Transplant Infectious Diseases UHN

Deuxieme Journee Du G21 Groupe Infection et Immunodepression

Infections in Lung Transplantation: Where do we stand (5 past Years)

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Disclosures

- Received Research Grants from
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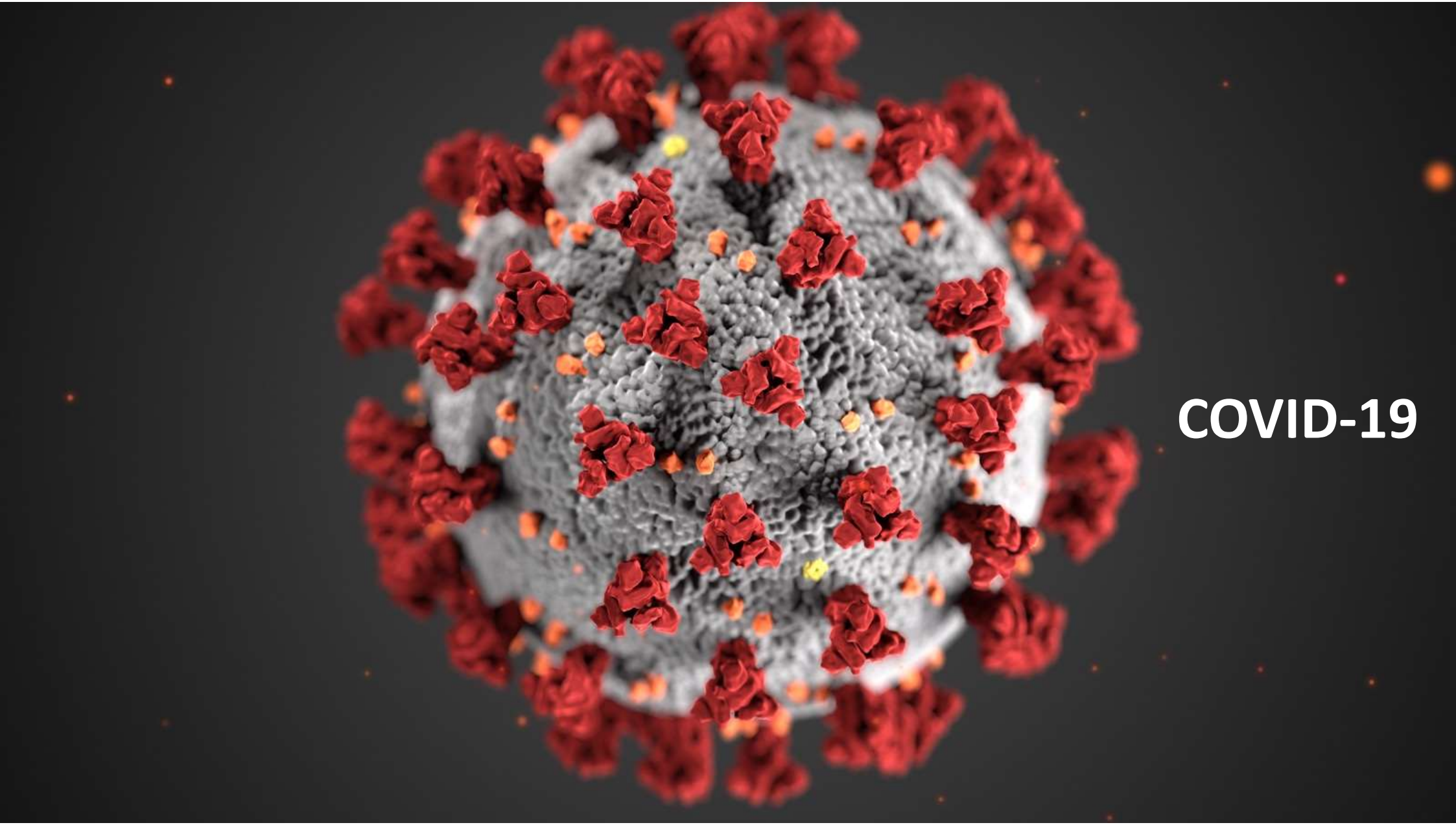
  - Cidara,
  - Merck,
  - Pfizer,
  - Pulmocide,
  - Synergia
- Consultancy fees from Takeda

Objectives

- To review the COVID-19 vaccine response in lung transplantation and indications of lung transplantation in COVID-19pateints
- To Review newer data on CMV Prophylaxis and other viruses in Lung Transplantation.
- To review the updated epidemiology, the antifungal prophylaxis strategies employed in lung transplant recipients.
- To appreciate the CAPA in lung transplant recipients.
- To understand the role of newer antifungals in the management of invasive fungal infections in solid organ transplant recipients.
- A brief review of Phage therapy in M.abcessus and Hyperammonemia syndrome


COVID-19

Clinical Presentation and Initial Laboratory Values at Hospital Admission by COVID-19 severity In Lung Transplant Recipients

	Moderate (n = 14)	Severe (n = 13)	P-value
Days of symptoms prior to testing, median (IQR)	6.5 (3-7)	3 (0-5)	.15
Fever (%)	7 (50)	4 (31)	.31
Cough (%)	13 (93)	10 (77)	.24
Dyspnea (%)	11 (79)	9 (69)	.58
GI upset (%)	9 (64)	4 (31)	.082
Hypoxemia (%)	8 (57)	10 (77)	.28
Tachypnea (%)	2 (14)	3 (23)	.56
Tachycardia (%)	0 (0)	1 (8)	.29
Hypotension (%)	0 (0)	4 (31)	.025
WBC count, median (IQR)	3.9 (1.5-6.4)	4.3 (3.4-6.3)	.66
Lymphocyte count, median (IQR)	0.4 (0.3-0.6)	0.4 (0.1-0.8)	.67
AST, median (IQR)	34 (27-56)	37 (24-57)	.87
ALT, median (IQR)	24 (18-29)	15 (13-28)	.24
Ferritin, median (IQR)	796 (502-2092)	850 (613-1048)	.94
ESR, median (IQR)	67 (36-82)	46 (32-55)	.24
CRP, median (IQR)	67 (56-113)	97 (77-109)	.27
Procalcitonin, median (IQR)	0.18 (0.07-0.6)	0.27 (0.21-0.71)	.10
D-dimer, median (IQR)	1.9 (0.8-2.7)	0.7 (0.6-2.2)	.32
IL-6, median (IQR)	23 (11-32)	16 (11-23)	.64

Mortality rate of 34%
100% mortality on Mechanically ventilated patients

Am J Transplant. 2020;20:3072–3080.

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Outcomes of COVID-19 by Type of Transplant

Outcomes	No. (%) of patients						
	Kidney *n* = 325	Heart *n* = 23	Lung *n* = 48	Liver *n* = 79	Kidney–pancreas *n* = 25	Other *n* = 9	*p* value*
Hospital admission related to COVID-19	182 (56.0)	9 (39.1)	34 (70.8)	29 (36.7)	17 (68.0)	5 (55.6)	0.002
Pneumonitis	147 (45.2)	8 (34.8)	31 (64.6)	19 (24.1)	16 (64.0)	5 (55.6)	< 0.001
Acute rejection	3 (0.9)	2 (8.7)	1 (2.1)	1 (1.3)	1 (4.0)	0	0.09
Cytomegalovirus viremia	9 (2.8)	0	7 (14.6)	1 (1.3)	0	0	< 0.001
Acute kidney injury (any)	70 (21.5)	3 (13.0)	14 (29.2)	9 (11.4)	4 (16.0)	2 (22.2)	0.2
ICU	64 (19.7)	1 (4.4)	16 (33.3)	8 (10.1)	4 (16.0)	1 (11.1)	0.01
Ventilator	53 (16.3)	1 (4.4)	13 (27.1)	6 (7.6)	2 (8.0)	1 (11.1)	0.03
All-cause mortality within 28 d of diagnosis	33 (10.2)	1 (4.4)	12 (25.0)	4 (5.1)	1 (4.0)	1 (11.1)	0.002
All-cause mortality within 90 d of diagnosis	48 (14.8)	1 (4.4)	15 (31.3)	9 (11.4)	3 (12.0)	2 (22.2)	0.02

CMAJ 2022 August 29;194:E1155-63. doi: 10.1503/cmaj.220620

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Predictors of Hospitalization with Omicron Variant

114 consecutive immunocompromised patients were enrolled. Eighty-nine percent had previously received 3 mRNA vaccinations.
16 lung transplant

Independent Variable	*P* Value	Odds Ratio (95% Confidence Interval)
Sex (male/female)	.43	0.69 (.27–1.7)
Age (year)	.00036	1.1 (1.0–1.1)
Ethnicity	.12	2.1 (.81–5.6)
Chronic kidney disease[a] (yes vs no)	.090	2.3 (.88–5.9)
Use of mycophenolate mofetil (yes vs no)	.058	2.8 (.96–8.3)
Fully vaccinated (yes vs no)	.091	0.35 (.10–1.2)
Boosted (yes vs no)	.11	2.7 (.79–9.0)
Immunoglobulin G titer (BAU/mL)	.091	0.99 (.99–1.0)
Being an adequate responder (≥300 BAU/mL)	.0064	0.053 (.0060–.44)
Being a kidney transplant recipient (yes vs no)	.88	1.1 (.42–2.8)
Being a lung transplant recipient (yes vs no)	<.000010	16 (4.7–53)
Obesity[b] (yes vs no)	.22	2.6 (.57–12)
Number of comorbidities (0–5)	.00065	2.1 (1.4–3.2)
Frailty score (1–9)	.00092	1.8 (1.3–2.6)

https://doi.org/10.1093/cid/ciac571

COVID-19 vaccine (3 doses) Antibody Response in Lung Transplant Recipients

- 1071 adults (551 [52%] males) at nine transplant centers in France.
- Each had received three COVID-19 vaccine doses in 2021 after lung transplantation.
- An anti-spike protein IgG response, defined as a titer >264 BAU/mL after (median, 3.0 [1.7–4.1] months) the third dose was the primary outcome.
- The median time from transplantation to the first dose was 64 [30–110] months.
- Median follow-up after the first dose was 8.3 [6.7–9.3] months.
- A vaccine response developed in 173 (16%) patients.
- Factors independently associated with a response were younger age at vaccination, longer time from transplantation to vaccination, and absence of corticosteroid or mycophenolate therapy.
- After vaccination, 51 (5%) patients (47 nonresponders [47/898, 5%] and 4 [4/173, 2%] responders) experienced COVID-19, at a median of 6.6 [5.1–7.3] months after the third dose.
- No responders had severe COVID-19, including six who died of the disease.

. Eur Respir J 2022; in press (https://doi.org/10.1183/13993003.00502-2022).

SCIENCE TRANSLATIONAL MEDICINE | REPORT

CORONAVIRUS

Lung transplantation for patients with severe COVID-19

Ankit Bharat[1]*, Melissa Querrey[1], Nikolay S. Markov[2], Samuel Kim[1], Chitaru Kurihara[1], Rafael Garza-Castillon[1], Adwaiy Manerikar[1], Ali Shilatifard[3], Rade Tomic[2], Yuliya Politanska[2], Hiam Abdala-Valencia[2], Anjana V. Yeldandi[4], Jon W. Lomasney[4], Alexander V. Misharin[2], G. R. Scott Budinger[2]

Multicenter Cohort Study

	Age, years	Centre	Comor-bidities	Body-mass index, kg/m²	Time from MV initiation to LTx, days	Tracheostomy	Time on ECMO at time of LTx, days	Awake or mobilising during bridging	CT findings before LTx	Total ischaemic time, h	Time in ICU after LTx, days	Time in hospital after LTx, days	Follow-up, days	Alive or dead
Patient 1	44	A	Yes	26·5	52	Yes	45	No	Consolidations, large necrotic areas	506	63	108	160	Alive
Patient 2	18	B	No	21·6	71	No	55	Yes	Pneumatocele, GGO, crazy paving, PNX	815	24	42	160	Alive
Patient 3	28	C	Yes	31·8	40	Yes	34	Yes	Extensive airspace opacities	315	21	28	143	Alive
Patient 4	48	B	No	26·1	70	Yes	54	Yes	UIP-like pattern	626	61	61	61	Dead
Patient 5	62	C	Yes	23·5	69	Yes	69	Yes	Complete opacification of the lungs bilaterally	301	15	38	112	Alive
Patient 6	51	D	Yes	25·3	103	Yes	103	Yes	Coarsened interstitial markings, subpleural cysts bilateral PNX	307	10	14	93	Alive
Patient 7	48	E	No	27·7	39	Yes	32	Yes	Multifocal consolidations with patchy ground glass opacities	353	10	26	90	Alive
Patient 8	52	F	Yes	26·7	114	Yes	86*	Yes	Traction bronchiectasis, diffuse ground glass	260	4	11	70	Alive
Patient 9	43	C	Yes	20·7	88	Yes	86	Yes	NA	306	24	42	63	Alive
Patient 10	34	D	Yes	36·6	77	Yes	77	Yes	Cystic bronchiectasis and extensive lower bilateral airspace disease, bilateral PNX	445	21	37	46	Alive
Patient 11	66	C	Yes	25·8	39	No	39	Yes	Fibrosis, honeycombing	318	15	Still admitted	33	Alive
Patient 12	51	D	No	25·4	67	Yes	53	Yes	Bilateral fibrotic changes with traction bronchiectasis	396	19	28	32	Alive

