk of progression to lower RTI (HSCT, lymphopenia)
Treat all the lower RTI

Adapté de ECIL-4, Hirsch H.H et al., Clin Infect Dis 2013
*Chemaly R et al., Clin Infect Dis **2014;59(**S5):S344–51*

Message 3
Algorithme thérapeutique



* forme aérosol non disponible en France
# ATU nominative ANSM

Ribavirine (RBV): toujours jeune et pétillante
…mais quasi plus en stock

ansm
Agence nationale de sécurité du médicament et des produits de santé

Arrêt de commercialisation des spécialités de Ribavirine Biogaran 200mg cp et Ribavirine Biogaran 400 mg cp effectif depuis le 30/09/2021.

Mise à disposition à titre exceptionnel et transitoire par Intsel Chimos auprès des pharmacies hospitalières d'unités de la spécialité Ribarivin 200 mg film-coated tablets, initialement destinées au marché anglais

Mise à disposition à titre exceptionnel et transitoire par Intsel Chimos auprès des pharmacies hospitalières d'unités de la spécialité Ribavirin capsules 200 mg, initialement destinées au marché anglais

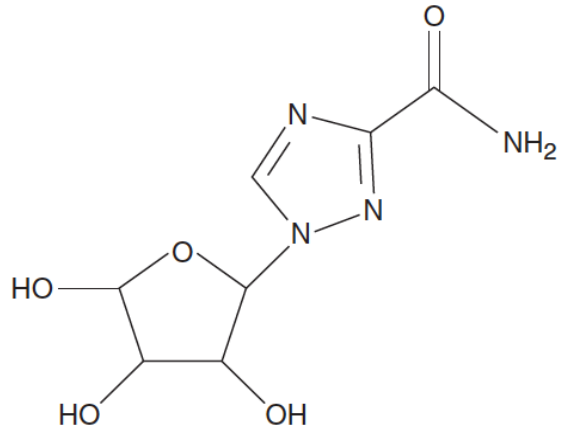
Ribavirine (RBV): toujours jeune et pétillante …mais quasi plus en stock

Biodisponibilité orale **45-65%** (après effet 1er 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)



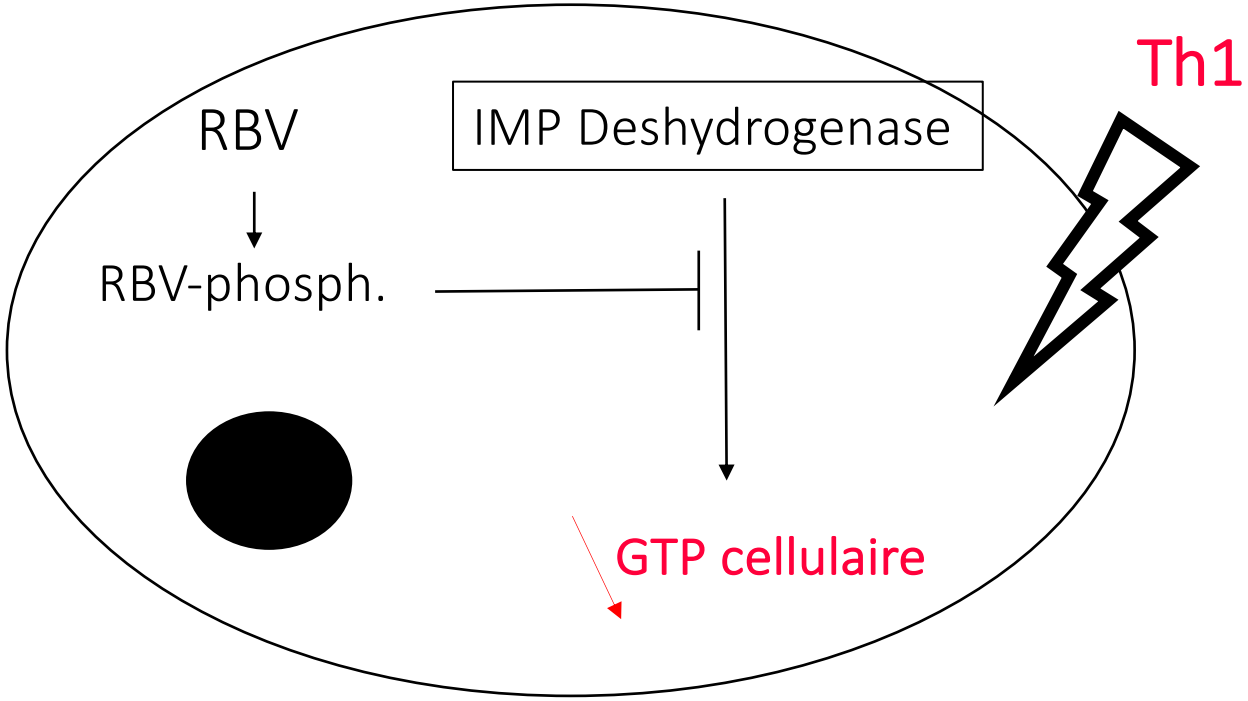
Pas de métabolisation hptq = pas d'adaptation de dose hépatotpathie chnq

Clairance dpdte du :

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

GS Naik, MG Tyagi, J Clin Exp Hepatol 2012;2:42–54

RBV: analogue guanosine



Maniement de la RBV orale ou IV: reco ECIL-4 encore d'actualité

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	
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[b]

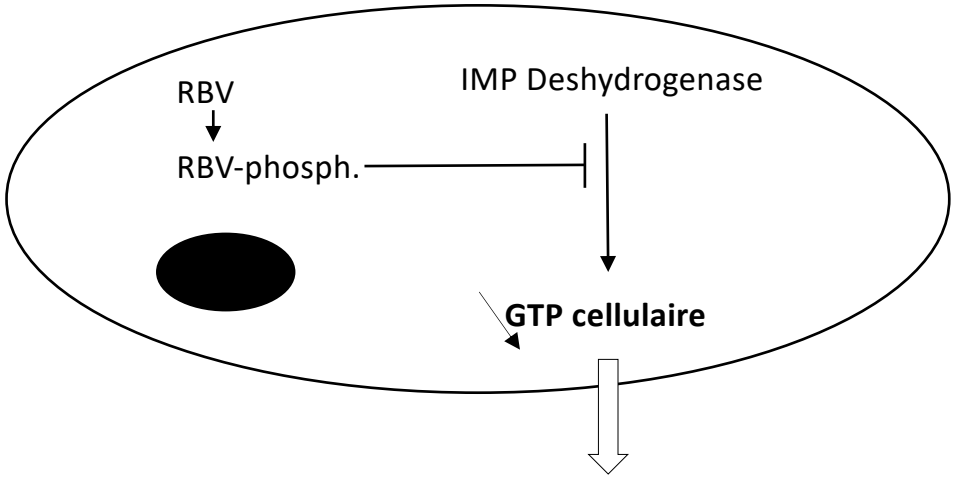
[b] Some experts use 200 mg once daily under close clinical and laboratory monitoring.

