26es JNI 2025 TOURS
et la région Centre - Val de Loire VINCI
Journées Nationales d'infectiologie
du mercredi 11 juin 2025 au vendredi 13 juin 2025
Journée Nationale de Formation des Paramédicaux en Infectiologie
Jeudi 12 juin 2025

Session en partenariat avec la SFM

Transplantation: existe-t-il encore un risque infectieux

Infections respiratoires virales chez les transplantés (hors SARS-CoV-2)

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Lyon HémInf Study group

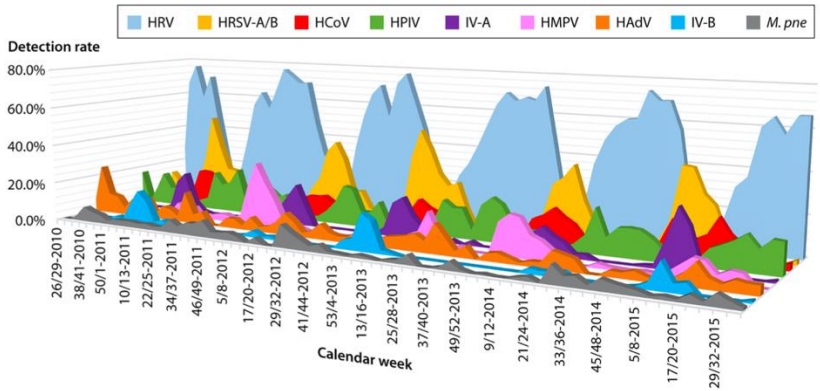
Déclaration de liens d'intérêt avec les industriels de santé
en rapport avec le thème de la présentation (loi du 04/03/2002) :

- Intervenant : ADER Florence
- Titre : Infections respiratoires virales chez les transplantés

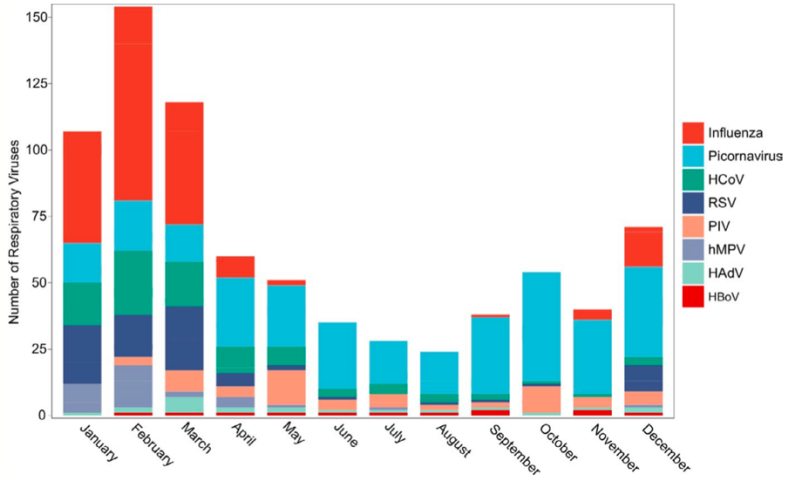
- Consultant ou membre d'un conseil scientifique **NON**
- Conférencier ou auteur/rédacteur rémunéré d'articles ou documents **NON**
- Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations **NON**
- Investigateur principal d'une recherche ou d'une étude clinique **NON**

Community-acquired respiratory virus (CARV)

General population



Solid organ transplantation

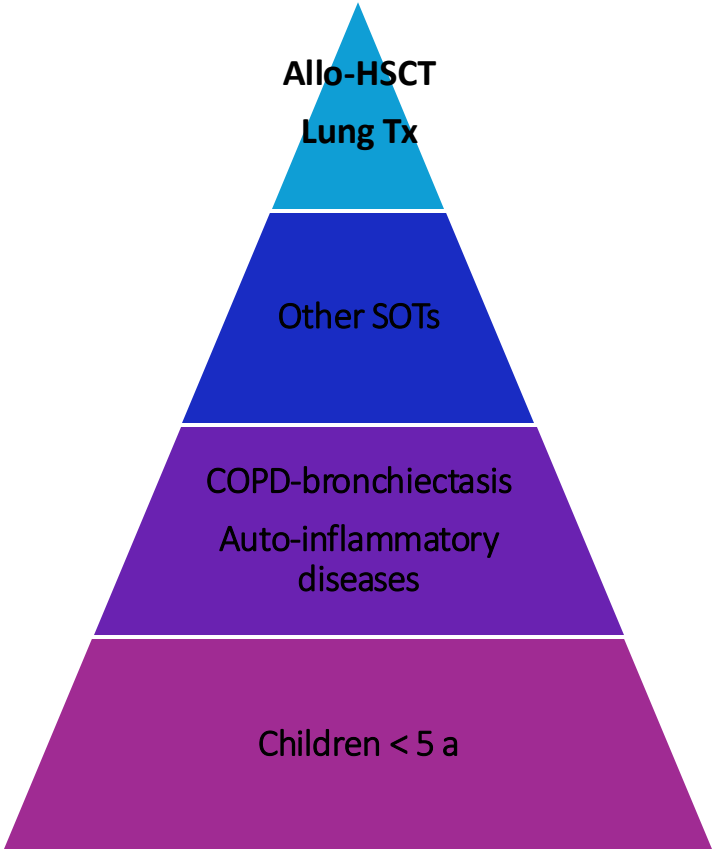


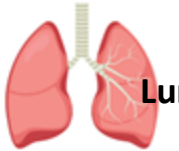
Similar seasonality	
Fall ---- > winter	Influenza virus A/B, RSV, Metapneumovirus
Spring, summer --- > fall	Picornavirus/Rhinovirus, CoV, Parainfluenza virus

Ison MG, Hirsch HH. Clin Microbiol Rev 2019. doi: 10.1128/CMR.00042-19
Jain S,; CDC EPIC Study Team. N Engl J Med. 2015. doi: 10.1056/NEJMoa1500245
Mombelli M, et al; Swiss Transplant Cohort Study. Am J Transplant. 2021. doi: 10.1111/ajt.16383.