Lancet Respir Med 2021;9: 487–97

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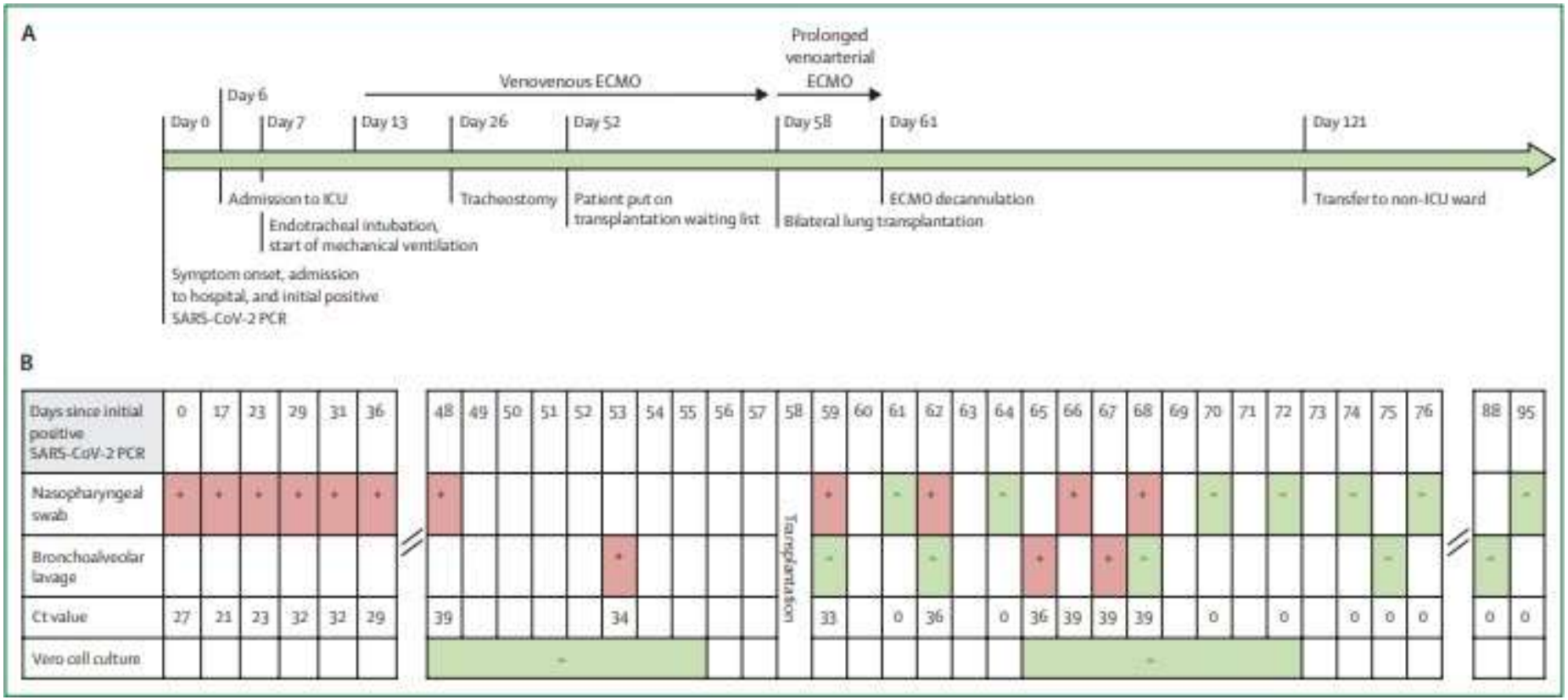
Timing for Lung transplantation in COVID-19 Positive Patient



www.thelancet.com/respiratory Vol 8 October 202

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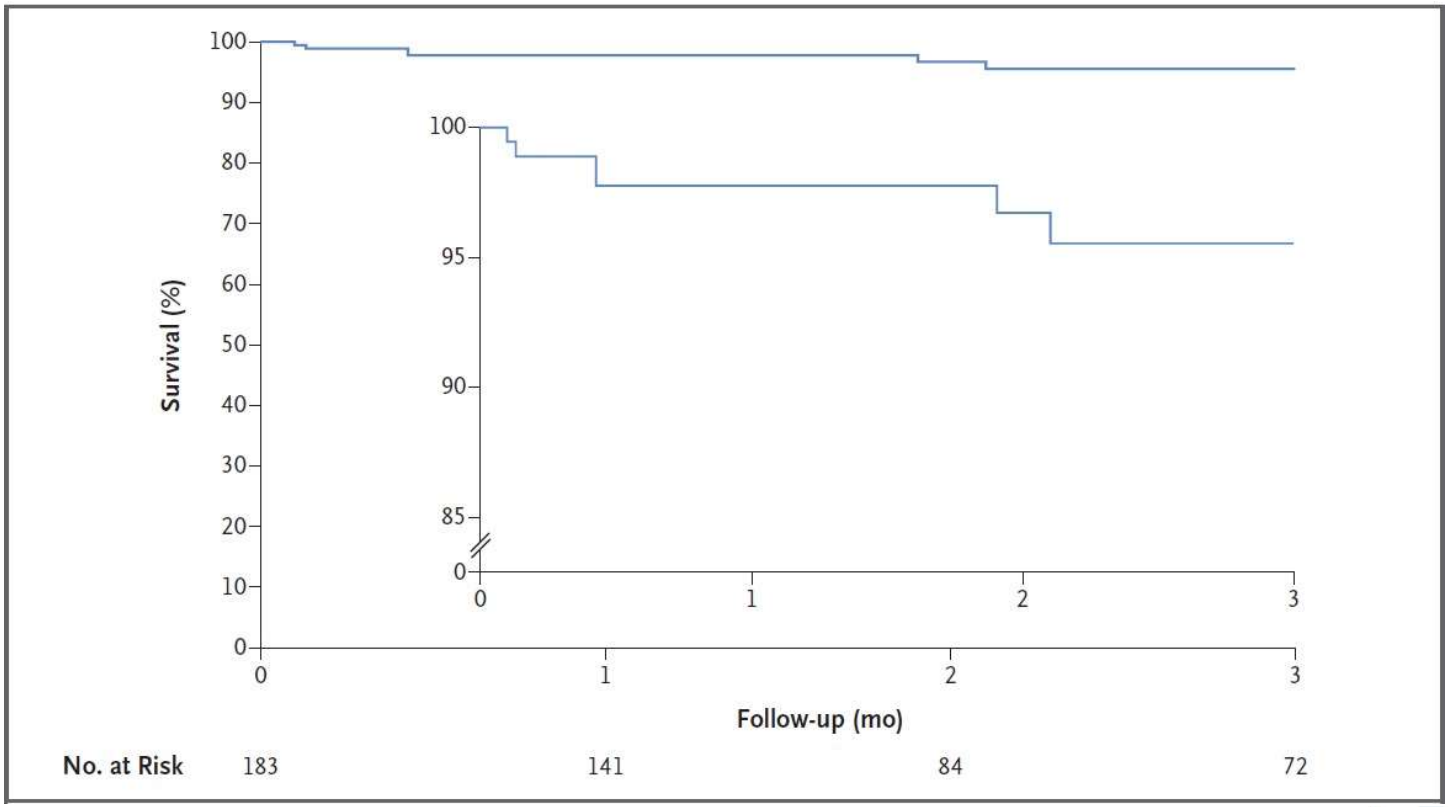
Survival through 3 Months after Lung Transplantation among Patients with Respiratory Failure Due to Covid-19.



n engl j med 386;12 nejm.org March 24, 2022

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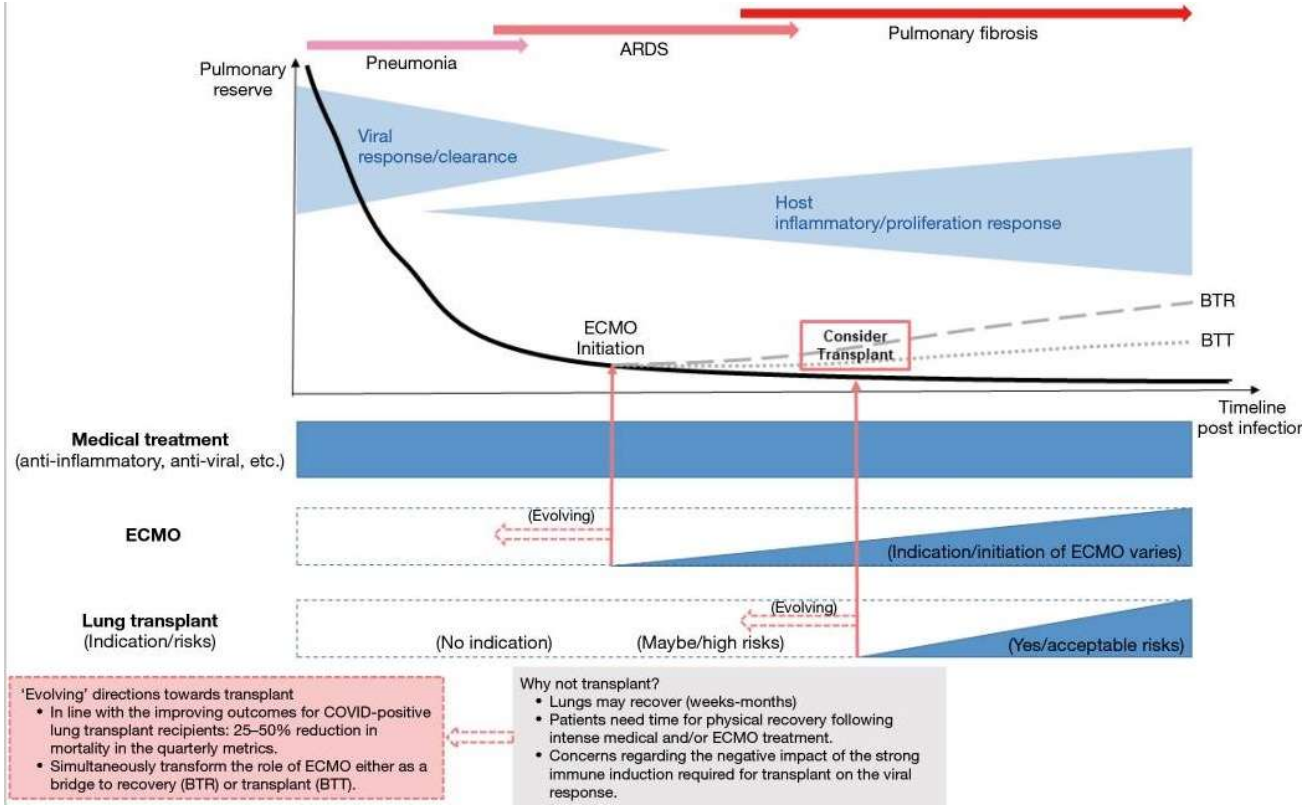
Timing of lung transplantation



J Thorac Dis. 2021 Dec; 13(12): 6755–6759.

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Proposed Criteria for the Selection of Lung Transplantation

General criteria

- Age younger than 65 years, extended to younger than 70 years in exceptionally fit individuals
- Single-organ failure; in selected cases, multiorgan transplantation can be considered
- No malignancy or disabling comorbidities
- No dependence (alcohol, drugs, other) and not an active smoker
- Body-mass index in the range of 17–32 kg/m², with exceptions on a case-by-case basis
- Postoperative social support available (at least one reliable primary and one secondary caregiver identified)
- Insurance approval obtained or financial support established for transplant-related care, as applicable
- Patient and caregivers agreeable to lung transplantation and willing to relocate close to the transplantation centre for a period established by the transplantation centre

Neurocognitive status

- Patient is awake and interactive, with exceptions in selected cases if sedation wean is associated with severe hypoxaemia and haemodynamic changes
- If not awake and interactive, evidence supporting the absence of irreversible brain injury is obtained through physical assessment and brain imaging or neuropsychological consultation; an individual with medical power of attorney is identified who can make informed decisions consistent with patient's goals and consent to transplantation

General condition

- Patient is participating in physical therapy while hospitalised; exceptions can be made in selected cases if transplant evaluation is urgent, the patient has a high potential for post-transplantation recovery, and rehabilitation is hindered mainly due to lung injury associated with severe COVID-19

COVID-19 status

- Two negative PCR tests of bronchoalveolar lavage fluid are obtained, 24 h apart; in such cases, transplantation can be considered regardless of nasopharyngeal swabs when at least 4 weeks have elapsed since COVID-19 symptom onset, although both might be requested in some patients with a pre-existing immunosuppressive state, owing to concerns of prolonged shedding of replication-competent virus
- If separated from the ventilator with no tracheostomy, two negative PCR tests of nasopharyngeal swabs are obtained, 24 h apart
- When available, viral cultures are negative, confirming the absence of replication-competent virus in the potential transplant recipient; bronchoalveolar lavage should be used, when possible

Evidence of irreversible lung damage

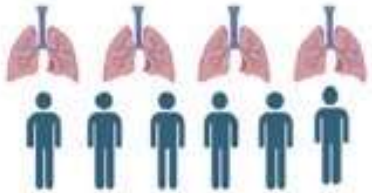
- At least 4 weeks have elapsed since the onset of severe acute respiratory distress syndrome; rarely, evaluation for lung transplantation can be considered earlier than 4 weeks if potentially lethal pulmonary complications develop that cannot be managed medically or through the use of extracorporeal membrane oxygenation
- Lung recovery is deemed unlikely by at least two physicians from two different specialties (surgery, critical care, or pulmonary medicine), despite optimised medical care; transplantation should not be considered if ongoing lung improvement is seen, regardless of the time elapsed

Lancet Respir Med 2021;9: 487–97

Real-time Transcription Polymerase Chain Reaction Cycle Threshold Values as Criteria for Utilization of Incidental COVID-19 Positive Lung Donors

The emergence of COVID-19 pandemic placed significant strain on lung transplantation

Lung Allografts recovered
Lung Transplants performed



Algorithm for organ evaluation of donors with incidental positive nasopharyngeal COVID-19 RT-PCR ***to increase organ utilization***

Algorithm for Organ Evaluation

Incidental Positive COVID-19 Nasopharyngeal RT-PCR

Cycle Threshold Cut Off

< 35 → **Decline Organ**

> 35 → LRT COVID-19 RT-PCR

LRT COVID-19 RT-PCR → Positive → **Decline Organ**

LRT COVID-19 RT-PCR → Negative → **Accept organ**

7 donors with incidental positive NP COVID-19 RT-PCT were included

1 donor with incidental positive LRT COVID-19 RT-PCT was included

ZERO donor-to-recipient transmissions of COVID-19 were observed

100% Survival at 30 and 90 days

Transplanting Thoracic COVID-19 Positive Donors: An Institutional Protocol and Report of the First 14 cases

- Lungs were eligible if the donor first tested PCR positive on nasopharyngeal swab (NPS) for COVID-19 > 20 days prior to procurement and had a negative lower respiratory tract specimen.
- 14 thoracic transplants in 13 recipients using organs from COVID-19 positive donors. ONLY TWO LUNG TRANSPLANTS
- None of the recipients or healthcare members acquired COVID-19. No recipients suffered unexpected acute rejection.
- Patient survival is 92% to date, with graft survival 93%.