30 mg/kg/jour max

Doses progressivement croissantes sur 3j

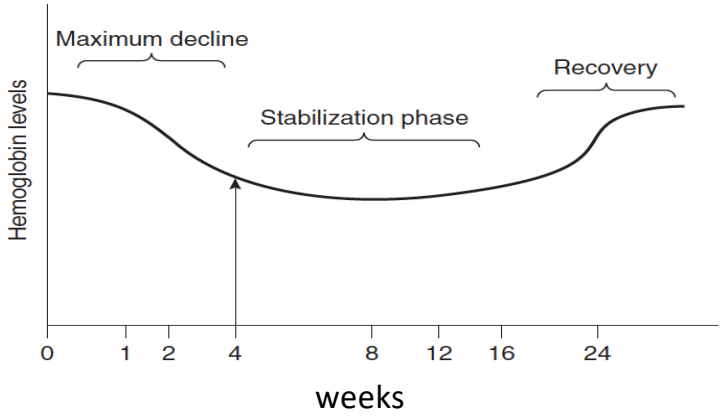
Adaptation fn rénale

ECIL-4, Hirsch H.H et al., Clin Infect Dis 2013



Anémie hémolytique dose-dpdte et réversible

Déplétion GTP et ATP
Acidose lactique



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

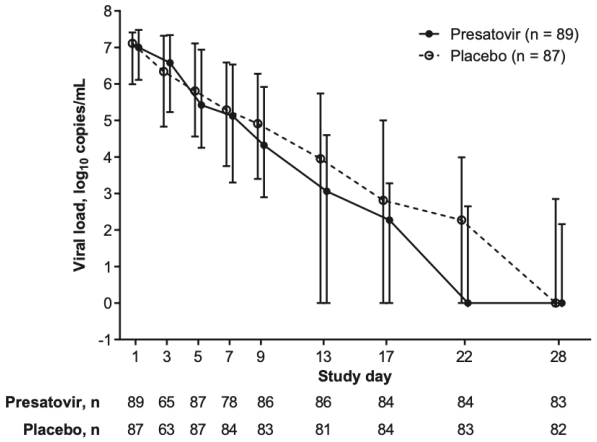
GS Naik, MG Tyagi, J Clin Exp Hepatol 2012;2:42–54

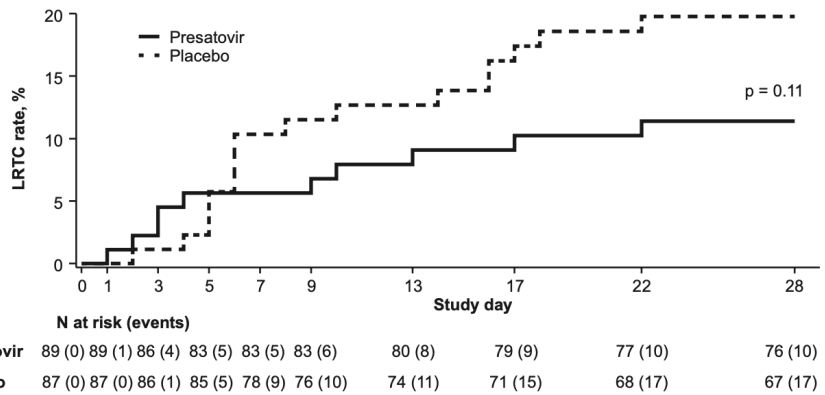
Riner A et al. Postgraduate Medicine 2009; 121:3, 5-15
Gross AE et al. Annals of Pharmacotherapy 2015; 49(10) 1125–1135

Pipeline thérapeutique: RSV fusion inhibitor **presatovir**

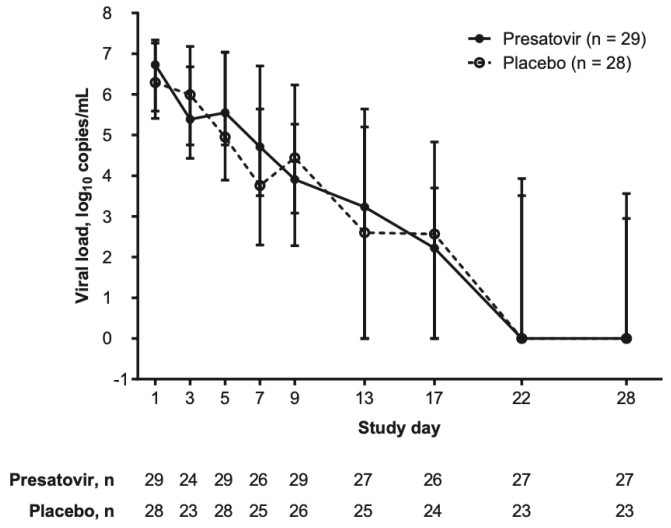
2b, RCT, placebo, double-blind, multi-center,
Time-weighted average change in nasal RSV viral load measured by RT-qPCR (log10 copies/mL)

HSCT URTI, n=185





HSCT LRTI, n=59



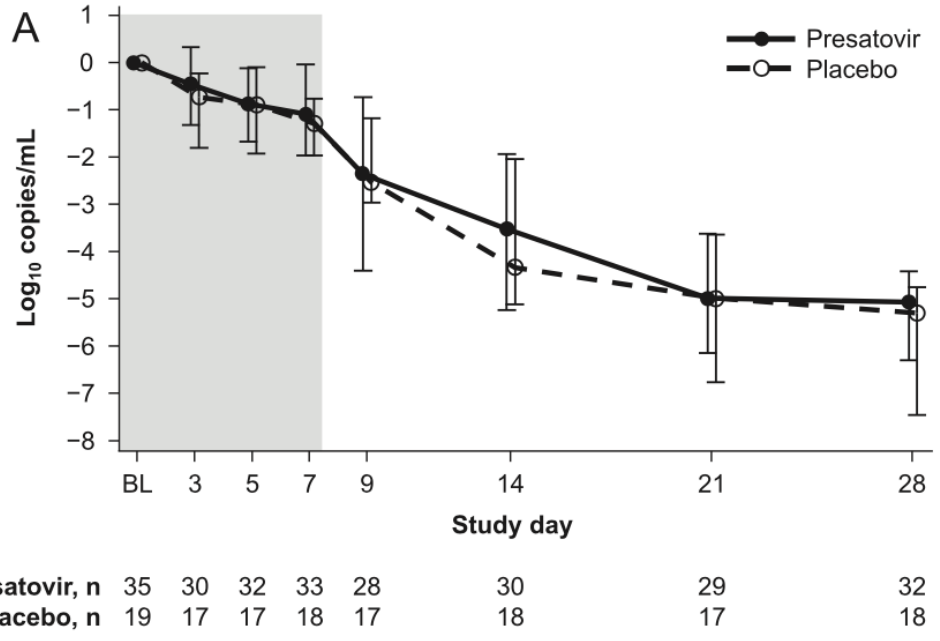
	Presatovir (n = 29)	Placebo (n = 28)
Time-weighted average change in nasal RSV RNA (log_{10} copies/mL) from baseline to day 9		
Mean (SD)	−1.12 (1.23)	−1.09 (1.03)
Adjusted mean[a] (95% CI)	−1.00 (−1.43, −.56)	−0.97 (−1.41, −.53)
P value[a]	.94	
Number of supplemental oxygen-free days through day 28		
Median (min, max)	26 (0, 33)	28 (0, 30)
P value[b]	.84	
Patients who developed respiratory failure requiring mechanical ventilation through day 28		
n (%)	3 (10.3)	3 (10.7)
P value[c]	1.00	
All-cause mortality through day 28		
n (%)	0	2 (7.1)
P value[c]	.24	