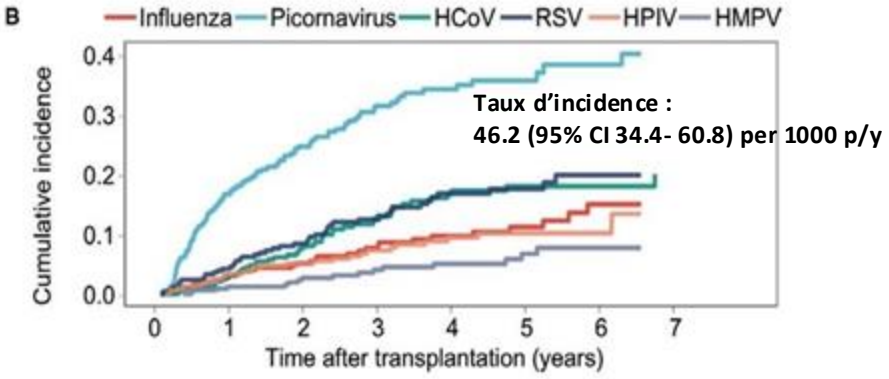
Highest impact

Lowest impact





Lung Tx – Overall post-transplant survival **6.2 y**

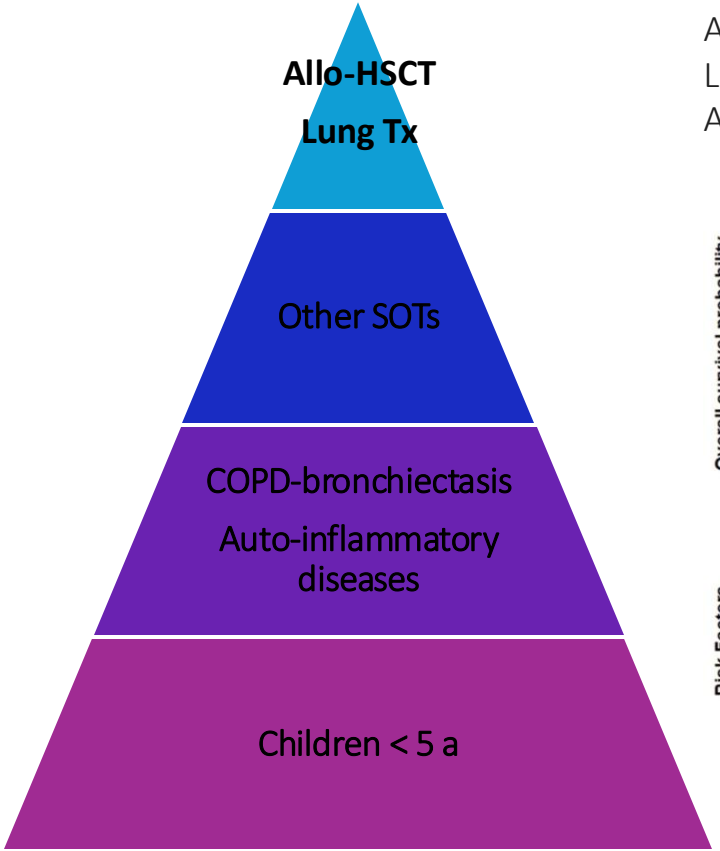


Allograft rejection

Bronchiolitis obliterans/chronic lung allograft dysfunction

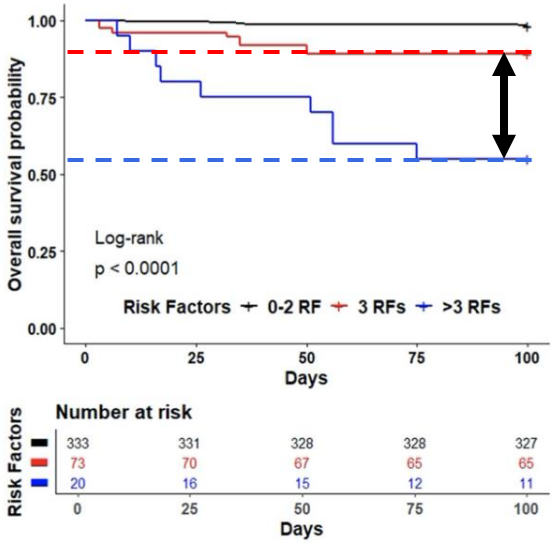
Ison MG, Hirsch HH. Clin Microbiol Rev 2019. doi: 10.1128/CMR.00042-19
Mombelli M, et al; Swiss Transplant Cohort Study. Am J Transplant. 2021. doi: 10.1111/ajt.16383
van der Mark SC, et al. Eur Respir Rev. 2020. doi: 10.1183/16000617.0132-2019

Highest impact



Lowest impact

Allo-HSCT, n= 426 – 1070 CARV episodes
Lower RTD progression rate = 26%
All-cause mortality rate at day 100 = 5%



Overall survical at day 100 after CARV detection in allo-HSCT recipients with lower RT disease according to risk factors :

- Donor/recipient HLA mismatch
- CST use
- GvHD
- ALC < 0.1
- Neutropenia
- Age ≥ 40y

Piñana JL, et al. Clin Infect Dis. 2024 doi: 10.1093/cid/ciae602

Highest impact

Allo-HSCT

Lung Tx

Other SOTs

COPD-bronchiectasis

Auto-inflammatory diseases

Children < 5 a

Lowest impact

→ Key factors influencing net immune status

Highest impact

Allo-HSCT

Lung Tx

Other SOTs

COPD-bronchiectasis

Auto-inflammatory diseases

Children < 5 a

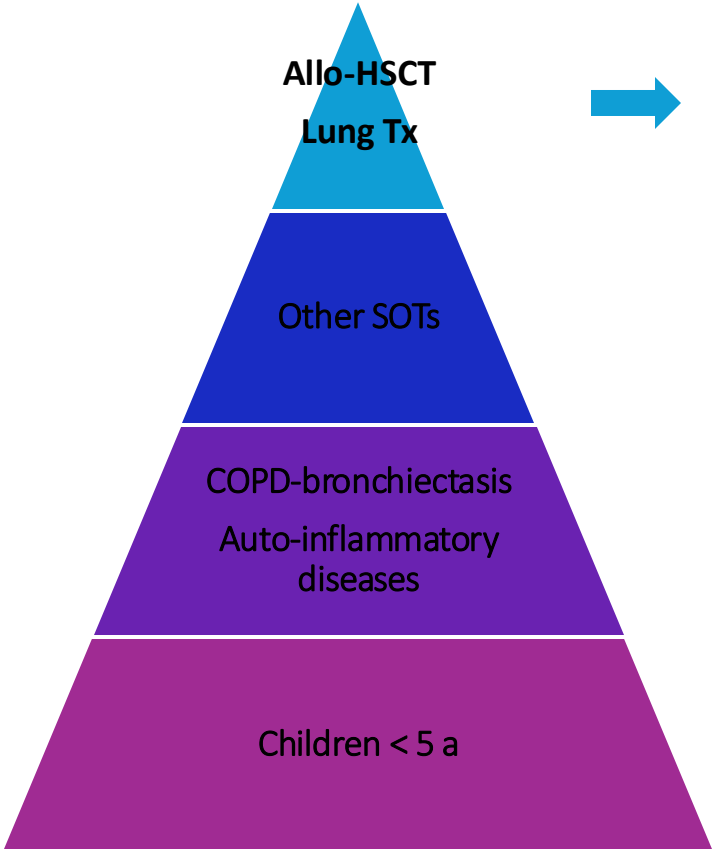
Lowest impact

<u>At transplantation</u>

Age (threshold 40 yr)
Multiple transplants
End-organ disease
Malnutrition
Conditioning
Graft source
Related *vs*. unrelated (HLA mismatch)
Receipt of lympho-depleting agents

Highest impact

Lowest impact

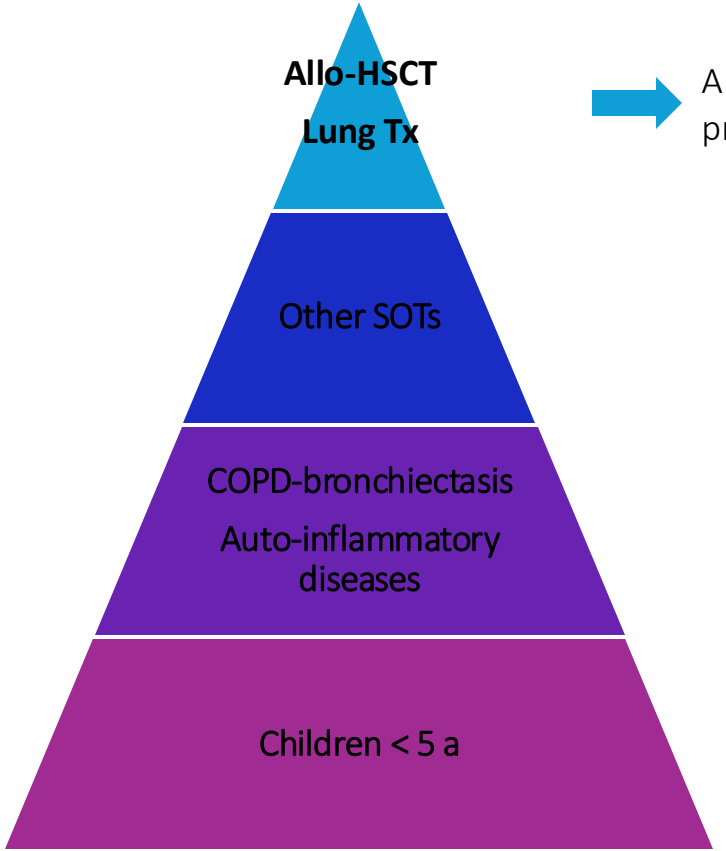


Post-transplantation

Age and malnutrition
IS regimen <---> anti-donor/graft immunity
Hypogammaglobulinemia (HSCT)
Slow/poor immune reconstitution

Noell BC, et al. Transplant Proc. 2013. doi: 10.1016/j.transproceed.2012.11.010

Highest impact



Lowest impact

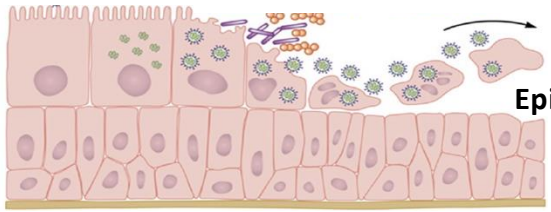
Allo-HSCT with CARV (RSV, PIV, MTPv and Influenza A/B) at risk for progression from upper RTI to lower RTD

Allo-HSCT – Immunodeficiency Scoring Index	
Criterion or parameter	
Neutropenia, <0.5x10^9 /L	3
Lymphopenia, <0.2x10^9 /L	**3**
Myeloablative conditioning	1
Pre-engraftment or allo-HCT < 1 month	1
GvHD (acute/chronic)	1
Corticosteroids	1
Age, > 40 yr	2
Maximal	12

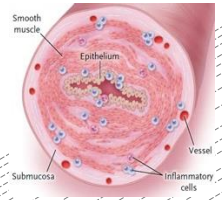
Stratification	
Low risk	0-2
Moderate risk	3-6
High risk	7-12

+ multiple transplants

Houist AL, et al. Bone Marrow Transplant. 2021 doi: 10.1038/s41409-021-01462-z
Shah DP, et al. Blood 2014. doi: 10.1182/blood-2013-12-541359
Ogimi C, et al. Bone Marrow Transplant. 2022 doi: 10.1038/s41409-022-01575-z.
Micó-Cerdà M at al. Transplant Cell Ther. 2025 doi: 10.1016/j.jtct.2025.02.012.