J Heart Lung Transplant 2022;41:1376–1381

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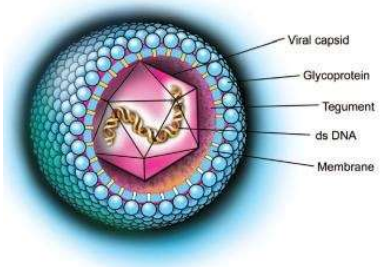

HCMV Human Cytomegalovirus

Update on CMV and Other Viruses in Lung transplantation

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QuantiFERON Directed CMV Prophylaxis in Lung Transplant Recipients

Table 4 Results of Cox Proportional Hazards Analyses Demonstrating Unadjusted and Adjusted Hazard Ratios (HR) for CMV infection ($n = 263$)

Site	Quantiferon-CMV result and serostatus	Unadjusted HR[a] (95% CI)	*p*-value	Adjusted HR[a] (95% CI)	*p*-value
Overall	Negative/indeterminate (vs positive)	2.07 (1.32-3.24)	0.001	0.95 (0.53-1.72)	0.88
	D+/R- (vs R+)	4.76 (3.02-7.51)	<0.0001	4.90 (2.68-9.00)	<0.0001
Blood	Negative/indeterminate (vs positive)	4.80 (2.33-9.90)	<0.0001	0.89 (0.37-2.15)	0.79
	D+/R- (vs R+)	18.19 (9.16-36.14)	<0.0001	19.66 (7.99-48.34)	<0.0001
BAL	Negative/indeterminate (vs positive)	1.37 (0.82-2.29)	0.23	1.09 (0.55-2.16)	0.81
	D+/R- (vs R+)	1.61 (0.91-2.86)	0.10	1.52 (0.71-3.23)	0.28

Abbreviations: BAL, bronchoalveolar lavage; CMV, cytomegalovirus; CI, confidence interval; CMV, cytomegalovirus; D, donor; HR, hazard ratio; R, recipient.

[a]All models also adjusted for prophylaxis duration.

263 LTR (59 D+/R-, 204 R+).

QF-directed prophylaxis was associated with reduced CMV infection (84/195, 43% vs 41/68, 60%, $p < .001$).

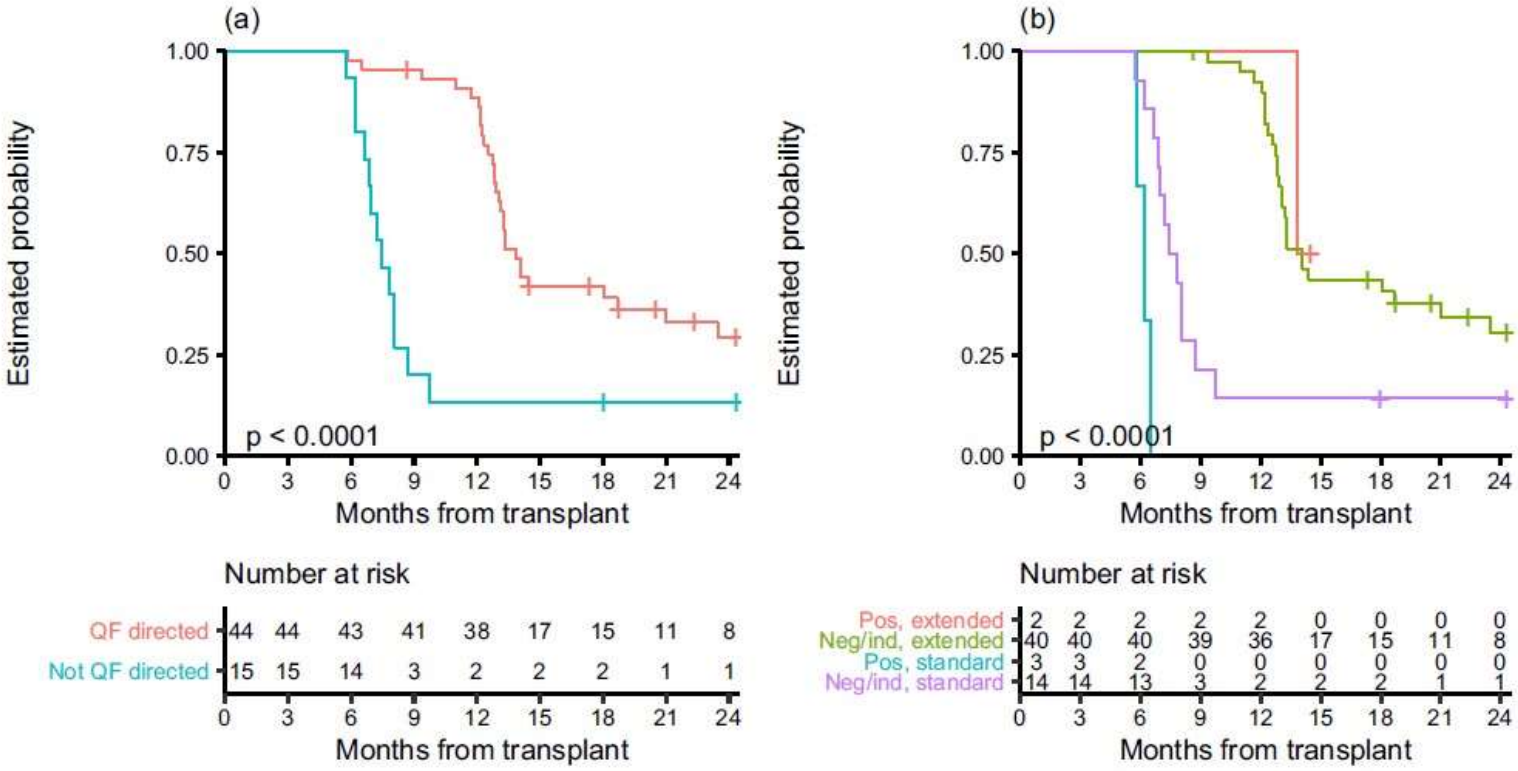
Patients receiving extended prophylaxis experienced less CMV if negative and/or indeterminate (43% vs 70%, $p < .01$) or positive (10% vs 51%, $p < .01$).

Only (8%) D+/R- patients were QF-CMV positive compared to (76%) R+ patients (adjusted OR 0.03, 0.01-0.07, $p < .001$).

After controlling for prophylaxis duration, only D+/R- serostatus remained associated with CMV infection

The Journal of Heart and Lung Transplantation, Vol 41, No 9, September 2022

Unadjusted Kaplan-Meier estimates of freedom from CMV infection amongst D+/R- patients (n = 59)



Quantiferon-CMV result at 5 months post-transplant and prophylaxis

J Heart Lung Transplant 2022;41:1258–1267

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Letermovir Prophylaxis in lung transplantation

Prophylaxis variable	Primary PPx (N = 26)	Secondary PPx (N=16)
LET initiation, median days post-transplant (IQR)	315 (125-1139)	695 (537-1156)
LET duration, median days (IQR)[a]	280 (91-353)[b]	290 (196-629)
LET median dose, mg (range)	480 (240-480)	480 (240-720)
Rationale for LET use, no. (%)		
Myelosuppression[c]	25 (96.2)	10 (62.5)
Viral resistance	0	6 (37.5)[d]
Other	1 (3.8)[e]	0
Successful completion of LET prophylaxis, no. (%)	5 (19.2)	3 (18.8)
Remain on LET prophylaxis at end of study, no. (%)	11 (42.3)	9 (56.3)
Early discontinuation of LET prophylaxis, no. (%)	10 (38.5)	4 (25)
Adverse effects	5 (19.2)[f]	0
Clinically significant CMV infection	0	1 (6.3)
Other	5 (19.2)[g]	3 (18.8)[h]
Low level CMV DNAemia on LET prophylaxis, no. (%)[i]	5 (19.2)	10 (62.5)

J Heart Lung Transplant 2022;41:508–515

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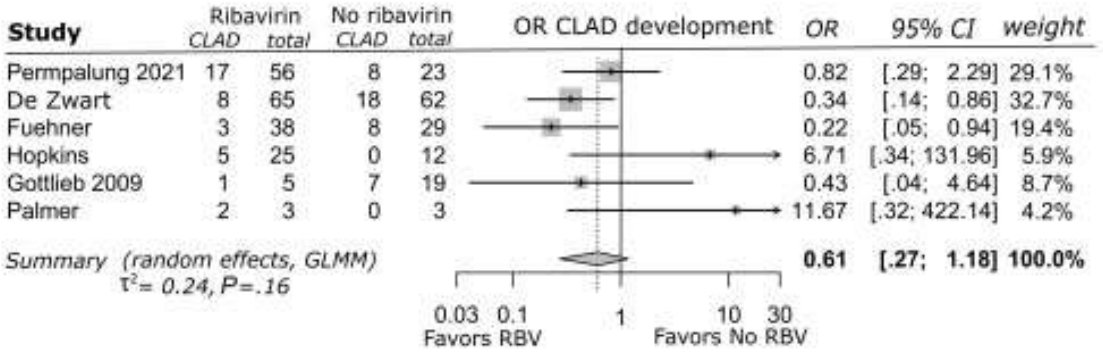
Leteromovir Treatment In Lung Transplantation

- 28 lung transplant recipients
- CMV disease was present in 15 patients (53.6%).
- In 23 patients (82.1%), rapid response was noticed, and CMV-viral load could be significantly decreased (>1 log10) after a median of 17 [14–27] days and cleared subsequently in all of these patients.
- Five patients (17.9%) were classified as non-responder.
  - Development of a mutation of the CMV UL56 terminase (UL-56-Gen: C325Y) conferring letermovir resistance could be observed in three patients (60%).
- Common side effects were mild and mostly of gastrointestinal nature.
- Mild adjustments of the immunosuppressive drugs were mandatory upon treatment initiation with letermovir.

Am J Transplant. 2021;21:3449–3455.

Respiratory Syncytial Virus, Human Metapneumovirus, and Parainfluenza Virus Infections in Lung Transplant Recipients:

Nineteen retrospective and 12 prospective studies were included (total of 1060 cases). Pooled 30-day mortality was low (0–3%), but CLAD progression 180–360 days post-infection was substantial (pooled incidences 19–24%) and probably associated with severe infection. Ribavirin trended toward effectiveness for CLAD prevention in an exploratory meta-analysis (odds ratio [OR] 0.61, [0.27–1.18]), although results were highly variable between studies



Clinical Infectious Diseases® 2022;74(12):2252–60

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Elevated cell-free DNA in Respiratory Viral Infection and Associated lung Allograft Dysfunction

Variable	Low %ddcfDNA ($n = 38$), n (%)	High %ddcfDNA ($n = 21$), n (%)	p-value
Isolated pathogens in 90 days			
Isolated respiratory bacteria	6/38 (15.8)	3/21 (14.3)	.88
Isolated respiratory fungus	6/38 (15.8)	1/19 (4.8)	.21
Histopathology and DSA in 180 days			
Abnormal biopsy in 180 days	12/29 (41.4)	4/17 (23.5)	.22
New DSA in 180 days	1/33 (3.0)	3/17 (15.8)	.10
Allograft function in 1 year			
CLAD progression	6/35 (17.1)	8/18 (44.4)	.03*
Allograft failure[a]	2/38 (5.3)	3/21 (14.3)	.25
CLAD progression/Allograft failure	8/37 (21.6)	11/21 (52.4)	.01*

Am J Transplant. 2022;22:2560–2570.