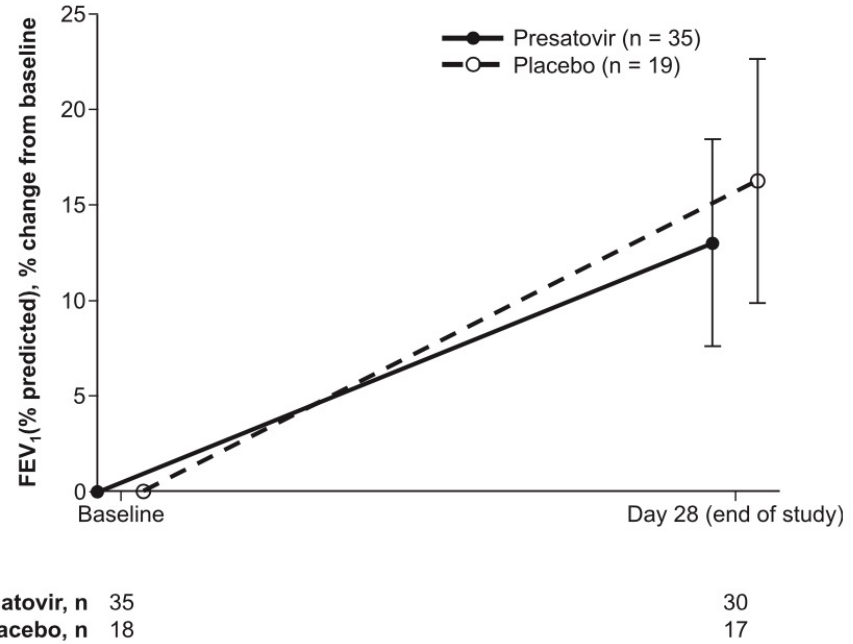
Marty FM et al., Presatovir for RSV LRTI After HCT, Clin Infect Dis 2020:71
Chemaly R et al., Presatovir for RSV URTI in HCT Patients. Clin Infect Dis 2020:71

Pipeline thérapeutique: RSV fusion inhibitor **presatovir**

2b, RCT, placebo, double-blind, multi-center
Time-weighted average change in nasal RSV viral load measured by RT-qPCR (log10 copies/mL)

Lung transplantation, n=61





Gootlieb J et al., The Journal of Heart and Lung Transplantation 2023

Au total : prophylactique/préemptif (?)

Nirsevimab : long-action mAb to the RSV fusion protein

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants

Laura L. Hammitt, M.D., Ron Dagan, M.D., Yuan Yuan, Ph.D., Manuel Baca Cots, M.D., Miroslava Bosheva, M.D., Shabir A. Madhi, Ph.D., William J. Muller, Ph.D., Heather J. Zar, Ph.D., Dennis Brooks, M.D., Amy Grenham, M.Sc., Ulrika Wählby Hamrén, Ph.D., Vaishali S. Mankad, M.D., Pin Ren, Ph.D., Therese Takas, B.Sc., Michael E. Abram, Ph.D., Amanda Leach, M.R.C.P.C.H., M. Pamela Griffin, M.D., and Tonya Villafana, Ph.D., for the MELODY Study Group*

N Engl J Med 2022; **386:** 837–46

Phase 3, RCT, *vs*. placebo 2:1, double-blind, multi-center
Primary end-point = medically attended RSV-associated lower respiratory tract infection

End Point and Analysis	Nirsevimab (N=994)	Placebo (N=496)	Efficacy (95% CI)†	P Value
	no. (%)			
Medically attended RSV-associated lower respiratory tract infection			74.5 (49.6 to 87.1)	<0.001
Poisson regression with robust variance				
Observed events	12 (1.2)	25 (5.0)		
Participants with imputation of data‡	15 (1.5)	6 (1.2)		
Hospitalization for RSV-associated lower respiratory tract infection			62.1 (–8.6 to 86.8)	0.07
Poisson regression with robust variance				
Observed events	6 (0.6)	8 (1.6)		
Participants with imputation of data‡	15 (1.5)	6 (1.2)		

---- > Phase 3 RCT *vs.* placebo, multicentrique, prophylaxie chez l'immunodéprimé, Septembre 2023

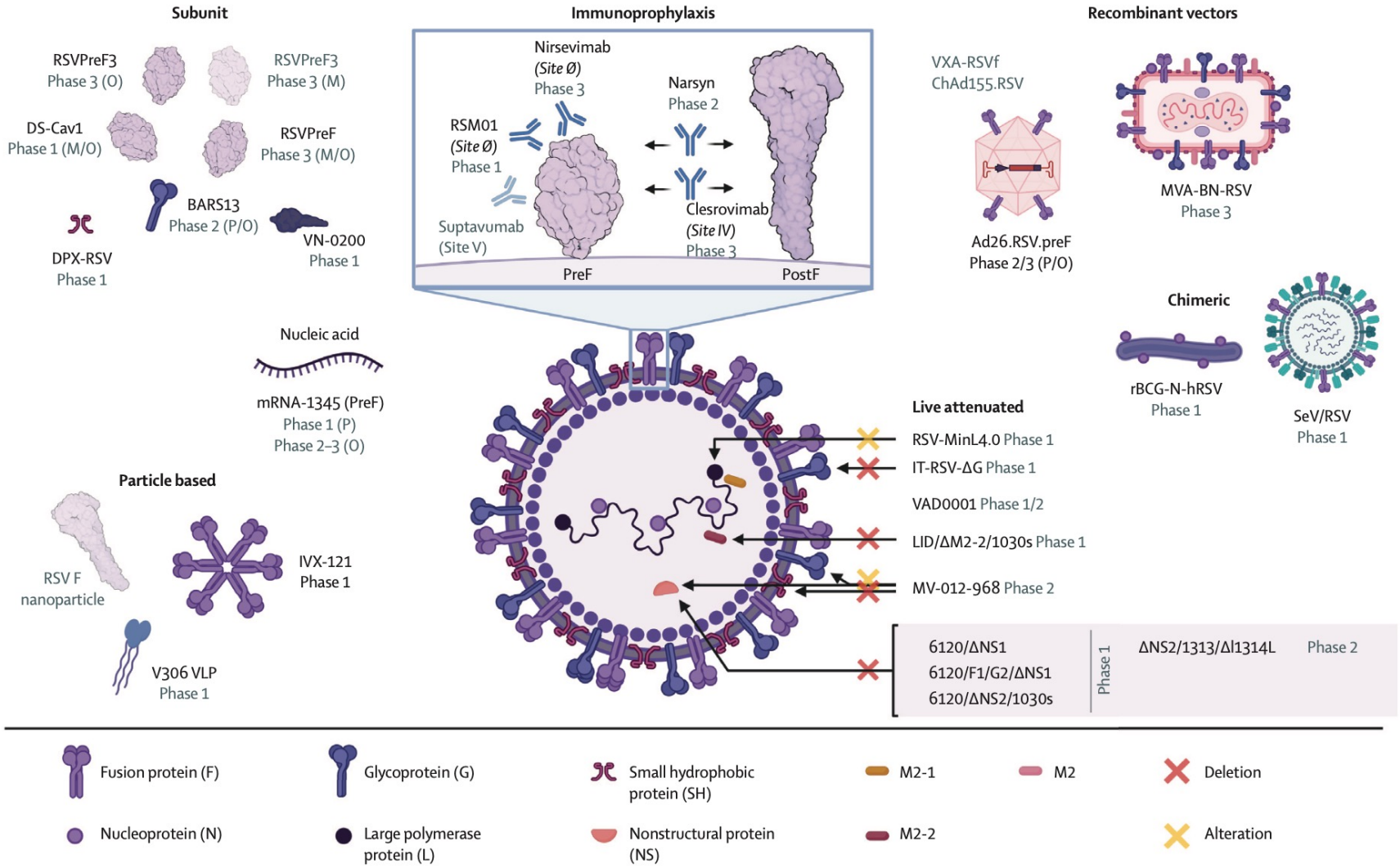
RSV prevention within reach: the vaccine and monoclonal antibody landscape