Long viral shedding



Bronchiolitis obliterans (BOS) syndrome
Chronic lung allograft dysfunction (CLAD)
Chronic GvHD

Epithelial cell necrosis

Peribronchial infiltrates

Mucus plugging

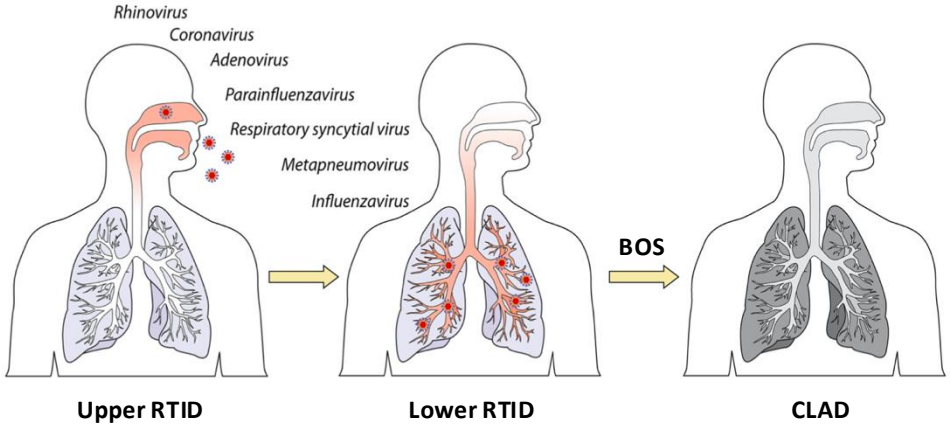
Lymphopenia => defect in :

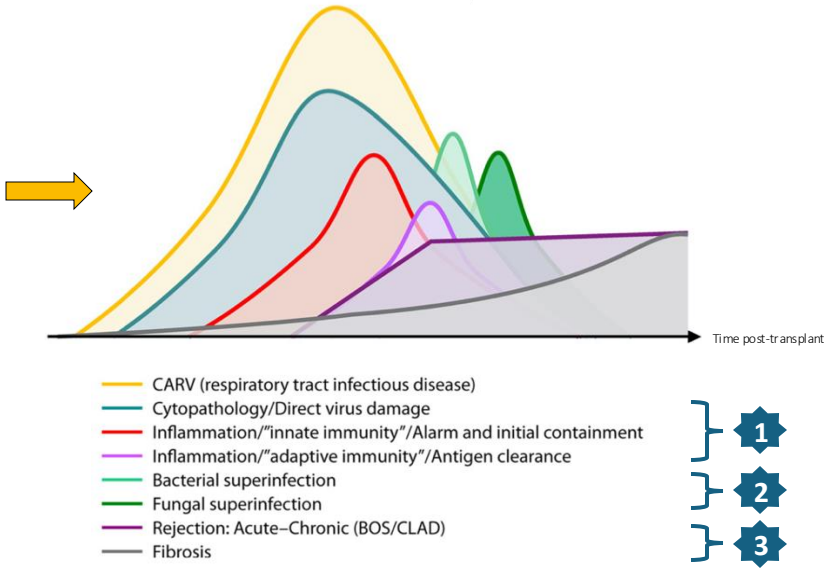
1. $CD4^+$ T cell-driven coordinated adaptive response
2. T/B cooperation --- > less high-affinity nAb --- > less ADCC
3. Cytotoxic T cell $CD8^+$ activity ---- > less cytolysis of infected cell and less viral clearance

Immune unbalance toward allo-immunity

Hypoxia^{++}

Adapted from various sources :
Griffiths C, Drews SJ, Marchant DJ. Clin Microbiol Rev 2017. doi: 10.1128/CMR.00010-16
Barker AF et al. New Eng J Med 2014. doi: 10.1056/NEJMra1204664
Janeway's Immunobiology. Kennet Murphy. 10th edition, 2022. Taylor & Francis





Adapted from various sources :Ison MG & Hirsch HH. Clin Microbiol Rev 2019. doi: 10.1128/CMR.00042-19

Diagnosis work up

Direct antigen detection (DAD) = lower sensitivity compared to CARV-NAT and reduced specificity in low prevalence setting, but if used for rapid (self-) testing, the result should be discussed with referent physician to evaluate the consequences for care including the need of early antivirals or for confirmation by NAT. **AII**

ENT symptoms/cough/fever

Naso-pharyngeal swab

Negative NPS – highly suggestive

BAL fluid

Nucleic acid testing (NAT) AII

Multiplex NAT kit (RhinoV, Influenza A/B, RSV, CoV, …)

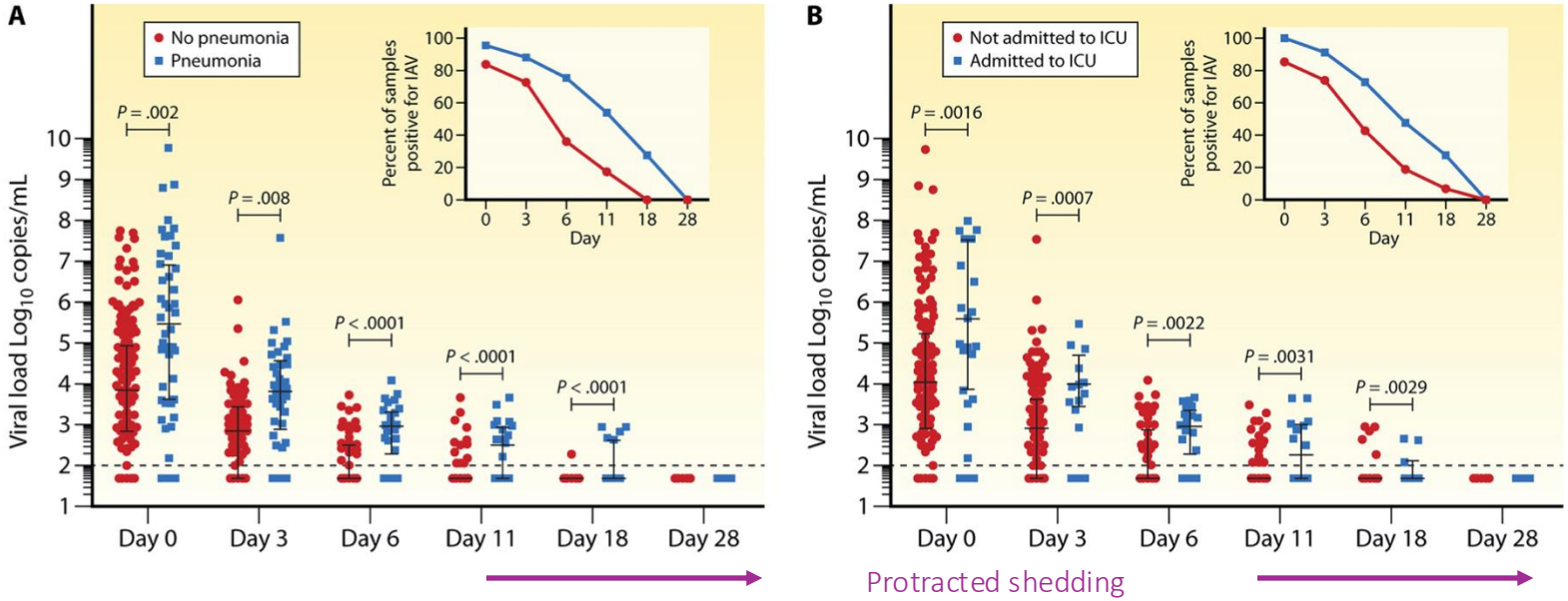
Turn-round time **< 2 hours** are preferred

(Semi-)quantitative NAT => [Cycle threshold] CIII

Center-dpdt – can be considered to follow the course of viral replication

Adapted from ECIL10 Sept 2024 update of 2019 guidelines https://www.ecil-leukaemia.com/en/resources/resources-ecil

5 consecutive influenza seasons
n=616 transplant recipients with influenza
Solid organ transplant, n=477 and HSCT recipients, n=139



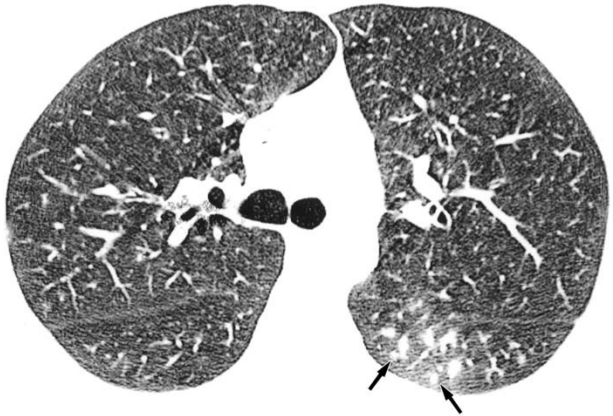
Adapted from Kumar D, et al. A 5-year prospective multicenter evaluation of influenza infection in transplant recipients. Clin Infect Dis 2018; 67:1322–1329. https://doi.org/10.1093/cid/civ294
Ison MG, Hirsch HH. Clin Microbiol Rev 2019. doi: 10.1128/CMR.00042-19