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Fungal Infections

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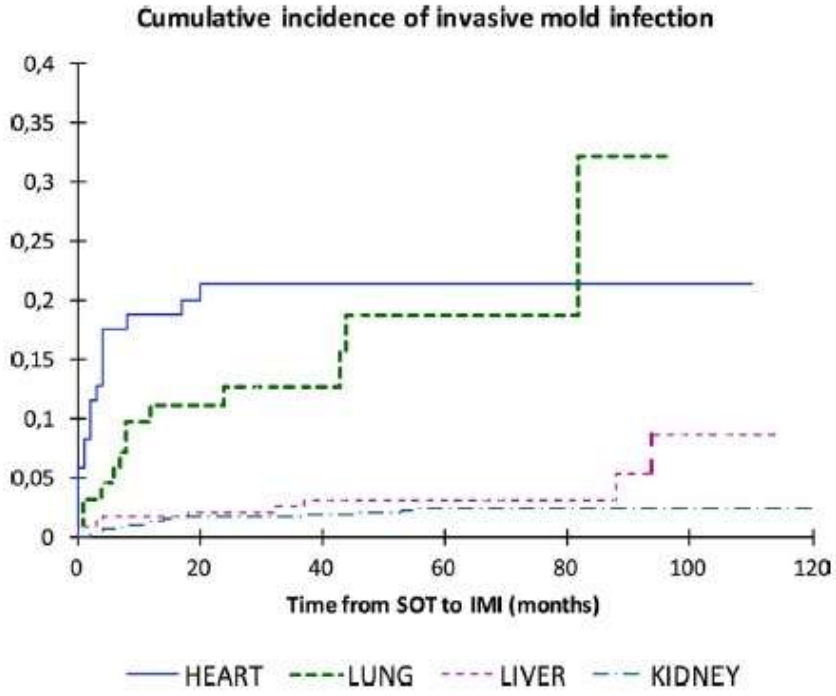
French Study 2008 - 2016

- Cumulative incidence of IMI at one year
  - Heart 18.8%
  - Lung 11.1%
  - Liver 1.7%
  - Kidney 1.2%

- Mortality at one year
  - Heart 56.2%
  - Lung 54.5%
  - Liver 67%%
  - Kidney 54%



Farges C Transpl Infect Dis. 2020;22:e13200.

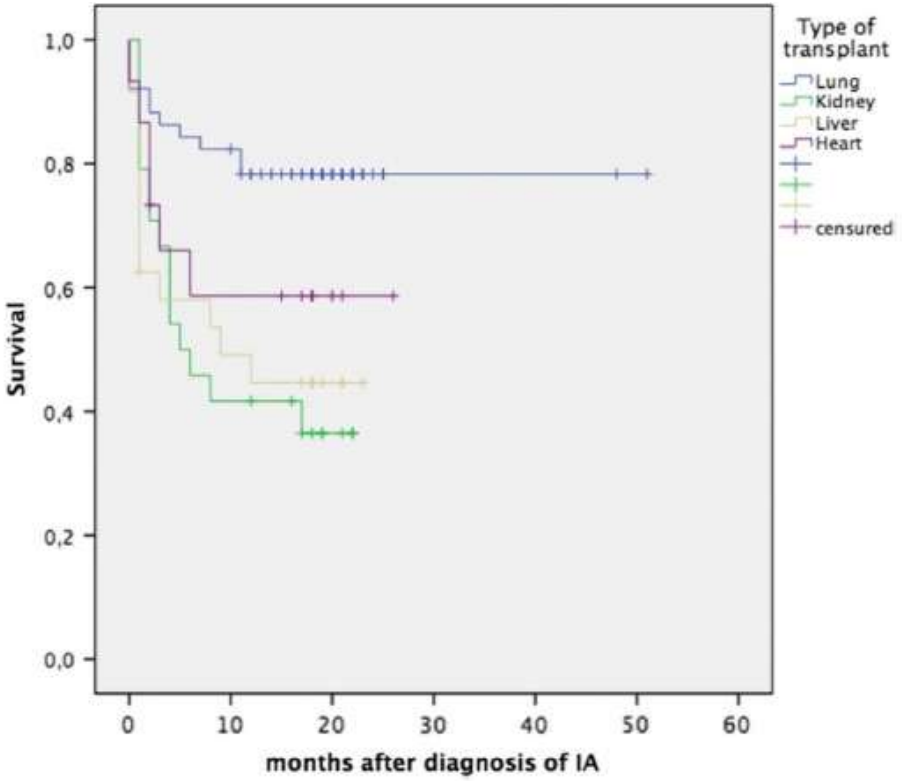
Spanish Study (Diaspersot): 2010 - 2019

- The incidences of IA
  - Lung 6.5%
  - Heart 2.9%
  - Liver 1.8%
  - Kidney 0.6%

- IA cases occurred despite the receipt of a prior mould antifungal prophylaxis in 53.9%

- Overall Mortality at 3 months 34.1%
- Attributed Mortality at 3 months 24.6%

- Lung Transplant at 3 months 14.8%



Francesca Gioia Mycoses. 2021;64:1334–1345.

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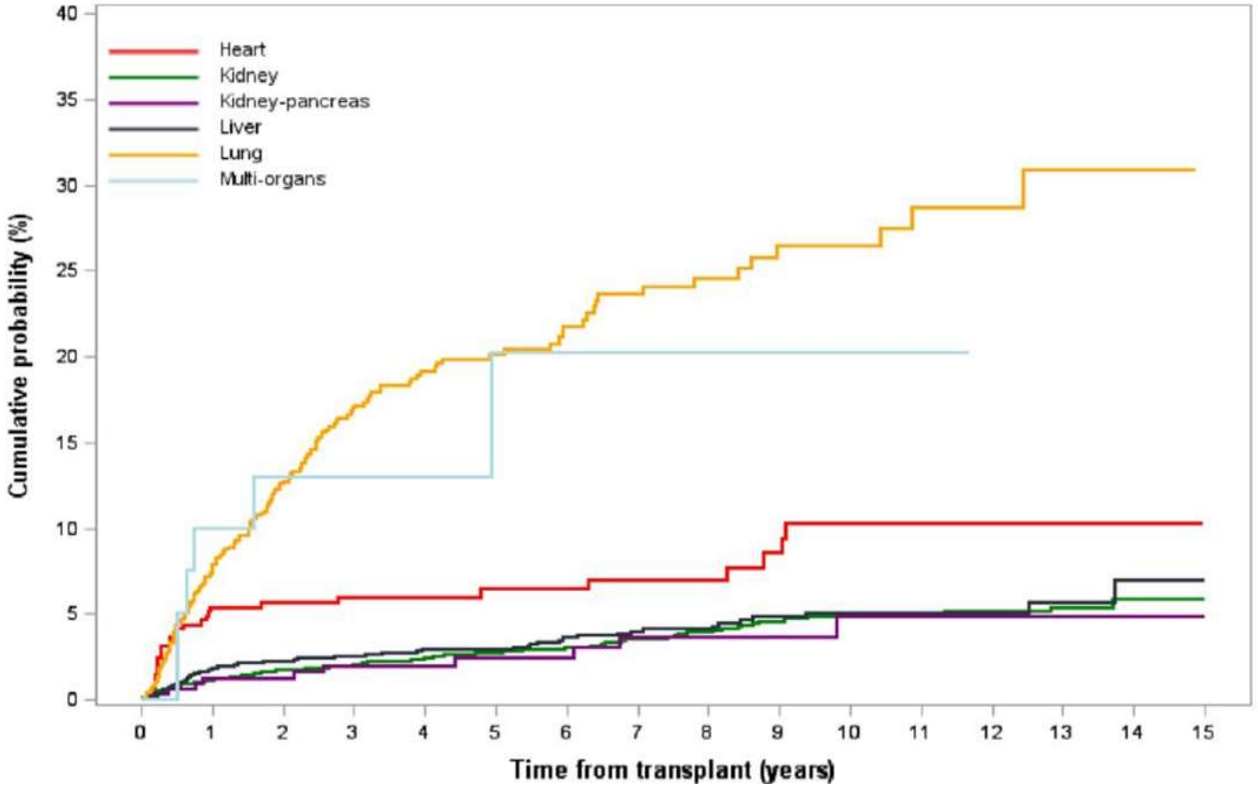
IFI Incidence in Solid Organ Transplantation, Long Term Follow-up

Overall, the incidence of IFI was 8.3 per 1000 person-years.



9326 transplants, 942 lung, Ontario. Shows long term data 2005-2016

Hosseini-Moghaddam et al. *Transpl Infect Dis* 2020;22(2)

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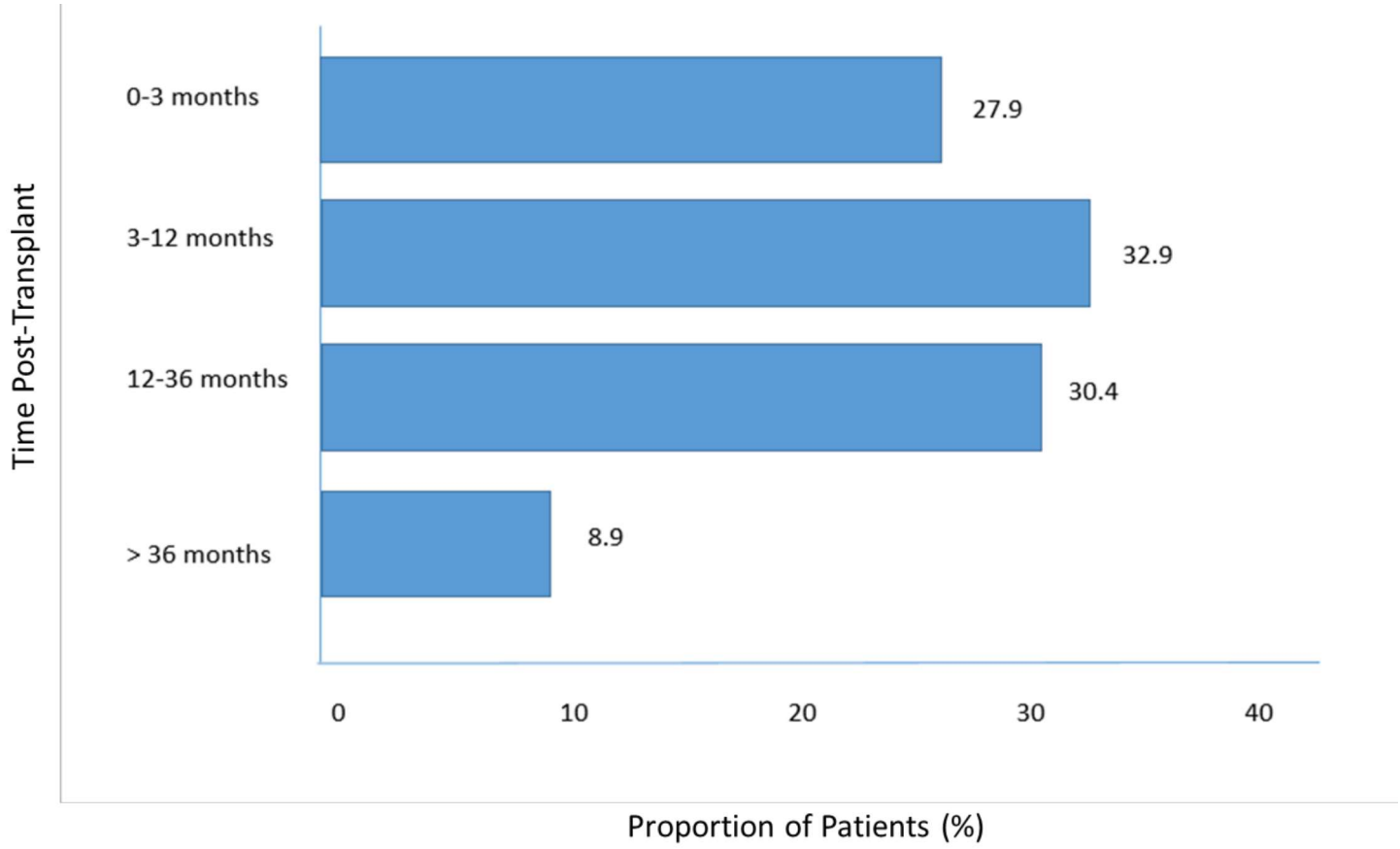
Invasive Aspergillosis in 900 Lung Transplant Recipients, 4 Year Follow-up



Aguilar et al. J Heart Lung Transplant 2018;37(10)

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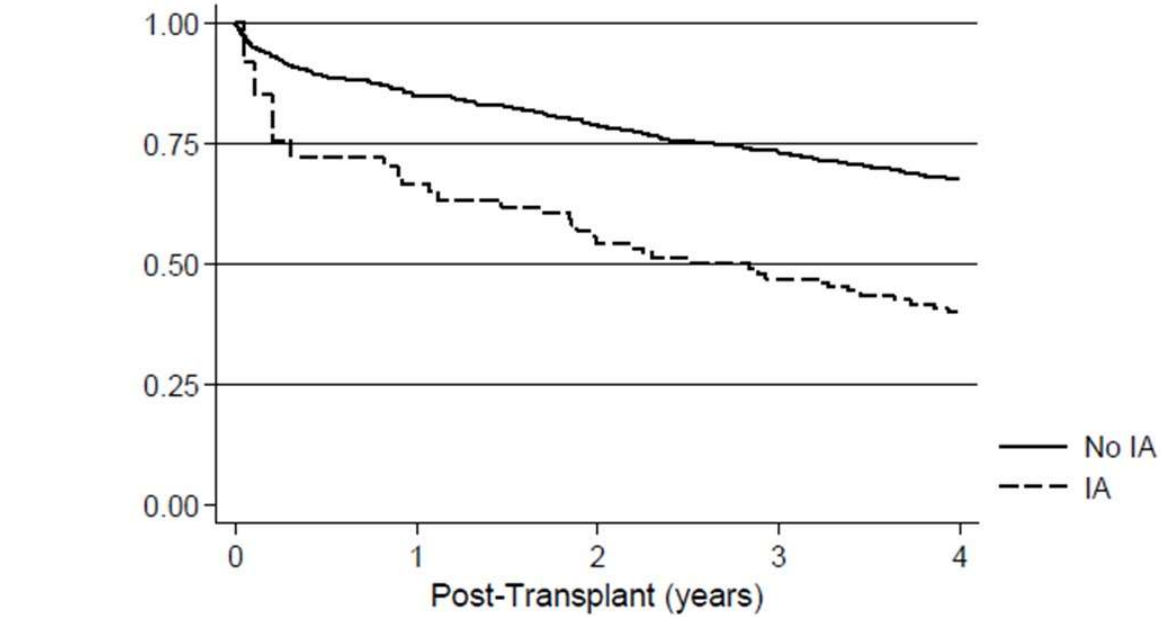
Mortality Associated with IFI in Solid Organ Transplantation