ORIGINAL ARTICLE

Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults

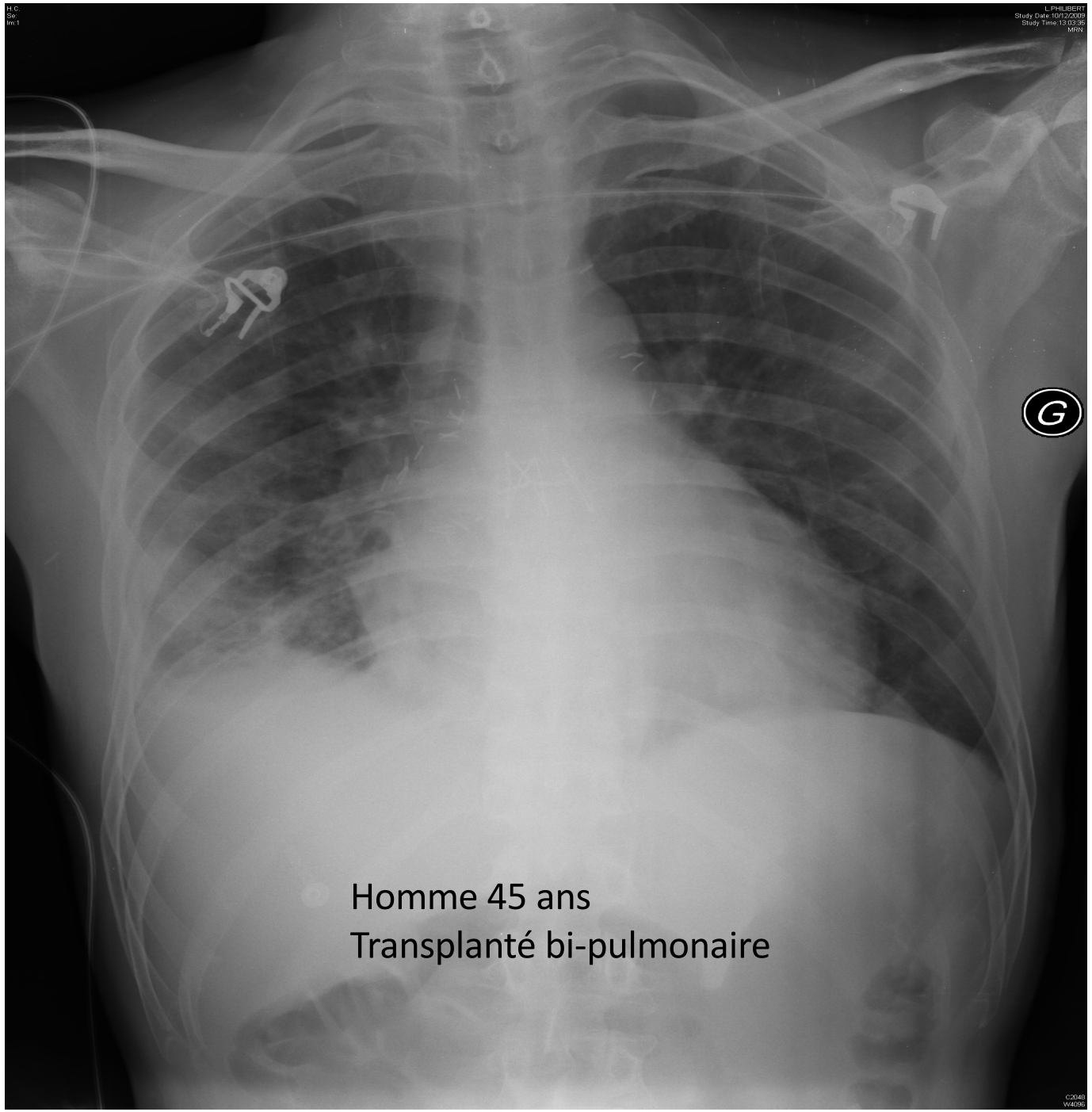
A. Papi, M.G. Ison, J.M. Langley, D.-G. Lee, I. Leroux-Roels, F. Martinon-Torres, T.F. Schwarz, R.N. van Zyl-Smit, L. Campora, N. Dezutter, N. de Schrevel, L. Fissette, M.-P. David, M. Van der Wielen, L. Kostanyan, and V. Hulstrøm, for the AReSVi-006 Study Group*

N Engl J Med 2023;388:595-608.
DOI: 10.1056/NEJMoa2209604



Mazur NI, Lancet Infect Dis 2023; 23: e2–21

Et la grippe…?



Homme 45 ans
Transplanté bi-pulmonaire

Inhibiteurs de la neuraminidase (INA)

- OSELTAMIVIR oral et ZANAMIVIR IV
- A commencer le plus vite possible

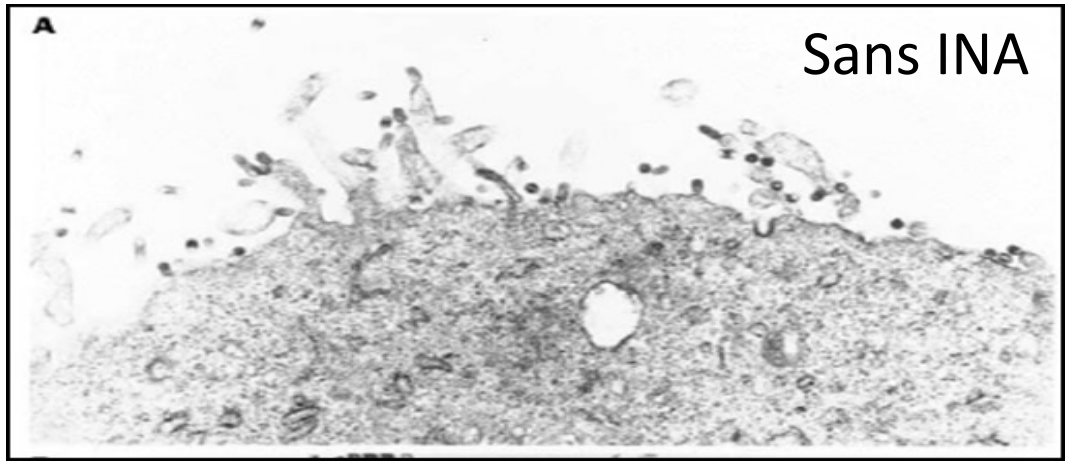
Oseltamivir 75mgx2/jour, jusqu'à 150mgx2/jour