Imagery work up -----> [HR] CT scan

Patches of **ground glass opacities**

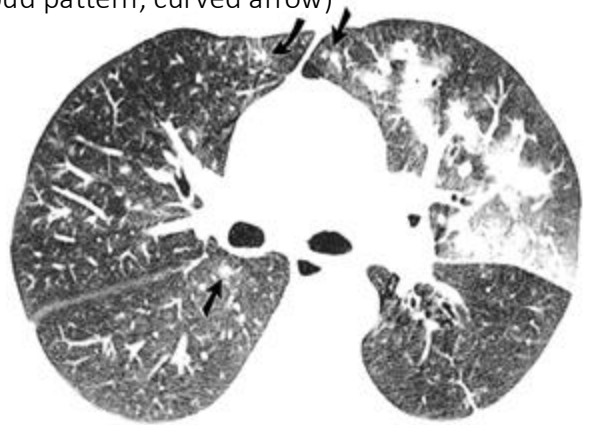
Airway inflammatory changes such as **tree-in-bud opacities** (20-50%), **bronchial wall thickening** (30-70%), **centrilobular nodules** (35-60%) and **peribronchiolar consolidation** (~ 50%) are associated with CARV LRTD.

Multifocal consolidation is commonly found in cases of CARV LRTD but is **non-specific**.



Centrilobular nodules (arrows) and adjacent ground-glass opacities

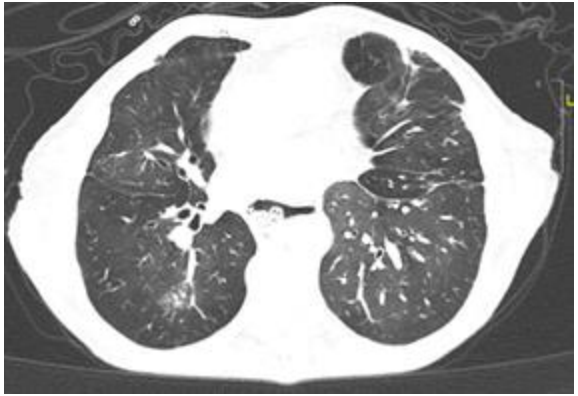
Centrilobular branching nodular opacities (tree-in-bud pattern, curved arrow)



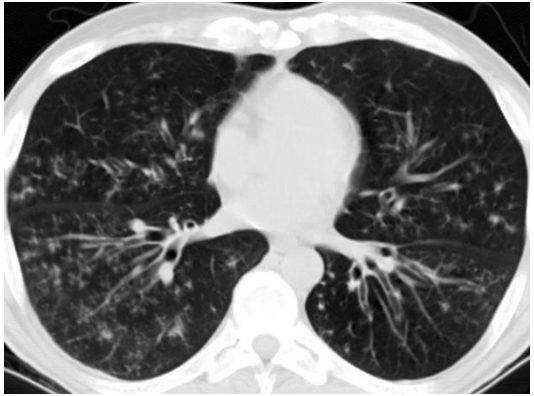
Ground-glass opacities and dense focal areas of consolidation

Centrilobular nodules (straight arrows)

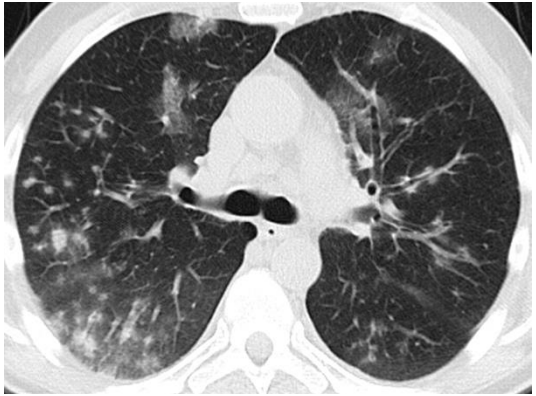
Gasparetto et al. AJR Am J Roentgenol. 2004 doi: 10.2214/ajr.182.5.1821133
Miller WT Jr et al. J Comput Assist Tomogr. 2011 doi: 10.1097/RCT.0b013e31821d6cd3
Kim MC, et al. Medicine (Baltimore). 2016 doi: 10.1097/MD.0000000000004003



Lung Tx – RSV LRTD

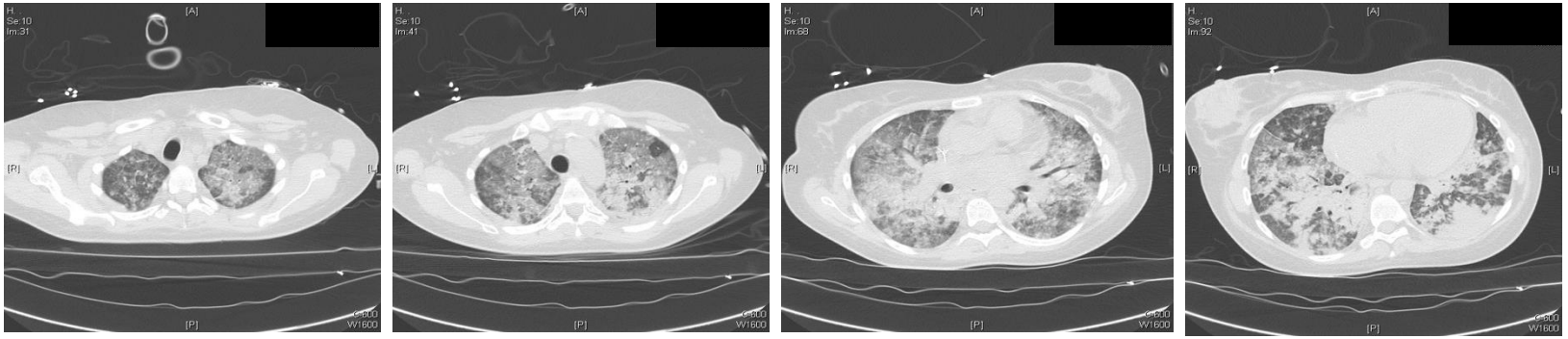


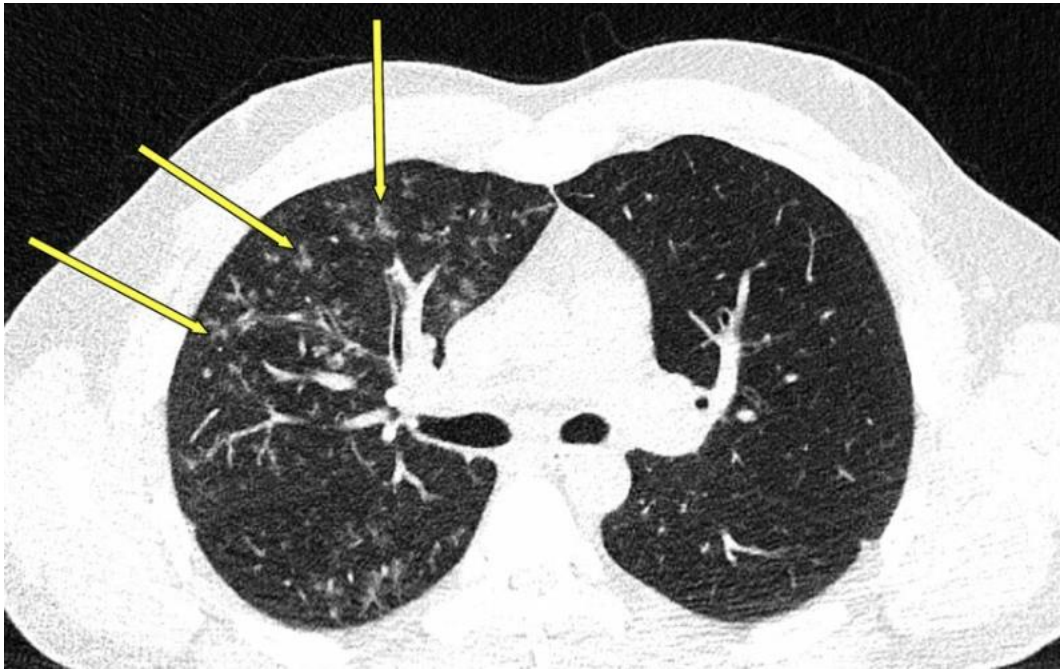
Allo-HSCT – Influenza LRTD



Allo-HSCT – RSV LRTD

Allo-HSCT day 10 post-transplantation – RSV ARDS





Drst, Lukas, Fehr, Thomas, Cusini (2022). Infections à Mycoplasma pneumoniae

Upper respiratory tract infection (URTI)

- detection of repiratory virus in a respiratory sample

AND

- at least one of: new onset of cough, or sore throat, or shortness of breath, or coryza, or fever , or nasal congestion

AND

- clinician judgement that the illness was due to the infection

AND

- no criteria for lower respiratory tract disease (LRTI)

Lower respiratory tract disease (LRTD)

- detection of respiratory virus in a respiratory sample

AND

- at least one of: new onset of cough, sore throat, shortness of breath, coryza, or fever

AND

- clinician judgement that the illness was due to the infection

AND

- at least one of:

✓ hypoxia defined as oxygen saturation <90% or need for supplemental oxygen, or

✓ radiologic infiltrate, or

✓ detection of respiratory virus in a lower respiratory tract sample

Who to treat ?