Aguilar et al. J Heart Lung Transplant 2018;37(10)

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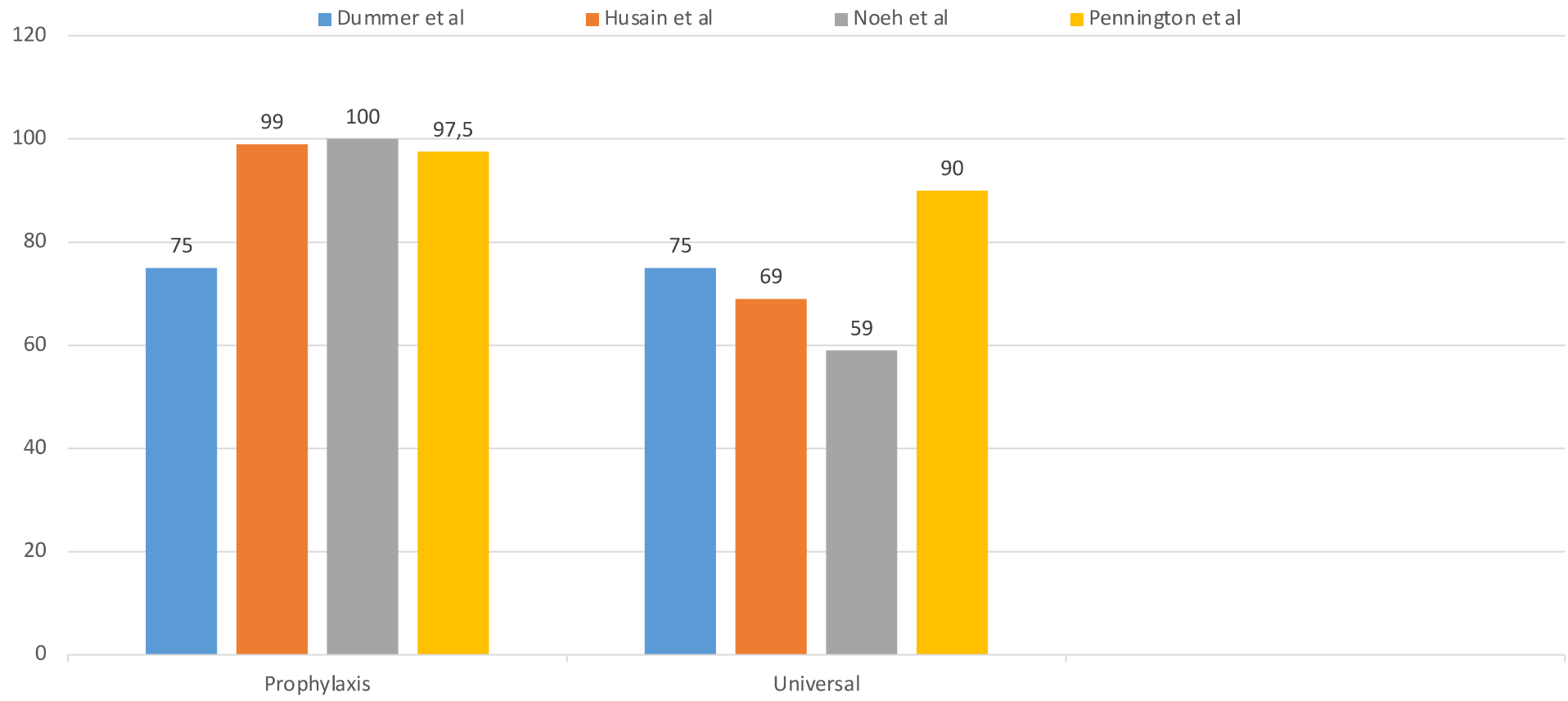
IA in SOT following Non Influenza Respiratory viruses Infection

- At a median post-transplant follow-up of 43.4 months, 221 of 2986 patients (7.4%) developed 255 RSV, parainfluenza,or adenovirus infections.
- IPA complicating these NI-RVIs was exclusively observed in lung and small bowel transplant recipients, in whom incidence was 5% and 33%, respectively.
  - Cumulative prednisone doses >140 mg within 7 days OR, 22.6; 95% CI, 4.5–112
  - Pneumonia at the time of NI-RVI OR 7.2; 95% CI, 1.6–31.7
- Mortality at 180 days following NI-RVI was 27% and 7% among patients with and without IPA, respectively (P = .04).

Apostolopoulou A Open Forum Infectious Diseases®2021

Antifungal Prophylaxis in Lung Transplant



Neoh. *Am J Transplant* 2011 Feb;11(2):361-6; Husain. *Transpl Infect Dis* 2006 Dec;8(4):213-8
Dummer. *J Heart Lung Transplant* 2004 Dec;23(12):1376-81; Pennington. *Clinical Transplantation* 2019;33

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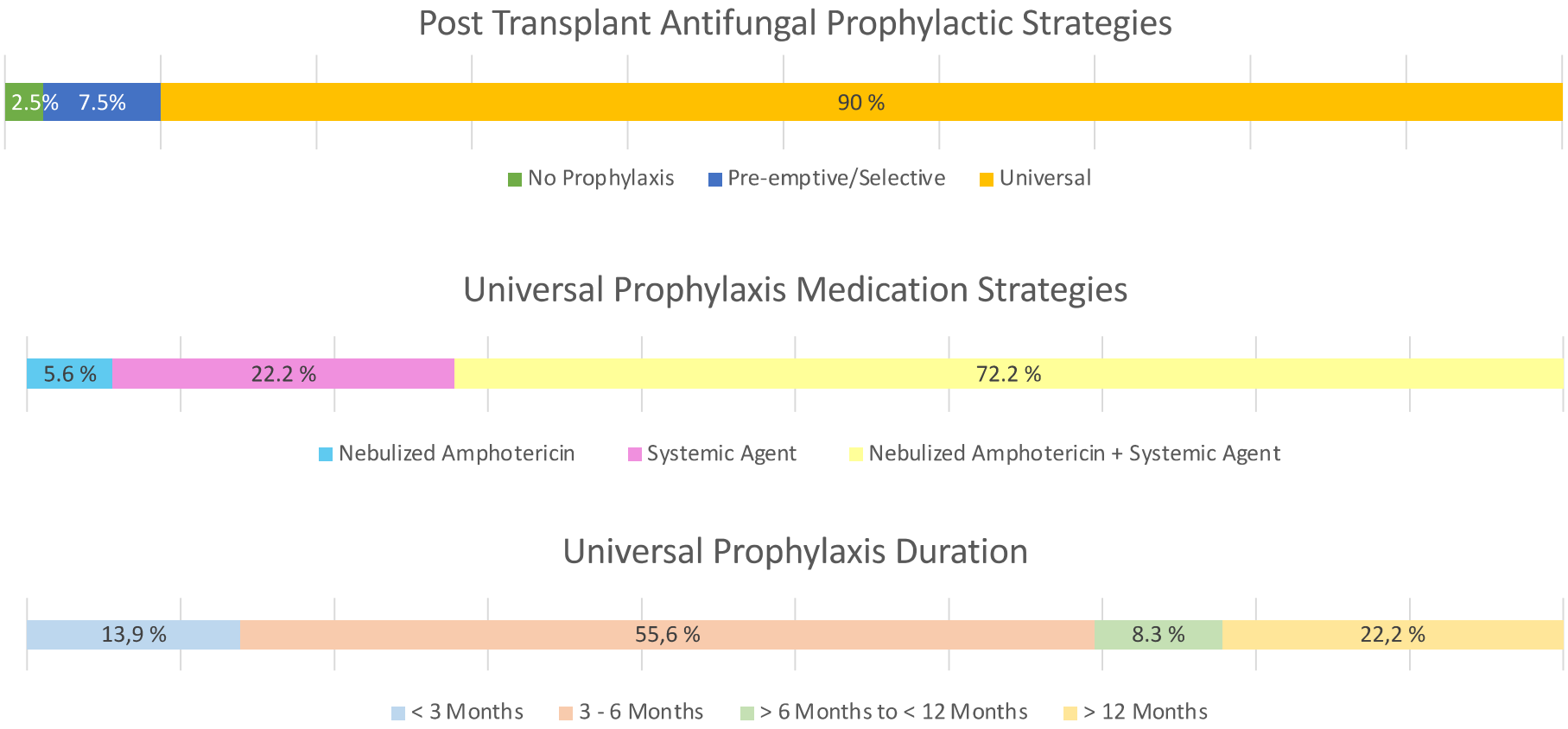
Antifungal Prophylaxis Strategies in 44 U.S. Transplant Centres 2018-19



Pennington et al. *Clinical Transplantation* 2019;33

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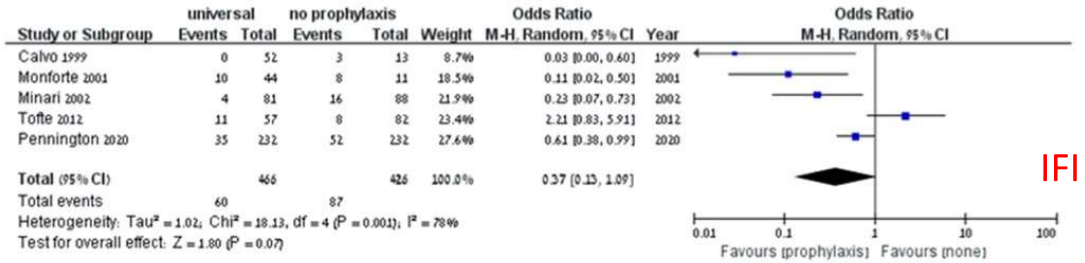
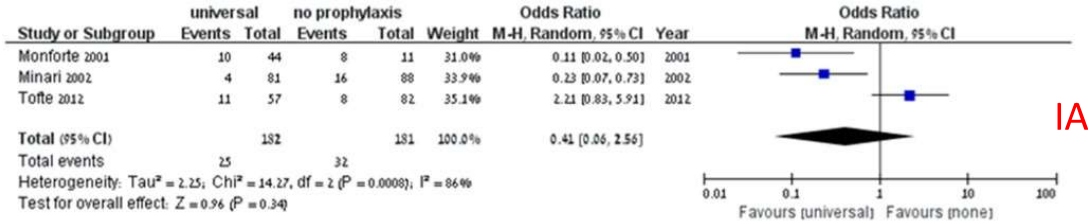
Recent Meta Analysis

Comparison of Universal vs No prophylaxis

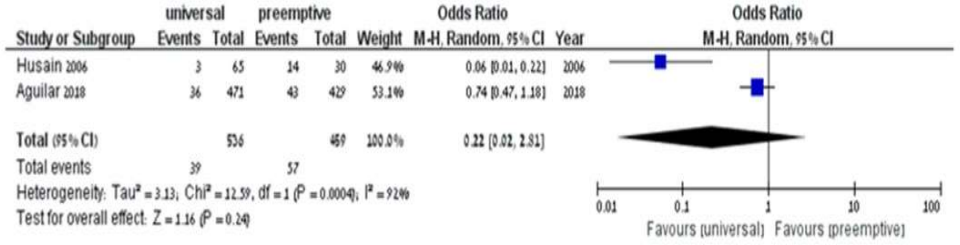


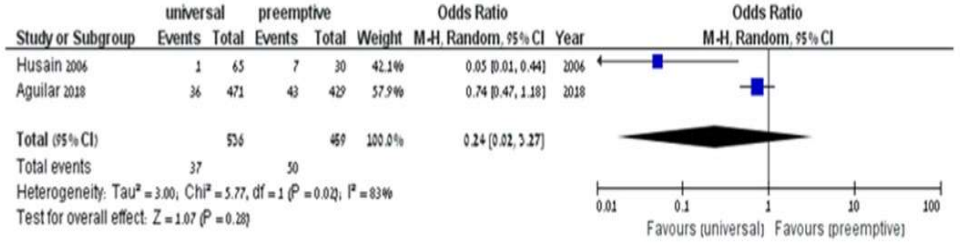
IFI



IA

Comparison of Universal vs Pre-Emptive





Bitterman et al. *J Fungi* 2021; 7,122

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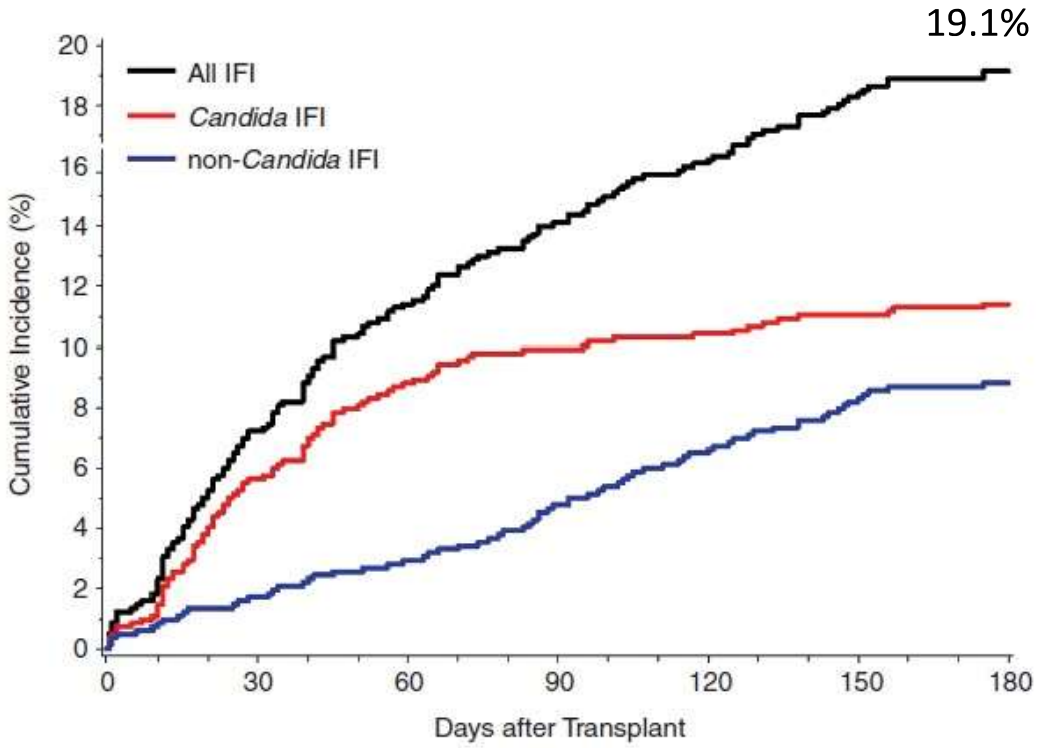
High IFI Rate Despite Universal Prophylaxis in 815 Lung Transplants