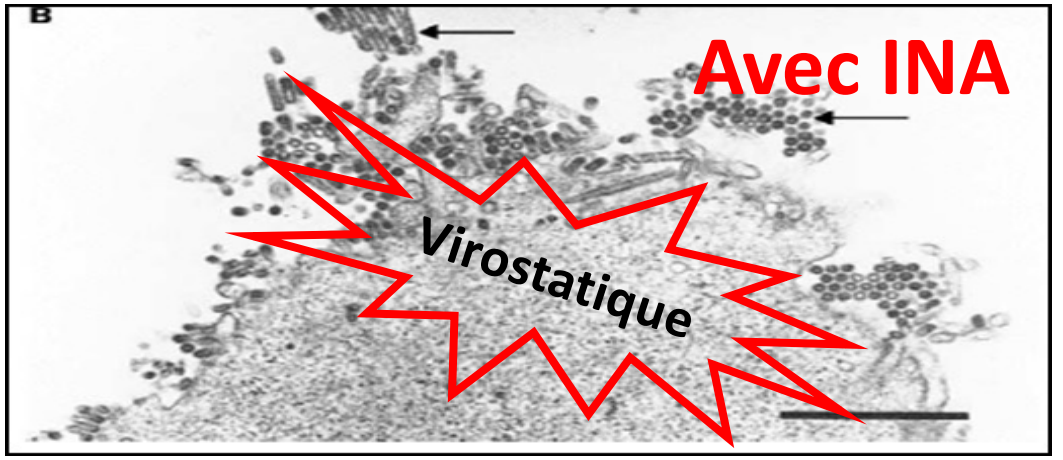
10 jours au moins

Adaptation fn rénale

Monitoring virocult/PCR de l'excrétion viralex1/sem : Ct ?

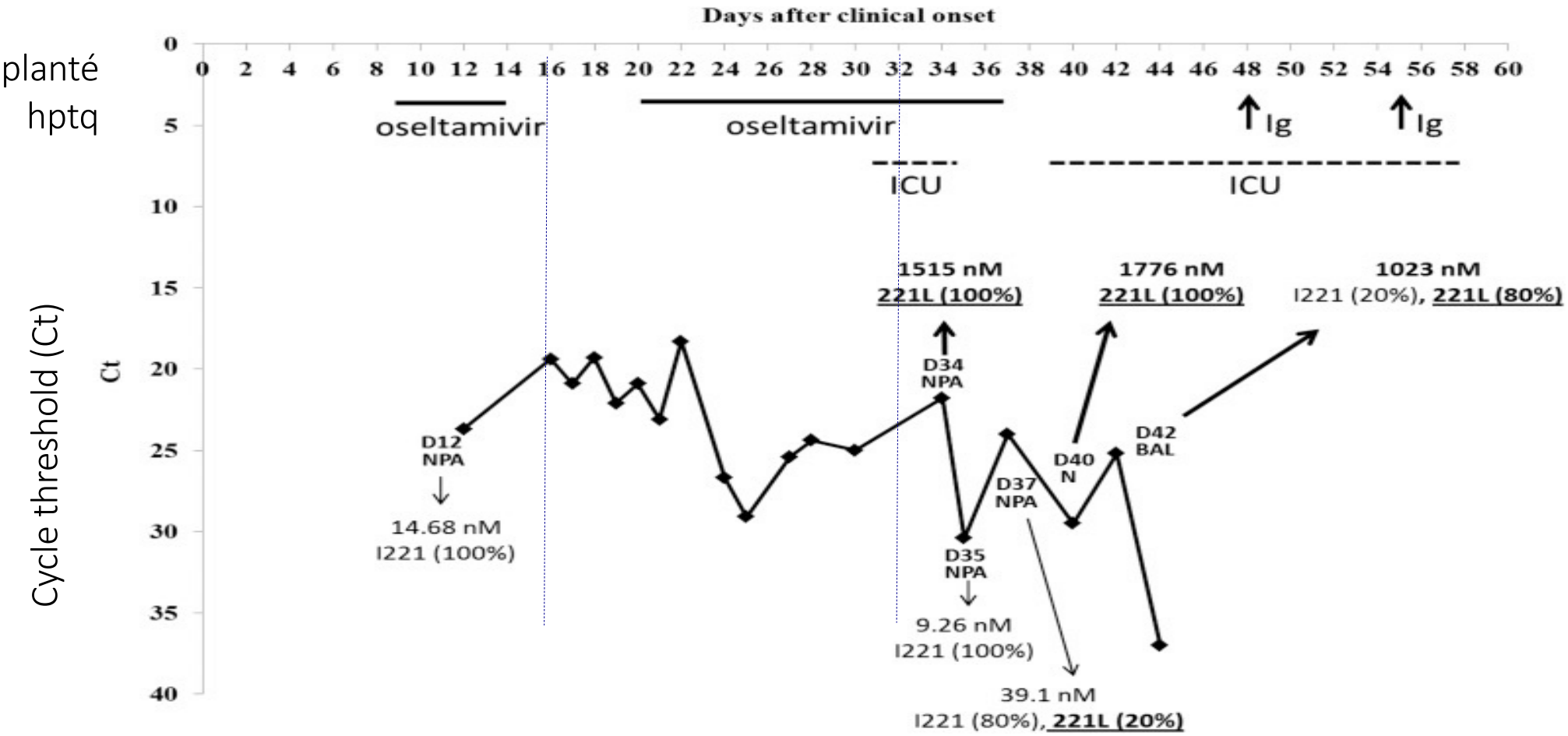
Culture de virus Influenza MDCK





Gubareva et al., 2000

Tranplanté hptq



Escuret V et al., JID 2014

Plus la charge virale est élevée dans le temps, plus le risque de sélection de résistance à l'oseltamivir augmente

ZANAMIVIR, disponible en ATU de 5j renouvelable (ANSM et GSK)

Non remboursé

- Infection **sévère** à Influenza
- Virus Influenza résistant à l'oseltamivir documenté
  - Souvent virus A(H1N1) avec mutation H275Y dans N1
  - sous Zanamivir IV développement possible de mutation I223R qui confère une résistance accrue à l'oseltamivir et une résistance au zanamivir

Nguyen et al., CID 2010
Van der Vries et al., Plos Pathog 2011
Le Goff et al., Plos One 2012

- **600 mgx2/j** à adapter à la fonction rénale, à l'âge, poids (si < 50kg)
- **10 jours** (5 jours + refaire une demande pour 5j)
- **Cytolyse hépatique** chez 13% des patients dans étude phase 2

Étude phase 2 : Marty et al., JID 2014

Autres pour le traitement de la grippe

Peramivir
AMM aux Etats-Unis, au Japon et en Corée du Sud
Enregistrement EMA
ANSM ?

Baloxavir marboxil :
AMM au USA
Enregistrement EMA
ANSM ?