Upper respiratory tract infection (RTI) at high-risk of progression to lower RT disease (20-30%)

Determinants of decision making

Type of transplantation [Allo-HSCT, lung Tx]
Time after transplantation
IS regimen
GvHD/rejection
Lymphopenia/neutropenia

Timing of decision

Treat ALL lower RT diseases

Therapeutic options in high-risk transplant settings

DIRECT-ACTING ANTIVIRALS

?

IMMUNOGLOBULINS

?

CORTICOSTEROIDS

?

VIRUS-SPÉCIFIC mAbs

Data on adjuvant treatments: IV Igs or corticosteroids

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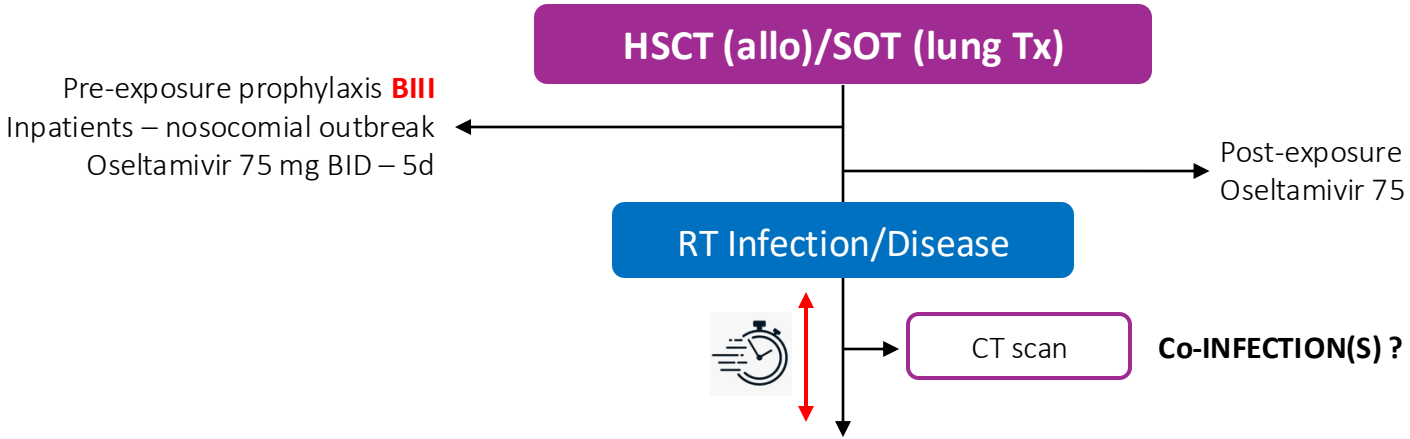
DOI: 10.1111/tid.14142

EDITORIAL

TRANSPLANT INFECTIOUS DISEASE

The role of systemic steroids in lung transplant recipients with community-acquired respiratory viruses: Time for a moratorium, or not?

Influenza : therapeutic algorithm



1st line : oseltamivir* 75 mg BID 5 ---- > 10d **BIII**
Severe LRTD from the start : consider 150 mg BID **CIII**

2d lines = 2 scenarii
- Severe LRTD prolonged : consider + baloxavir **BIII**
- Impaired gastro-intestinal absorption/no oral ingestion : switch to IV zanamivir or peramivir if available **CIII**

NAT monitoring
Genotypic resistance testing

* Full dose oseltamivir 75 BID > 40 kgs

Kumar et al. Clin Infect Dis. 2018 doi: 10.1093/cid/ciy294
Adapted from ECIL10 Sept 2024 update of 2019 guidelines https://www.ecil-leukaemia.com/en/resources/resources-ecil

Inactivated Influenza Vaccine (IIV)

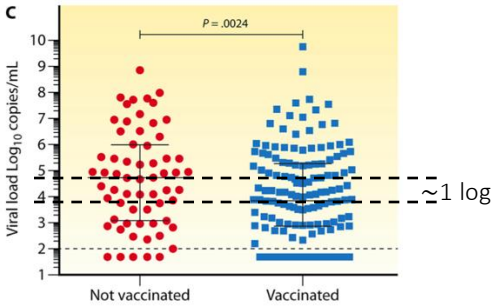
Risk Factor	No.	Pneumonia (n = 134)	No Pneumonia (n = 472)	*P* Value (Univariate)	Multivariate OR (95% CI)	*P* Value (Multivariate)
Influenza vaccination in the same season	543	63/119 (52.9)	306/416 (73.6)	**<.001**	0.34 (.21–.55)	**<.001**

Annual seasonal **IIV** is recommended to be given at the beginning of influenza season for all patients at **3 to 6 months** post-transplant. **AII**

Vaccination should be continued on a yearly basis. **AII**
+ vaccinations of **household individuals**

High-dose trivalent IIV-A/B is recommended for **allogeneic** HSCT-patients. **BI**

A **2nd dose after 4 weeks** may have a benefit **BIII** and should be considered in patients with **severe GvHD**, **low lymphocyte counts**, or during a prolonged **community outbreak**.



Kumar et al. Clin Infect Dis. 2018 doi: 10.1093/cid/ciy294
Ison MG, Hirsch HH. Clin Microbiol Rev 2019. doi: 10.1128/CMR.00042-19
Adapted from ECIL10 Sept 2024 update of 2019 guidelines https://www.ecil-leukaemia.com/en/resources/resources-ecil

STOP Flu Trial

Target population = **SOT**

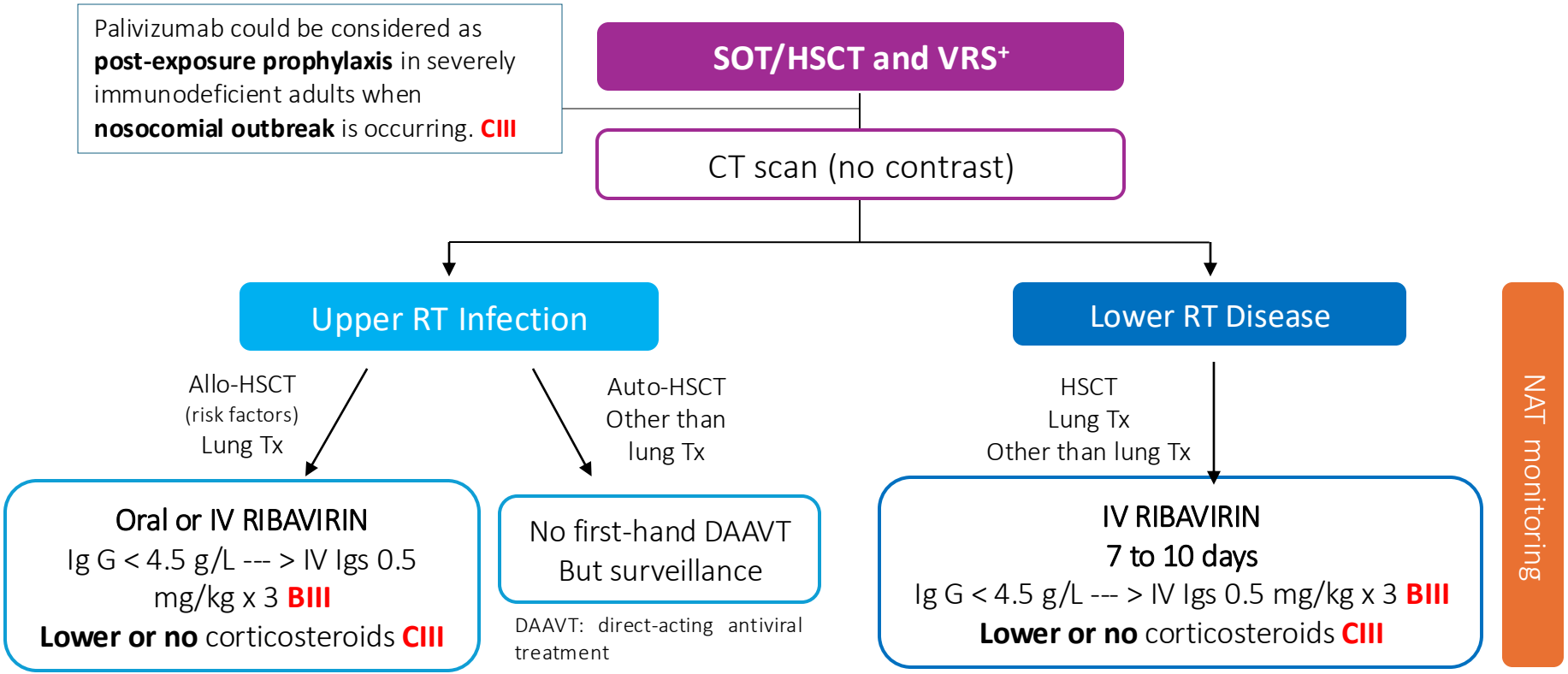
High-dose *vs* MF59-**adjuvanted** *vs* **standard** influenza vaccine – 1:1:1