Baker et al. *Clin Infect Dis* 2020;70(1)

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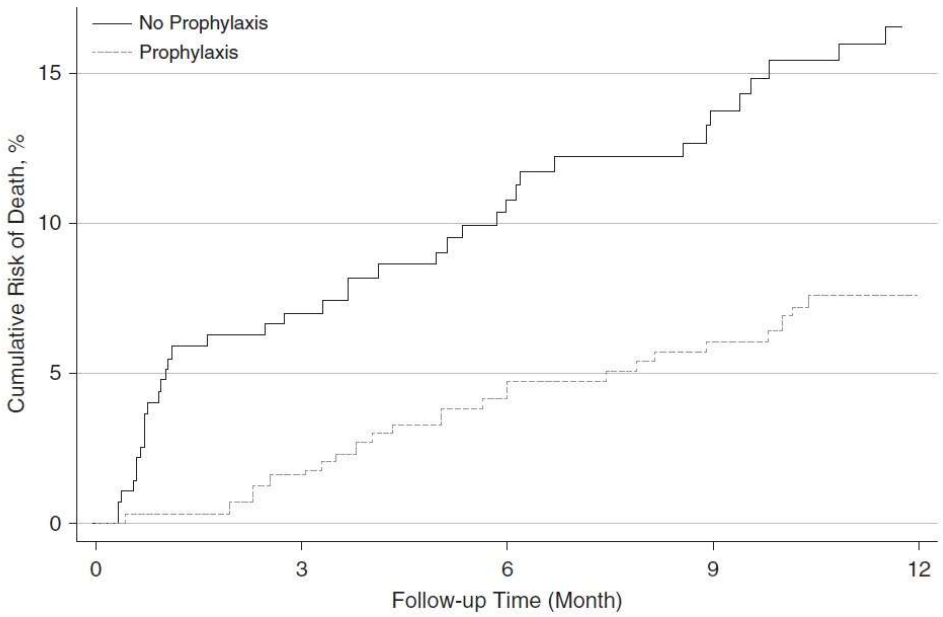
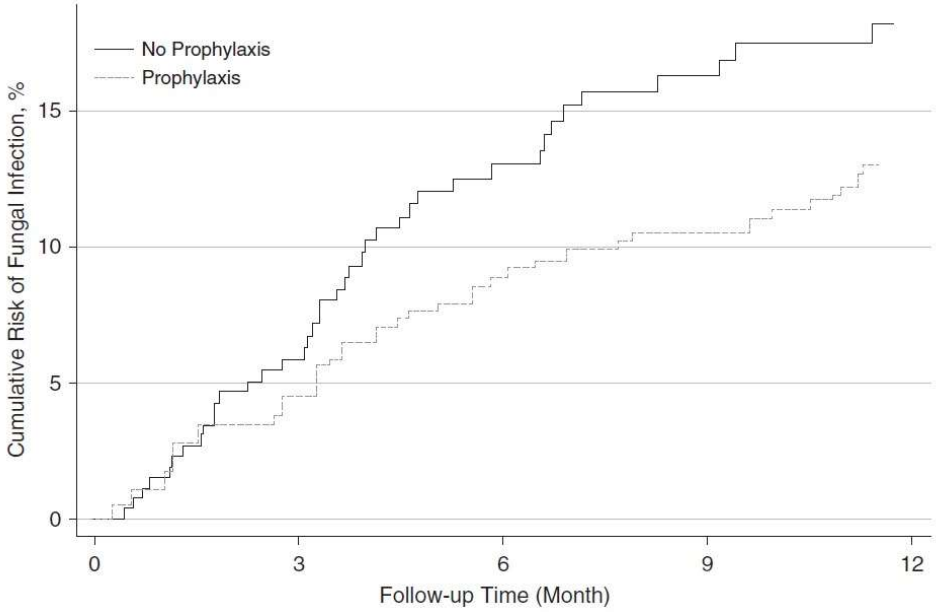
Mortality: Universal Prophylaxis Compared to None in 662 Lung Transplants

Mortality



Invasive Fungal Infection



Pennington et al. *Annals ATS* 2021;18(3)

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non
nocere

Outcomes of Prolonged Triazole Prophylaxis in 193 Lung Transplant Recipients

	Itraconazole	Voriconazole	Posaconazole	*P*-value
No. of Patients	180	73	60	--
Still Taking	31 (17.0)	0	24 (40.0)	< 0.05
Adequate Duration of Prophylaxis	7 (3.8)	2 (2.7)	3 (5.0)	0.73
Taking Until Death	52 (28.9)	20 (27.3)	22 (36.7)	0.19
Lost to Follow-up	7	0	0	n/a
No. of Exposure Episodes	204	77	60	--
Side Effect/Intolerance	20 (9.8)	42 (54.5)	4 (6.7)	< 0.05
Concern for Fungal Infection	21 (10.2)	1 (1.3)	1 (1.7)	0.09
Malabsorbtion	32 (15.7)	2 (2.6)	1 (1.7)	< 0.05
Airway Colonization	14 (6.9)	1 (1.3)	1 (1.7)	0.09
Expense	12 (5.9)	3 (3.9)	4 (6.7)	0.73
Drug Interaction	6 (2.9)	3 (3.9)	0	n/a
Actively Discontinued	126 (61.8)	53 (68.8)	11 (18.3)	< 0.05

Pennington et al. *Transpl Infect Dis* 2019;21

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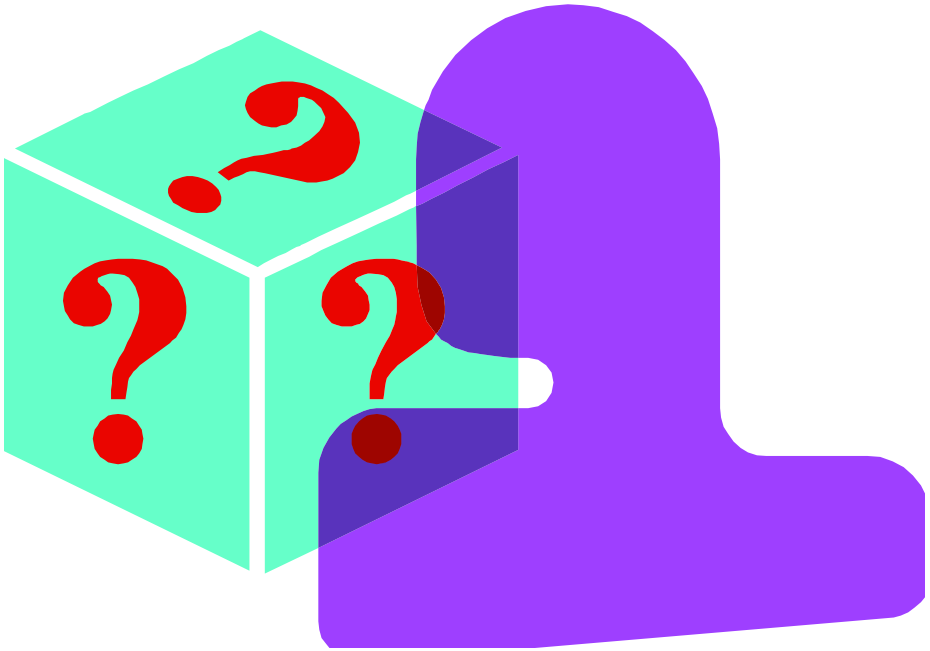
A stitch in time saves nine

But …

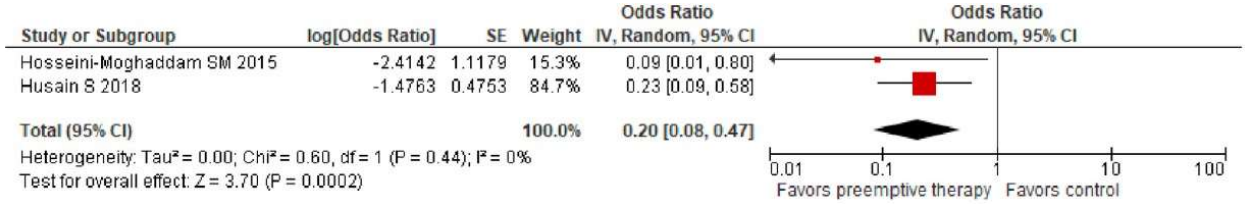
What type of stitches to use and when?

How to Better Risk Stratify Lung Transplant Recipients for Invasive Aspergillosis?



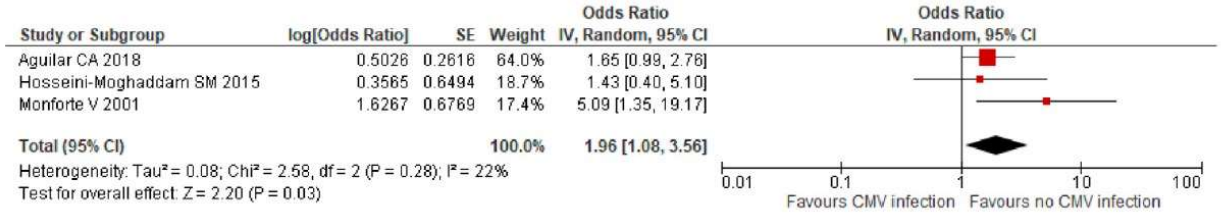
- Clinical risk stratification through cohort studies.
- Measurement of immunity against Aspergillus.
- Use of galactomannan assay or Aspergillus PCR to identify the patient at higher risk of IA.

Meta-analysis of Risk Factors of Invasive Fungal Infection in Lung Transplant Recipients



A. Pre-emptive antifungal therapy

B. Previous fungal colonization



C. Cytomegalovirus infection

J Heart Lung Transplant 2022;41:255–262

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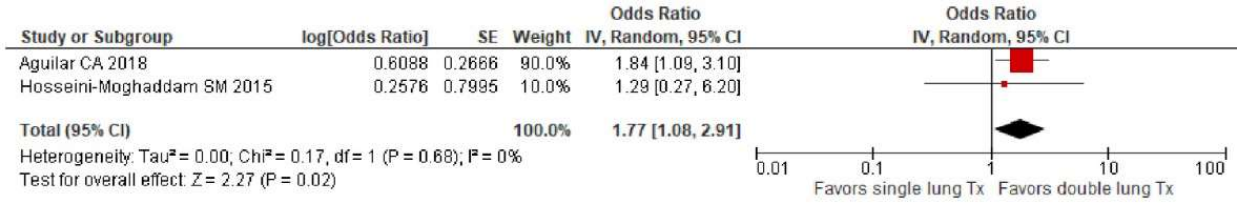
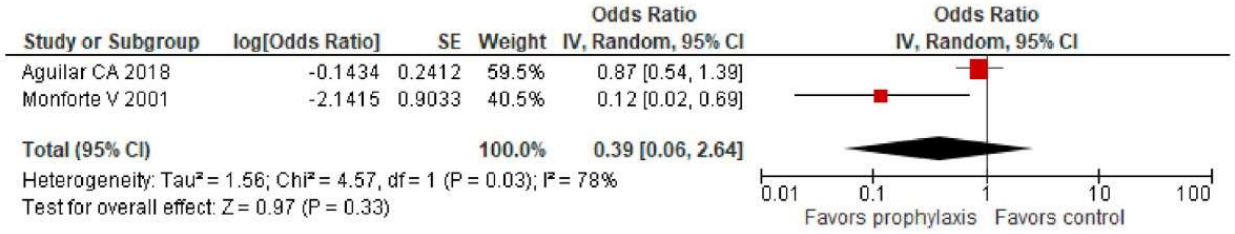
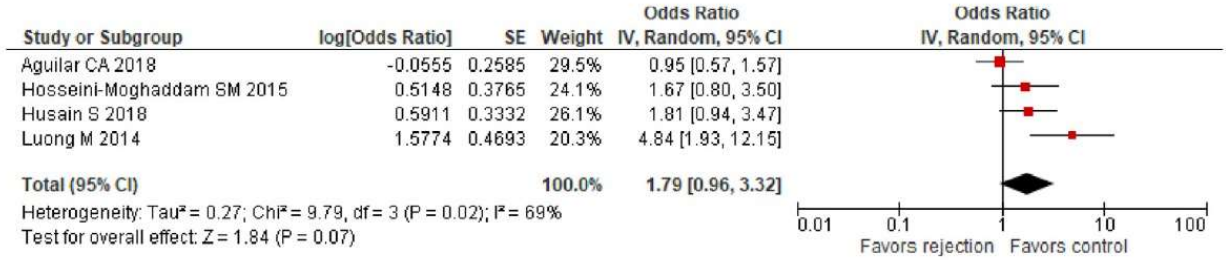
Meta-analysis of Risk factors of Invasive Fungal Infection in Lung Transplant Recipients