Laninamivir et Favipiravir
AMM au Japon

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

Plutôt **oui**, mais…peu d'evidence-based

Inactivated vaccine
Standard dose **15 µg** HA/strain *vs.* high-dose (HD) **60 µg** HA/strain

Target population	Design	Safety	Immunogenicity	Efficacy	References
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	**No data**	High-Dose Flu vaccine in SOT Natori Y et *al*. Clin Infect Dis 2018; 66: 1699

Influenza (trivalent)	Lai (2019) [44]	888 adults, 132 children (8)	Transplant or chemo-therapy recipients	High-dose vaccine (60 mcg) increased seroconversion over standard dose (15 mcg) by 13% for A/H1N1 strains, and was well-tolerated	High vs. standard dose
Influenza (trivalent)	Leibovici (2021) [45]	41,313 adults (3)	Older adults ≥65 years and IC	24% decreased risk of laboratory-confirmed influenza for high-dose (60 mcg) vs. low-dose (15 mcg) vaccine	High dose (4×) trivalent vaccine
Influenza	Zhang (2018) [51]	2015 adults (13)	HIV	Adjuvanted 7.5 mcg booster and 60 mcg single vaccine strategies provided 2–3 times better seroconversion and seroprotection outcomes, than single 15 mcg vaccine	High dose (4×) vaccine; adjuvanted vaccine

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…n'empêche pas le discussion au cas/cas

	Main result	References
CDC	2009 H1N1, Severe influenza in critically ills, 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 ---- > **No benefit** on primary end-point except for Influenza B + no overall difference in clinical outcome (02, H°, ICU)	1. Lee N, et al. A prospective intervention study on higher-dose oseltamivir treatment in adults hospitalized with Influenza A and B infections. Clin Infect Dis 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. BMJ 2013;346:f3039
Critically ill patients	Primary end-point: difference in ICU-free days **---- > No benefit**	Welch SC et al. High-dose *vs.* standard dose oseltamivir for treatment of severe influenza in adult ICU patients. Int Care Med 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 **2000- to 4000-fold higher** than the 50 % MIC for H1N1 isolates	Ariano RE et al. Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza. CMAJ 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 ?

Plutôt **non**, 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

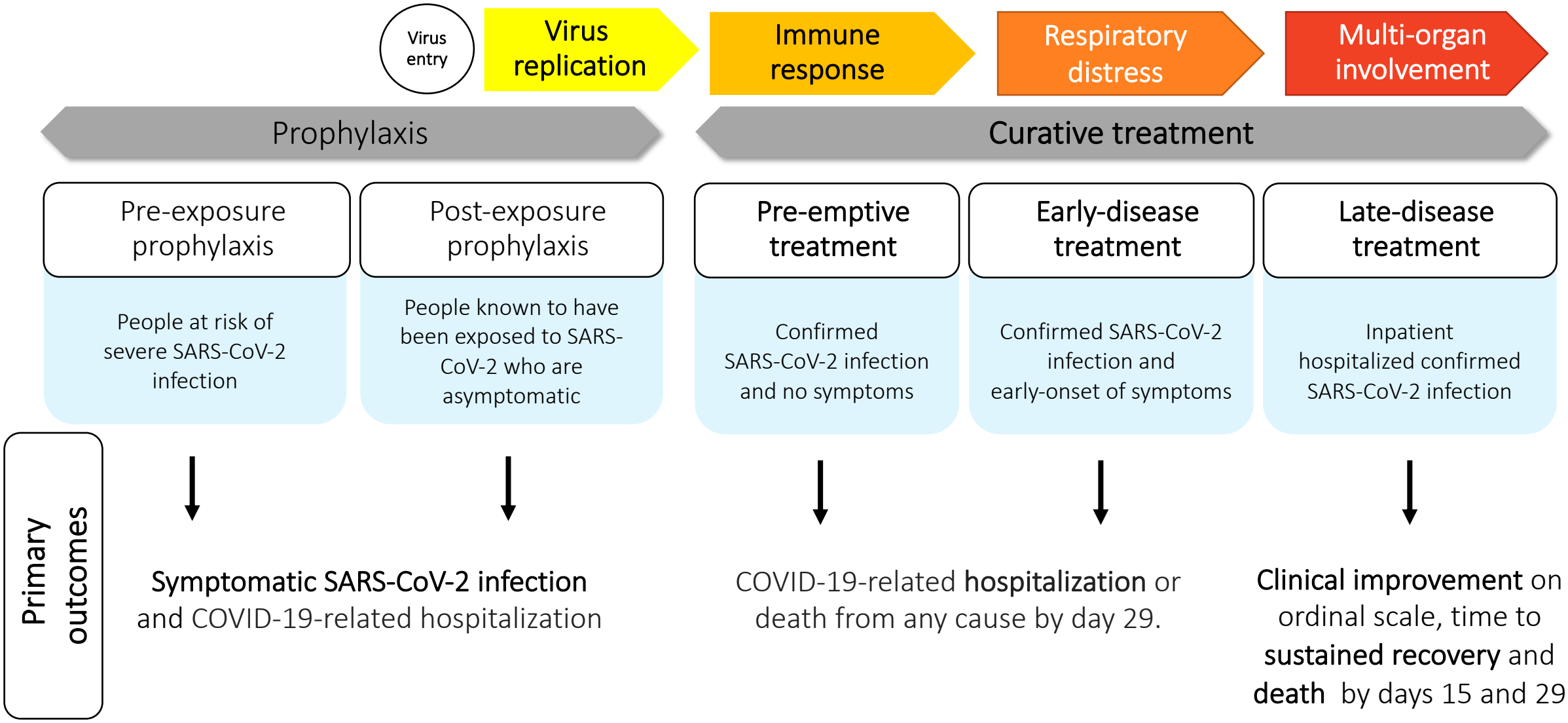
Combination therapy with amantadine, oseltamivir and ribavirin for influenza A infection: safety and pharmacokinetics

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

SARS-CoV-2, en bref



Antiviral treatments approved or under conditional authorization or « accessible » through emergency use authorization

Passive immunotherapy

Neutralizing monoclonal antibodies

Polyclonal convalescent plasma

Direct-acting antivirals

Remdesivir
Nirmatrelvir/rtv

Our daily life with COVID-19…

Choosing antiviral treatments…

…for at risk or at very high-risk patients for progression to severe Covid-19…

… basing our decision on the results of randomized clinical trials :

--- > which included very few of these subsets of patients,

--- > which were performed when another variant was prominently circulating,

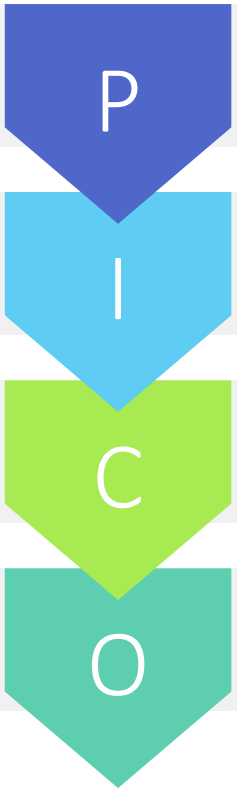
--- > which did not include vaccinated patients for most of them…

… and dealing with drug shortage, managing drug-to-drug adverse events, organizing outpatient circuits, etc…

Striking the balance between evidence-based and experience-based…

Remdesivir among hospitalized COVID-19 patients

IPDMA = Individual Patient Data Meta-Analysis



RCTs (unpublished or published, any format, in any language) that randomized adult patients (16 years or older) hospitalized with COVID-19

Remdesivir (any dose, any duration)