Primary outcome : **vaccine response rate at day 28** = > proportion of seroconversion for at least 1 viral strain (at least 4-fold increase of HAI titer from baseline)

	Vaccine Response Rate	Risk Difference	*P* Value
High-dose and MF59-adjuvanted versus standard vaccine[a]	63% (251/400) versus 42% (84/198)	0.20 (97.5% CI, .12–1)	<.001
High-dose versus standard vaccine[a]	66% (129/195) versus 42% (84/198)	0.24 (95% CI, .16–1)	<.001
MF59-adjuvanted versus standard vaccine[b]	60% (122/205) versus 42% (84/198)	0.17 (97.5% CI, .08–1)	<.001
High-dose versus MF59-adjuvanted vaccine[b]	66% (129/195) versus 60% (122/205)	0.07 (95% CI, −.01 to 1)	.085

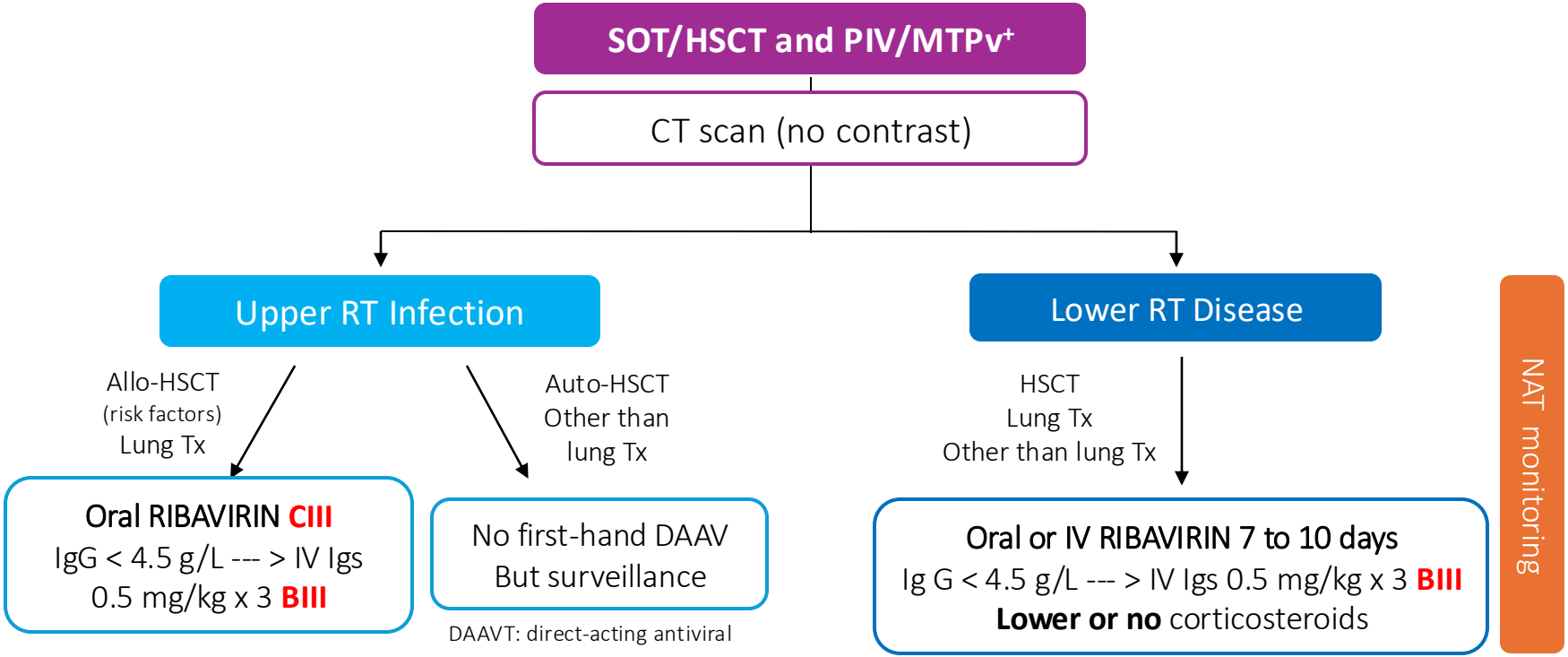
Mombelli M et al. Clin Infect Dis. 2024 doi: 10.1093/cid/ciad477

RSV : therapeutic algorithm



ECIL10 Sept 2024 update of 2019 guidelines https://www.ecil-leukaemia.com/en/resources/resources-ecil

PIV and MPV : therapeutic algorithm



ECIL10 Sept 2024 update of 2019 guidelines https://www.ecil-leukaemia.com/en/resources/resources-ecil

Ribavirin (RBV): 1972 !! Guanosine analogue

Bio-availibility **45-65%**

Ingestion with **fat meal** : bio-availibilty optimization **x 1.5**

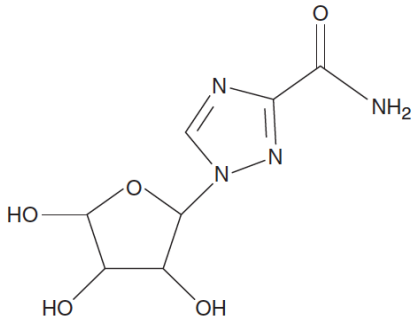
Important but slow **tissular diffusion index**, CNS included

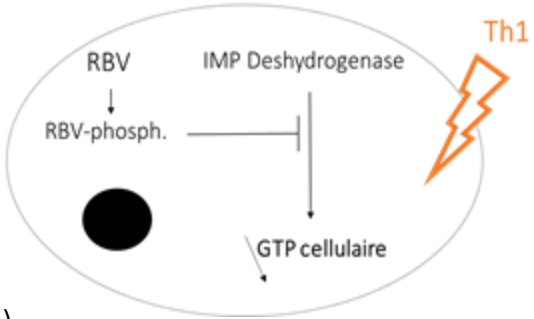
Long half-life = **150h** (1 dose) up to **300h** (cumulative doses)
---- > **loading dose**

Drug clearance dpdt on :

- **weight** (adaptation dose/weigth)
- **renal function**

<u>No</u> hepatic metabolization = no dose adaptation (end-stage liver diseases)





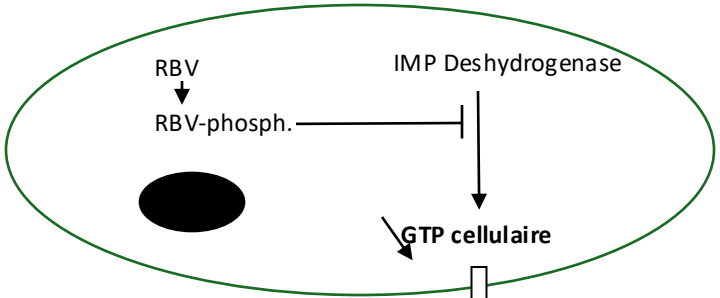
Naik GS & Tyagi MG. J Clin Exp Hepatol. 2012 doi: 10.1016/S0973-6883(12)60090-5

Use of systemic ribavirin for RTI/D with RSV, PIV, and MPV

Treatment course	Description
Oral or intravenous ribavirin maximal dosing at 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
Oral or intravenous administration according renal function	Dose for a creatinine clearance of 30 to 50 ml/min: a maximum of 200 mg every 8 h For a creatinine clearance of 10 to 30 ml/min, no dose recommendation can be given[b]

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

Ison MG, Hirsch HH. Clin Microbiol Rev 2019. doi: 10.1128/CMR.00042-19
ECIL10 Sept 2024 update of 2019 guidelines https://www.ecil-leukaemia.com/en/resources/resources-ecil