D. Single lung transplant



E. Antifungal prophylaxis



F. Acute rejection

J Heart Lung Transplant 2022;41:255–262

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Univariable and Multivariable Analyses Evaluating Risk Factors for IA in Lung Transplant Recipients

Risk Factors	Univariable Analysis			Multivariable Analysis		
	SubHR	95% CI	P.value	SubHR	95% CI	p.value
Gender	1.69	(0.96-2.97)	0.06	_	_	_
COPD	0.77	(0.24-2.48)	0.67	_	_	_
Anti-thymocyte globulin	0.32	(0.10-1.05)	0.06	_	_	_
Acute rejection	1.98	(0.99-3.95)	0.05	_	_	_
Pre-transplant Aspergillus colonization	1.66	(0.82-3.37)	0.15	_	_	_
Re-transplantation	2.67	(0.84-8.46)	0.094	_	_	_
CMV DNAemia	1.69	(0.99-2.88)	0.05	_	_	_
Respiratory Virus Infection	1.56	(0.79-3.07)	0.19	_	_	_
Pre-emptive Therapy	0.41	(0.2-0.81)	0.011	_	_	_
Statin use	0.24	(0.11-0.51)	0.000	0.30	(0.14 - 0.64)	0.002
Age	1.05	(0.98-1.02)	0.5	1.00	(0.97 - 1.03)	0.698
Single lung transplant	1.31	(0.69-2.4)	0.39	1.29	(0.67 – 2.49)	0.437
Cystic Fibrosis	0.90	(0.45-1.81)	0.78	0.76	(0.25 – 2.27)	0.626
Post-Transplant Aspergillus Colonization	8.35	(4.39-15.86)	0.000	9.05	(4.77 – 17.28)	0.000

Villalobos AP: Clinical infectious Diseases 2022

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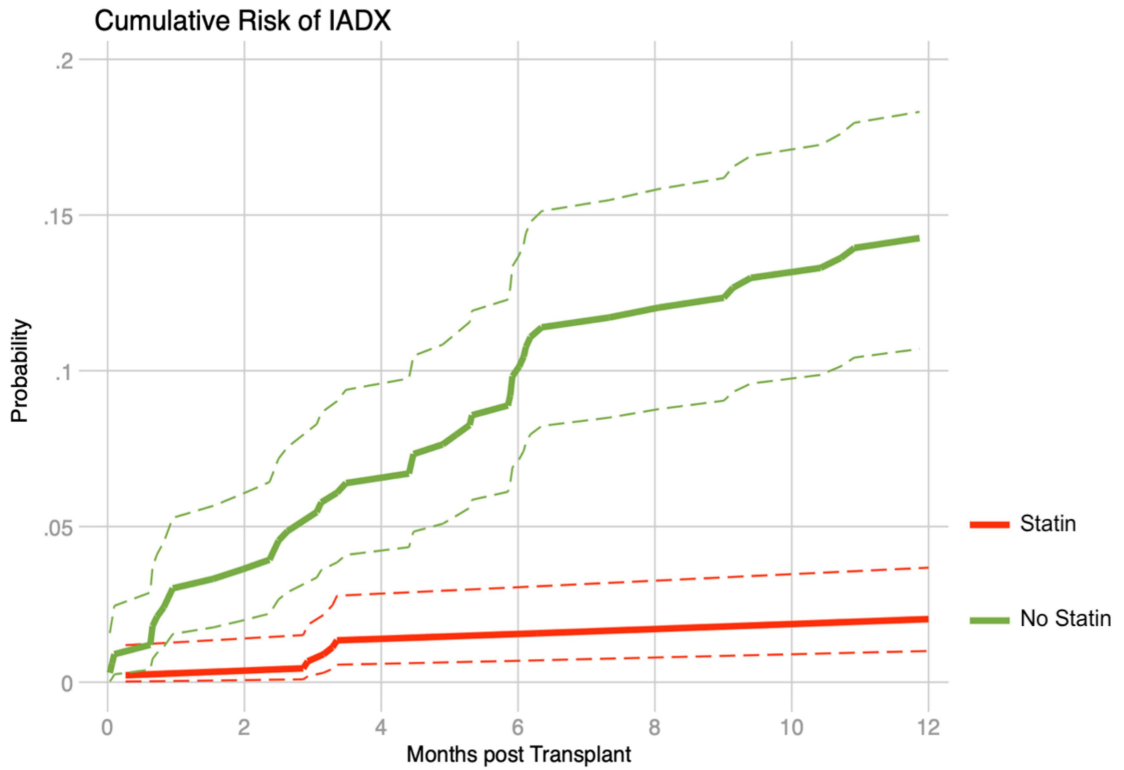
Cumulative Risk of Patients who Developed IA Post Lung Transplant Estimated by the Competing Risk Analysis Between LTRs with and without Statin Therapy with 95% Confidence Intervals



Villalobos AP : Clinical Infectious diseases 2022

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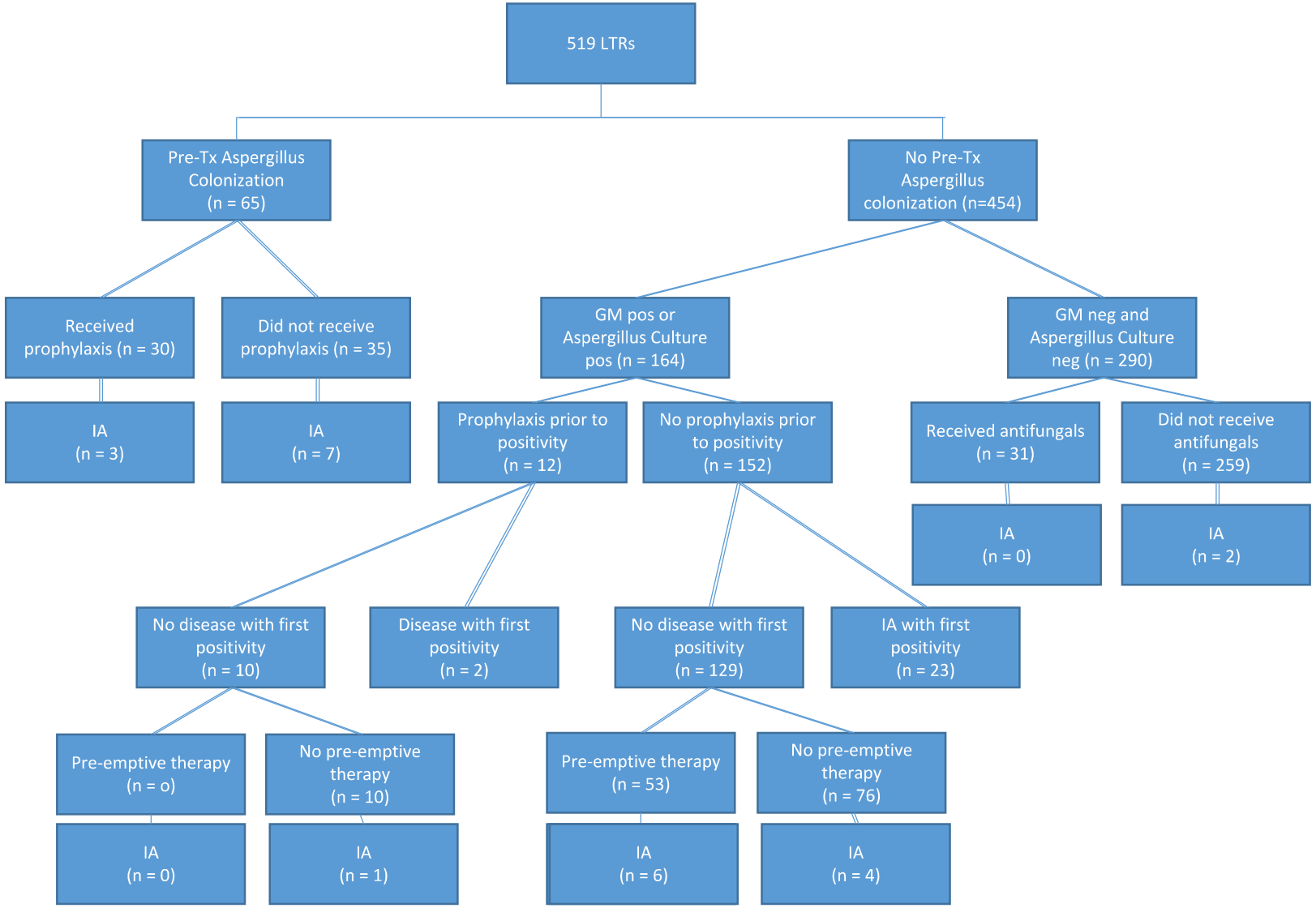
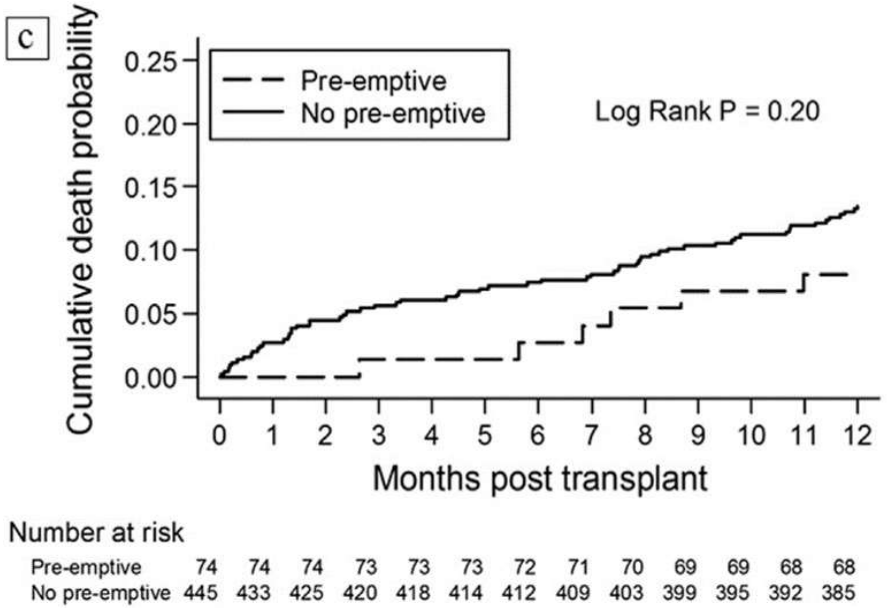
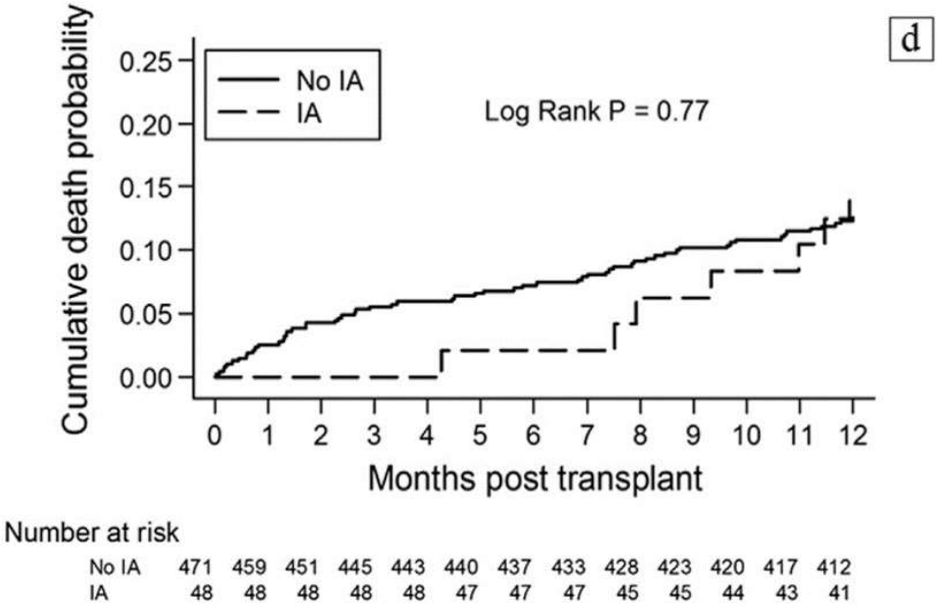


Husain et al. *J Heart Lung Transplant* 2018;37(7)

Pre-emptive Therapy or IA Diagnosis Did Not Increase Mortality at One Year





Husain et al. *J Heart Lung Transplant* 2018;37(7)