No Remdesivir (usual care as defined by the local context, +/- placebo)

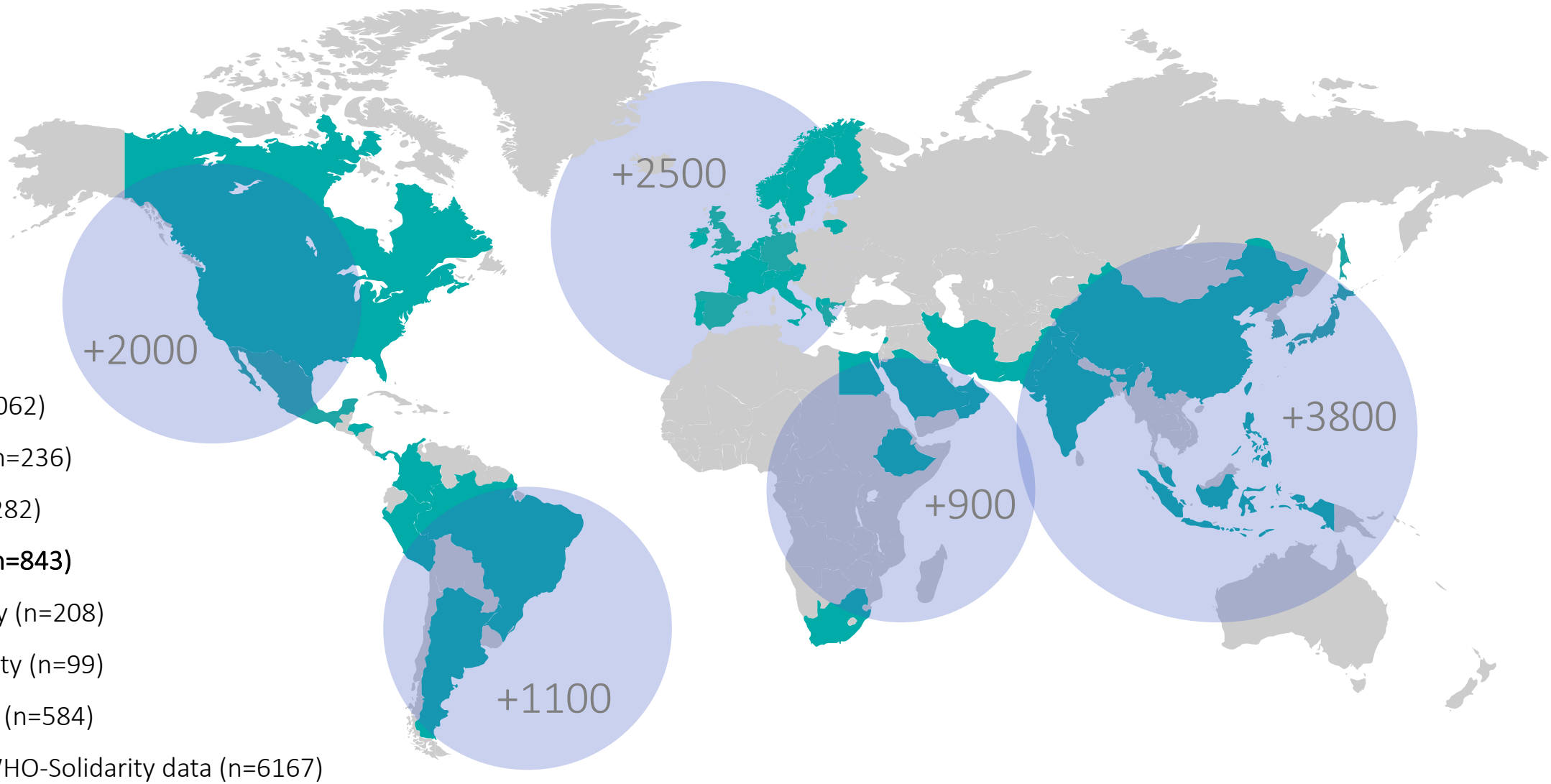
Primary outcome: Mortality at day 28 after randomization (in- and out-of-hospital data)

Do patients hospitalized with COVID-19 benefit from remdesivir – and if – who in particular?

Amstutz A, et al., Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials. Lancet Respir Med. 2023 Feb 21:S2213-2600(22)00528-8

n=10480

=> 99% of all eligible IPD globally, i.e., 99% of all patients that were ever randomized to remdesivir



ACTT-1 (n=1062)

Wang et al (n=236)

CATCO (n=1282)

DisCoVeRy (n=843)

FIN-Solidarity (n=208)

NOR-Solidarity (n=99)

Spinner et al (n=584)

Additional WHO-Solidarity data (n=6167)