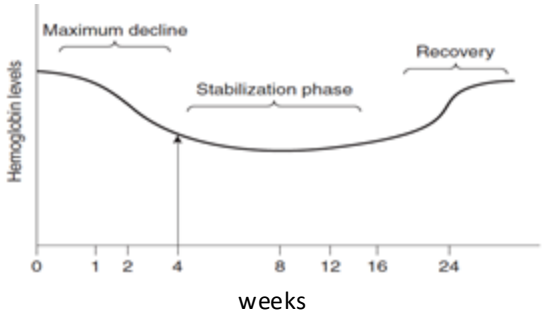


Anemia (11-35%)
Hemolytic anemia (10-13%)
Neutropenia (8-40%)
Lymphopenia (14%)
MOSTLY IF >14 days

Contre-indication pendant la grossesse

Anémie hémolytique dose-dpdte et réversible

Déplétion GTP et ATP
Acidose lactique



Chaer et al. Transpl Cell Ther, 2023
Riner A et al. Postgraduate Medicine 2009; 121:3, 5-15
Gross AE et al. Annals of Pharmacotherapy 2015; 49(10) 1125–1135

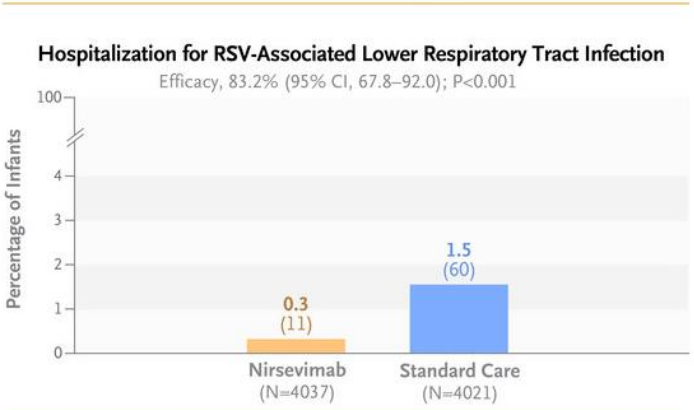
Prophylactic anti-RSV mAbs in high-risk adult transplant recipients ?

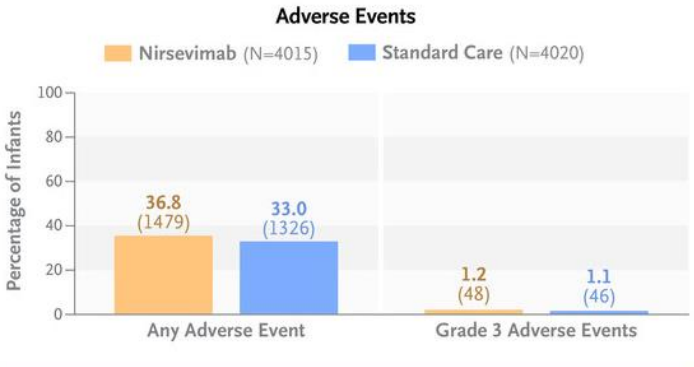
Randomized Controlled Trial > N Engl J Med. 2023 Dec 28;389(26):2425-2435.
doi: 10.1056/NEJMoa2309189.

Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants

Simon B Drysdale [1], Katrina Cathie [1], Florence Flamein [1], Markus Knuf [1], Andrea M Collins [1], Helen C Hill [1], Friedrich Kaiser [1], Robert Cohen [1], Didier Pinquier [1], Christian T Felter [1], Natalya C Vassilouthis [1], Jing Jin [1], Mathieu Bangert [1], Karine Mari [1], Rapi Nteene [1], Sophie Wague [1], Michelle Roberts [1], Pierre Tissières [1], Simon Royal [1], Saul N Faust [1]; HARMONIE Study Group

Phase III, open label RCT
1:1 nirsevimab *vs* SoC



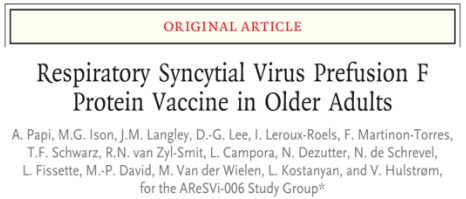


RSV vaccines

Nom, Fabricant	RSVpreF3-AS01, GSK	RSVpreF, Pfizer Inc	mRNA-1345, Moderna
Type de vaccin	Protéique recombinant, avec **adjuvant** AS01E	protéique recombinant, **bivalent** (A et B), sans adjuvant	**ARNm**
AMM FDA	50-59 ans « à risque » ≥60 ans	18-59 ans « à risque » ≥60 ans	≥60 ans
AMM EMA	50-59 ans « à risque » ≥60 ans	≥18 ans	≥60 ans
Disponible en France	✓	✓	✗
Remboursement	✗	✗	✗
Prix	libre, ≈200€	196,10€	✗

https://www.ema.europa.eu/en/documents/product-information/arexvy-epar-product-information_en.pdf
https://www.ema.europa.eu/en/documents/product-information/abrysvo-epar-product-information_en.pdf
https://www.ema.europa.eu/en/documents/product-information/mresvia-epar-product-information_en.pdf

International phase III RCT *vs* placebo, ≥60y, exclusion criteria = immunocompromised



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 Shrevel, L. Fissette, M.-P. David, M. Van der Wielen, L. Kostanyan, and V. Hulstrøm, for the AReSVi-006 Study Group*

ORIGINAL ARTICLE

Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults

E.E. Walsh, G. Pérez Marc, A.M. Zareba, A.R. Falsey, Q. Jiang, M. Patton, F.P. Polack, C. Llapur, P.A. Doreski, K. Ilangovan, M. Rämet, Y. Fukushima, N. Hussen, L.J. Bont, J. Cardona, E. DeHaan, G. Castillo Villa, M. Ingilizova, D. Eiras, T. Mikati, R.N. Shah, K. Schneider, D. Cooper, K. Koury, M.-M. Lino, A.S. Anderson, K.U. Jansen, K.A. Swanson, A. Gurtman, W.C. Gruber, and B. Schmoele-Thoma, for the RENOIR Clinical Trial Group*

ORIGINAL ARTICLE

Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults

E. Wilson, J. Goswami, A.H. Baqui, P.A. Doreski, G. Perez-Marc, K. Zaman, J. Monroy, C.J.A. Duncan, M. Ujiie, M. Rämet, L. Pérez-Breva, A.R. Falsey, E.E. Walsh, R. Dhar, L. Wilson, J. Du, P. Ghaswalla, A. Kapoor, L. Lan, S. Mehta, R. Mithani, C.A. Panozzo, A.K. Simorellis, B.J. Kuter, F. Schödel, W. Huang, C. Reuter, K. Slobod, S.K. Stoszek, C.A. Shaw, J.M. Miller, R. Das, and G.L. Chen, for the ConquerRSV Study Group*

		n LRTD VRS+	Vaccine efficacy
RSVPreF3 OA (adj.)	n = 24,966	47 (2S+ ou 3 S+)	82.6%
RSVpreF (biv.)	n = 34,284	44 (2S+)/16 (3S+)	66.7% (2S+)/85.7% (3S+)
mRNA-1345	n = 35,541	64 (2S+)/20 (3S+)	83.7% (2S+) / 82.4% (3S+)

Papi A, et al; AReSVi-006 Study Group. N Engl J Med. 2023 doi: 10.1056/NEJMoa2209604
Walsh EE, et al; RENOIR Clinical Trial Group. N Engl J Med. 2023 doi: 10.1056/NEJMoa2213836
Wilson E, et al; ConquerRSV Study Group. N Engl J Med. 2023 doi: 10.1056/NEJMoa2307079

Teasing : G2I – Dr. Anne Conrad

Audi Pierre de Ronsard (niveau +1)
Jeudi 12 juin
12h-13h15

SG03 • Session groupe G2I
Actualités thérapeutiques des infections chez l'immunodéprimé
Fanny LANTERNIER
Serge ALFANDARI
Anne COSTE
Benjamin GABORIT
Anne CONRAD

Tour d'horizon des approaches immuno-thérapeutiques contre le VRS : vaccins chez l'ID et mAbs

Conclusion

Prevention^{+++}/Education ---- > **what have we leaned from COVID-19 pandemics (??)**

Allo-HSCT/lung Tx

Frequency : RhinoV
Severity : influenza/RSV
Co-infections

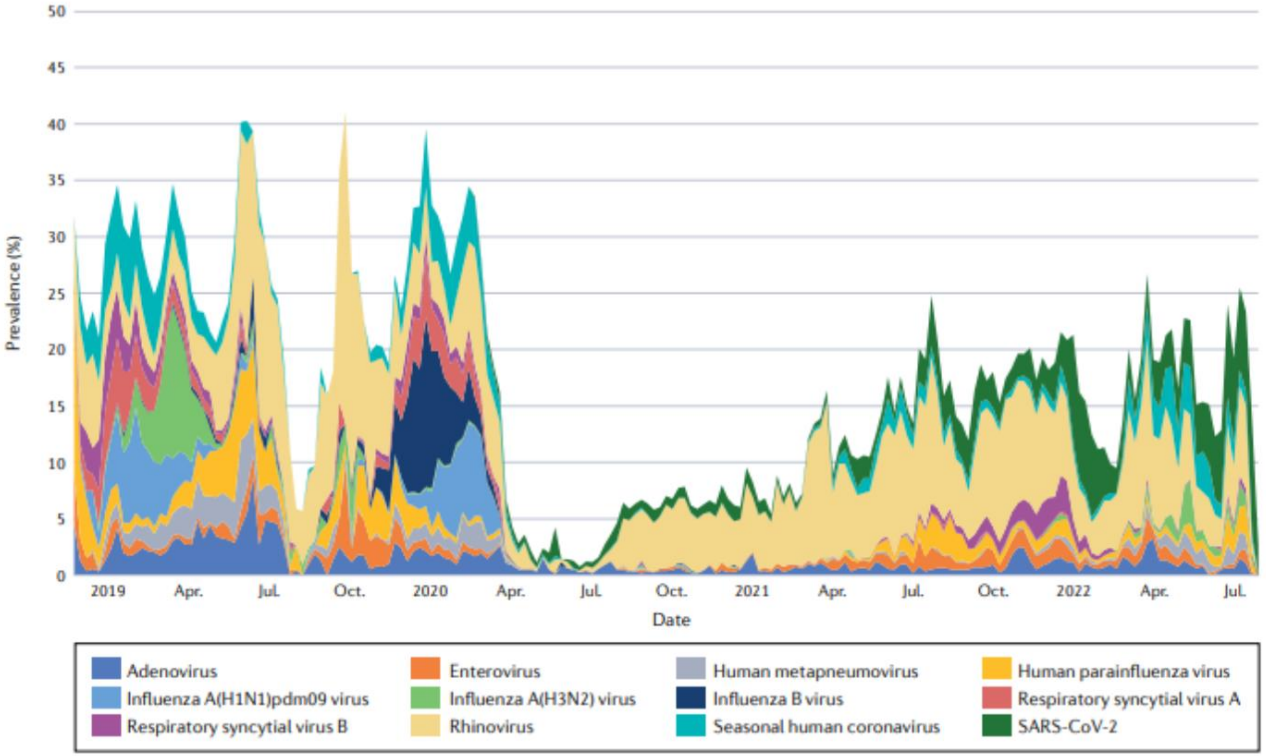
Proactive decision-making: risk factors + NAT + CT scan

Neuraminidase inhibitor/oseltamivir
Guanosine analogue/ribavirin

Influenza vaccine^{+++}
RSV vaccine ?
Prophylactic mAbs ?

Thanks

The effect of COVID-19 pandemics

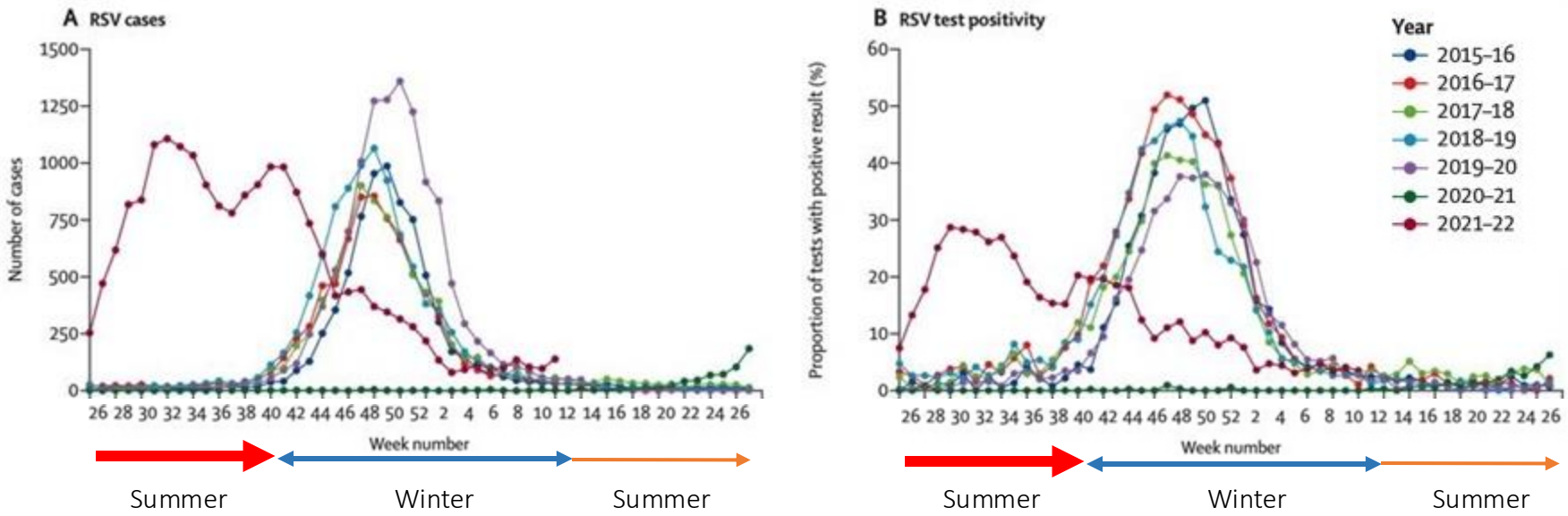


Less influenza and RSV infections

Less viral diversity

Chow EJ, Uyeki TM, Chu HY. The effects of the COVID-19 pandemic on community respiratory virus activity. Nat Rev Microbiol. 2023 doi: 10.1038/s41579-022-00807-9

Changes in seasonality during COVID-19 pandemics



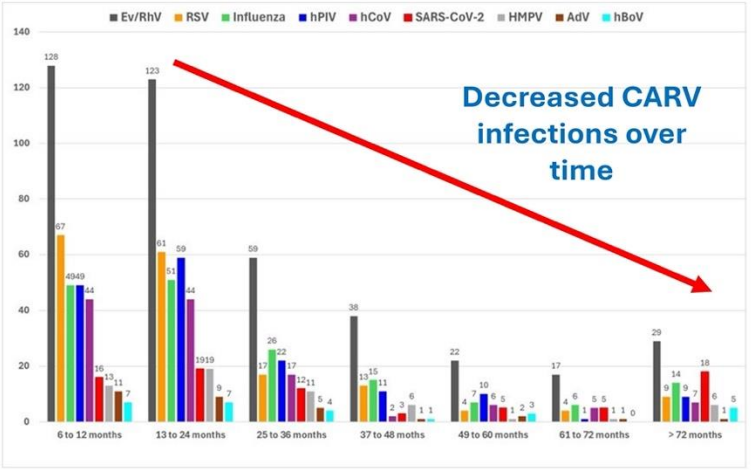
Strong decrease in RSV infections during 2020 -2021 winter

Peak during 2021-2022 summer

Bardsley M et al. Lancet Infect Dis, 2023

Community-Acquired Respiratory Virus Infections: A Threat to Long-Term survivors after Allogeneic Stem Cell Transplant?

Piñana J.L. et al, Clinical Infectious Disease

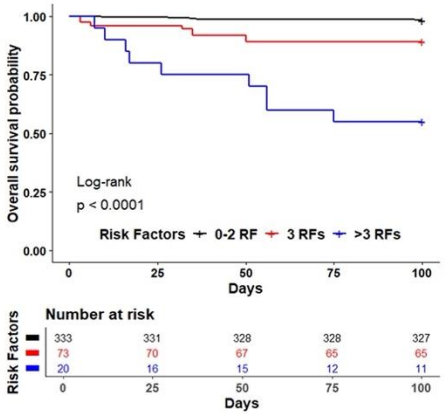


Progressive decrease in CARV detection over time post-transplant, which roughly **halved each year**

Probabilities of lower respiratory tract disease (LRTD) progression according to the number of risk factors:

GvHD prophylaxis, corticosteroid use, ALC <1 × 10^9/L, fever at CARV screening, RSV and human metapneumovirus

Number of RFs*	Only URTD n (%)	LRTD& n (%)	Total episodes
0	211 (89.7)	27 (11.3)	238
1	278 (86.9)	42 (13.1)	320
2	200 (73.3)	73 (26.7)	273
3	81 (55.2)	66 (44.8)	147
4	14 (21.6)	51 (78.4)	65
5	7 (26)	20 (74)	27



Overall survival at 100 days after CARV detection in recipients with LRTD according to risk factors:

- **donor/recipient HLA mismatch**
- **corticosteroids 0.1-30mg/d and >30mg/d**
- **ALC <1 × 10^9/L**
- **ANC <0.5 × 10^9/L**
- **Age ≥40 years.**

Clin Infect Dis, 2024 ciae602, https://doi.org/10.1093/cid/ciae602