For patients receiving no or only low-flow oxygen at treatment start

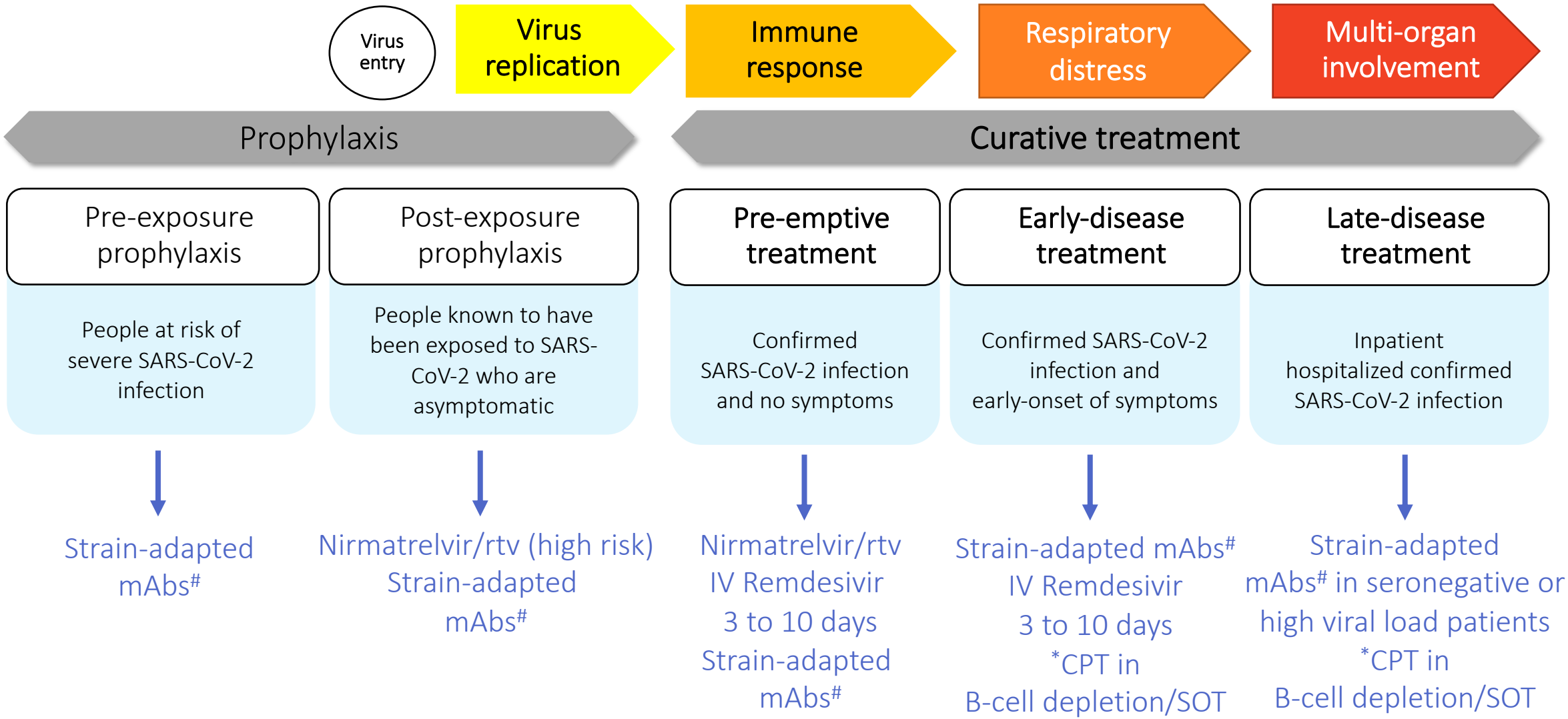
Outcome	Study Results and Measurements	Absolute Effect Estimates [a]		Certainty in Effect Estimates (Quality of Evidence)	Summary
		Remdesivir	No Remdesivir		
All-cause mortality at day 28	**aOR 0.80 (0.70-0.93)** Based on data from 8632 patients from 8 trials	92 per 1000	112 per 1000	**High**	**Remdesivir reduces 28-day mortality in this patient subgroup**
		Absolute Difference: 20 fewer per 1000 (95% CI, 31 fewer to 7 fewer); NNT 50 / If ACR [a] 2.5%: NNT 205			
New mechanical ventilation or death at day 28	**aOR 0.78 (0.69-0.87)** Based on data from 8662 patients from 8 trials	155 per 1000	190 per 1000	**High**	**Remdesivir reduces progression to mechanical ventilation or death**
		Absolute Difference: 35 fewer per 1000 (95% CI, 51 fewer to 21 fewer)			
Days until discharge/ reaching discharge criteria up to day 28	**aHR 1.02 (0.98-1.07)** Based on data from 8737 patients from 8 trials	7 (median)	7 (median)	Moderate[b]	Remdesivir probably has little or no effect on days until hospital discharge
		Absolute Difference: 0 day less (95% CI, 0 to 1 day more)‡			
Adverse event grade 3 or 4 or serious adverse event within 28 days	**aOR 0.82 (0.68-0.99)** Based on data from 2810 patients from 6 trials	214 per 1000	249 per 1000	Moderate[c]	Remdesivir probably reduces the risk of severe and serious adverse events
		Absolute Difference: 35 fewer per 1000 (95% CI, 65 fewer to 2 fewer)			

[a] Assumed control risks (ACR): weighted mean baseline risk across all trials. Alternative ACR for in-hospital mortality (2.5%) based on recent data (May 2022) from CDC
[b] Outcome was rated down for risk of bias
[c] Outcome was rated down for inconsistency

---- > For patients receiving more respiratory support: **Remdesivir may have little or no effect, inconclusive**

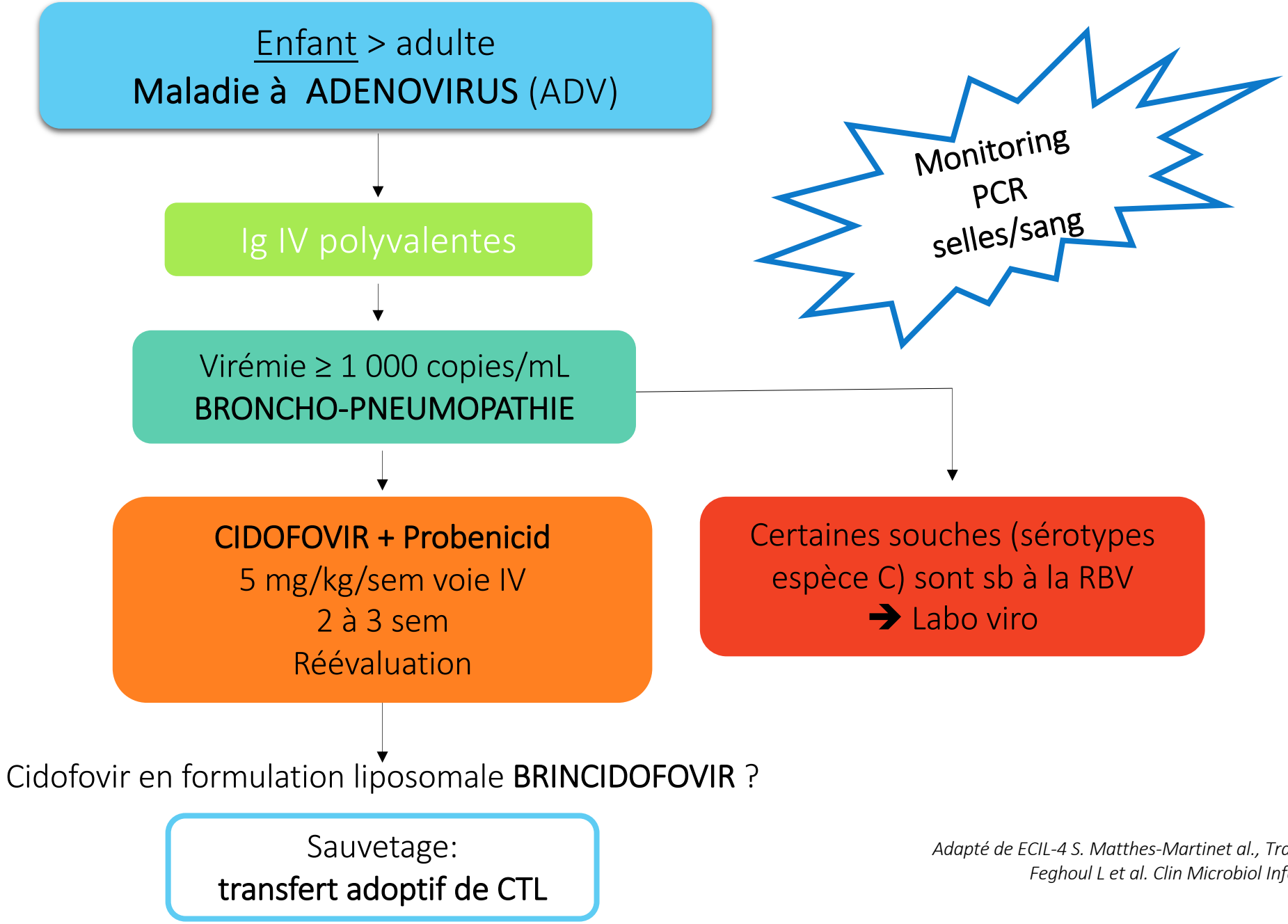
Amstutz A, et al., Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials. Lancet Respir Med. 2023 Feb 21:S2213-2600(22)00528-8

Summary antivirals



if a dominant-strain mAbs is/are available for use

*Possible alternative in case of inaccessibility/unavailability of mAbs



Adapté de ECIL-4 S. Matthes-Martinet al., Tranplant Infect Dis 2012
Feghoul L et al. Clin Microbiol Infect 2015; 21: 701–709

Merci tous…