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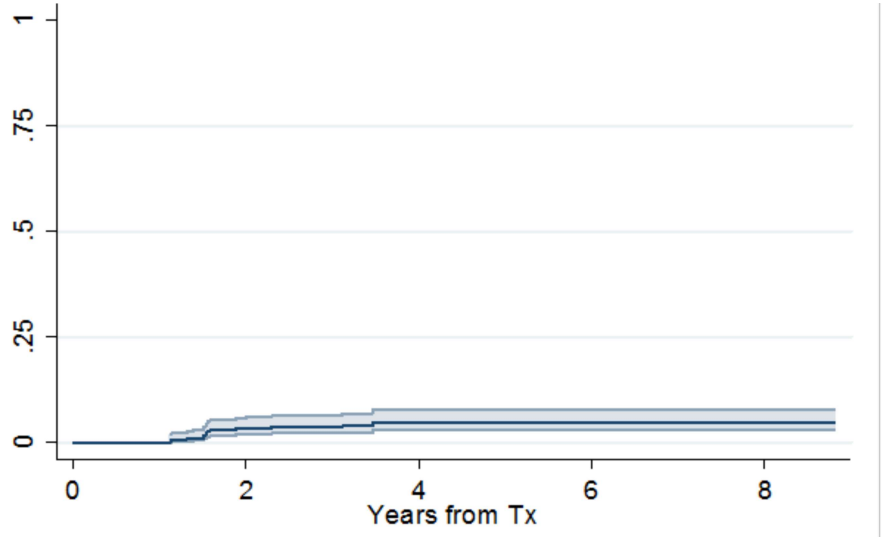
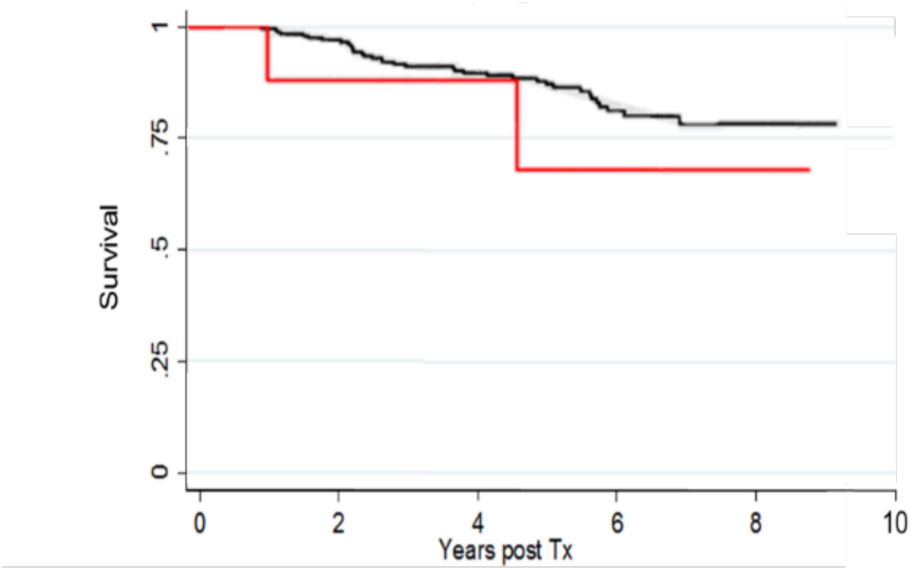
4 Year Follow-up in 350 LTRs who Received Pre-emptive Therapy During First Year

Incidence of IA after 1-year post-transplant was 4%



Mortality rate was similar between patients with or without IPA



Herrera et al. *Transplantation* 2020;104(12)

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Antifungal prophylaxis in adult lung transplant recipients: Uncertainty despite 30 years of experience. A systematic review of the literature and network meta-analysis

@TheTxIDJournal @marinelli_tina

Marinelli *et al.* ***Transplant Infectious Diseases***. 2022.

Systematic review and network meta-analysis

Lung transplant recipients >18y/o

All study designs

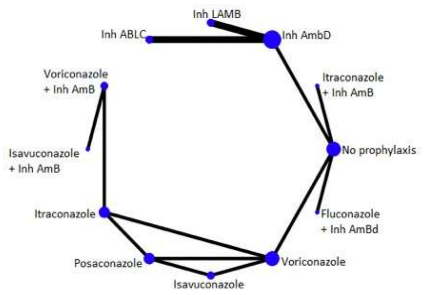
Comparison: Universal antifungal prophylaxis agents or no prophylaxis

Outcome: incidence of proven or probable invasive aspergillosis or invasive fungal infection

2348 abstracts and **86** full papers reviewed

13 studies included
- **1** RCT
- **12** observational cohort studies

Network diagram
- Strongest comparisons are between inhaled amphotericin formulations



SUCRA analysis:
- Top 3 ranked treatments inhaled LAMB, inhaled AmBd and itraconazole plus inhaled AmB
- Top ranked azole = isavuconazole
- Bottom ranked azole = itraconazole

Risk of bias: 12/13 studies assessed high risk of bias (ROBINS-I)
Certainty of evidence: very low (GRADE approach)

Conclusions: This exploratory network meta-analysis provides insight into the comparative effectiveness of various antifungal agents in preventing IA and should serve as a guide when selecting antifungals to be assessed in an RCT.

Transplant Infectious Diseases UHN

WILEY TRANSPLANT INFECTIOUS DISEASE

The Official Journal of Transplant Infectious Disease

TX NETWORK Transplant Peer Review Network

Fungal infection and colonization in lung transplant recipients with chronic lung allograft dysfunction

@TheTxIDJournal @DrKPennington

K Pennington *et al.* ***Transplant Infectious Diseases***. 2022.

While rare, fungal infection following CLAD onset significantly impacts survival

&

Methylprednisolone bolus appears to be a significant risk factor

	IFI		Fungal Colonization		Any Fungal Event	
Risk Factor	HR	p-value	HR	p-value	HR	p-value
Multivariable Model						
Methylprednisolone bolus	7.67	0.01*	11.95	0.03*	8.84	0.001*
ATG	1.22	0.77	2.52	0.20	1.80	0.20
IVIG	2.70	0.11	2.81	0.34	1.21	0.71

Background

Incidence, risk factors, and impact of de novo fungal infections in patients with CLAD is unknown

Results

Out 186 patients with CLAD, cumulative incidence for any fungal event was 11.8% (7.0% infection and 4.8% for colonization)

Peri-CLAD methylprednisone bolus increased the risk of fungal events (HR 8.84, p=0.001)

Median survival from CLAD onset for those who developed IFI (302.6 days, IQR 239.4, 401.2) was significantly less than those who did not develop IFI (1104.4 days, IQR 193.7, 659.8; p<0.001)

Conclusion

Fungal events following CLAD are rare

Peri-CLAD methylprednisolone bolus appears to be a significant risk factor

IFI following CLAD significantly impacts survival

WILEY TRANSPLANT INFECTIOUS DISEASE

The Official Journal of Transplant Infectious Disease

TX NETWORK

Transplant Infectious Diseases UHN

New entity CAPA

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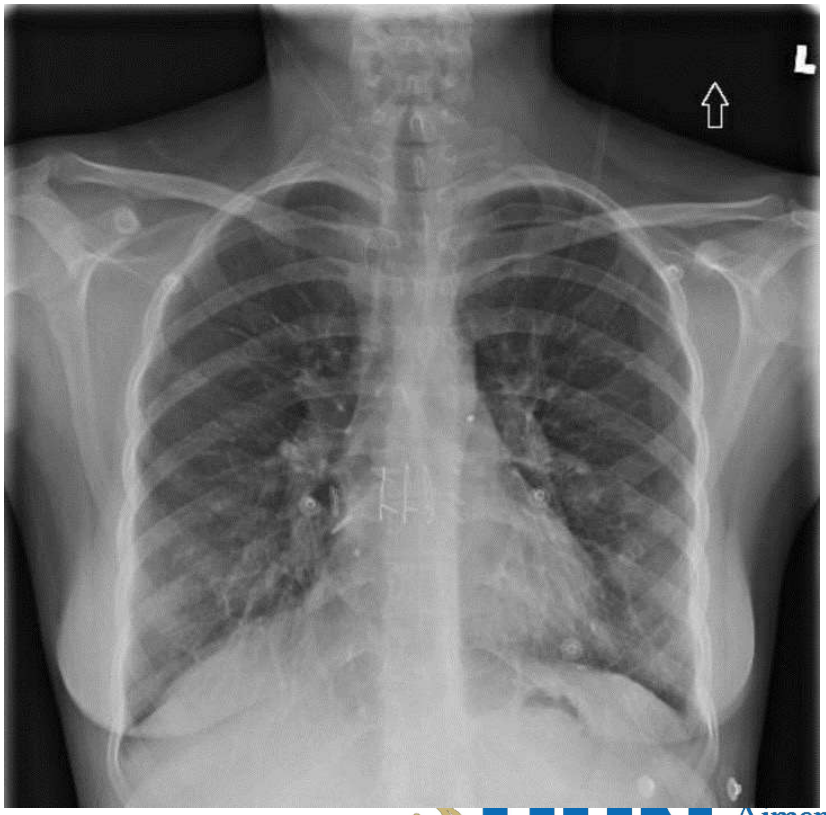
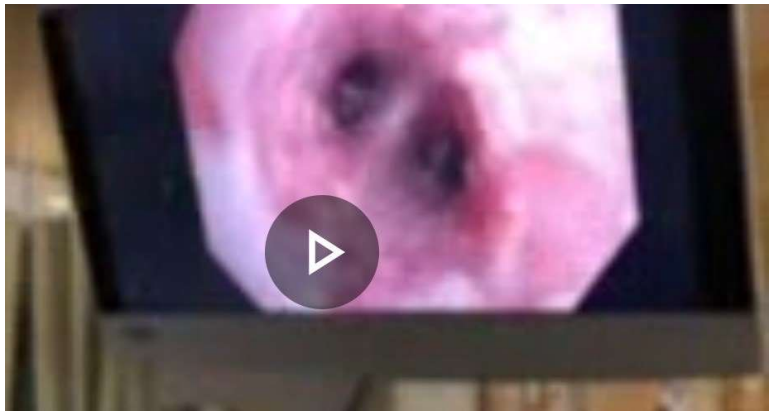
- 20 years old female

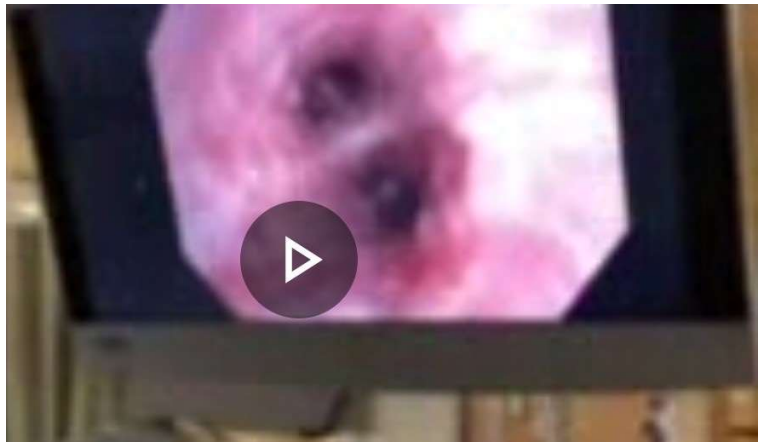
- Double lung transplant in 6/2019 for CF. Had CLAD and was relisted for Tx. Needed supplemental O_2 on exertion.
  - IS: prednisone 12.5 mg daily, TAC 10 mg BID, MMF 100 mg BID
  - Prophylaxis: septra
  - Pre-Tx infections: Stenotrophomonas, PsA, Achromobacter, MAC
  - Post-Tx infections: Stenotrophomonas (12/2019), A. niger (7/2019)

- CF-related DM

- Admitted on December 31 for COVID-19 infection
- Symptoms started 1d prior
- VS: 130/79, 129, 38.2c, 97%+O2 (NP-2L)
- Labs:
  - Hb 112, WBC 2, neutrophils 1.3, lymphocytes 0.2, platelet 209
  - CRP 80
  - Ferritin 99
  - D-Dimer 229
- Started on **Remdesivir and Dexamethasone**
- **tocilizumab was added**

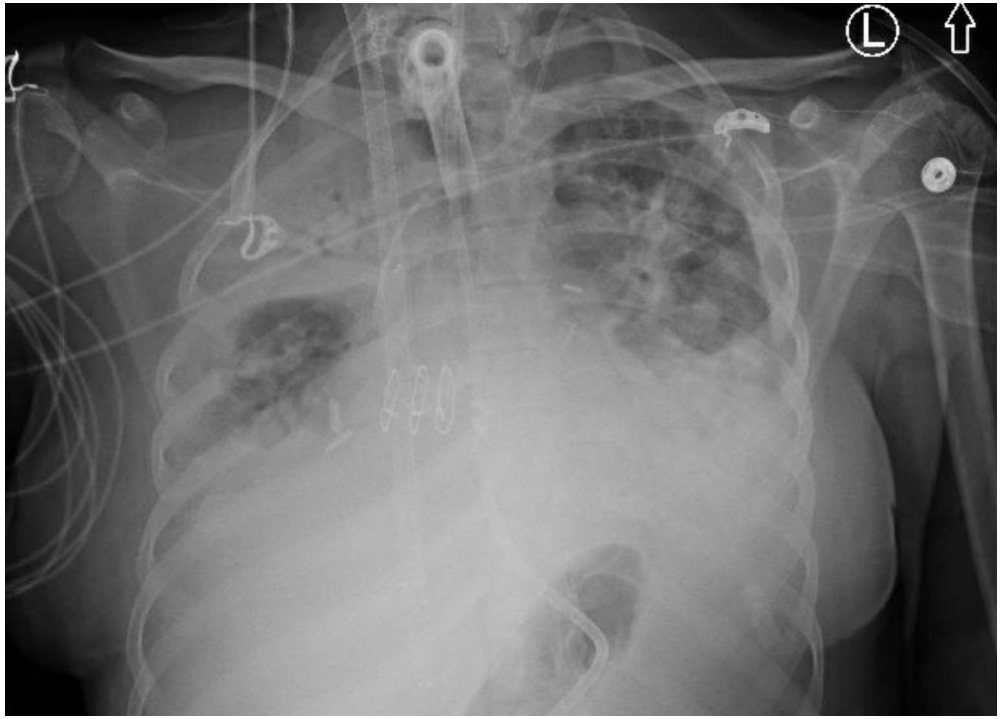




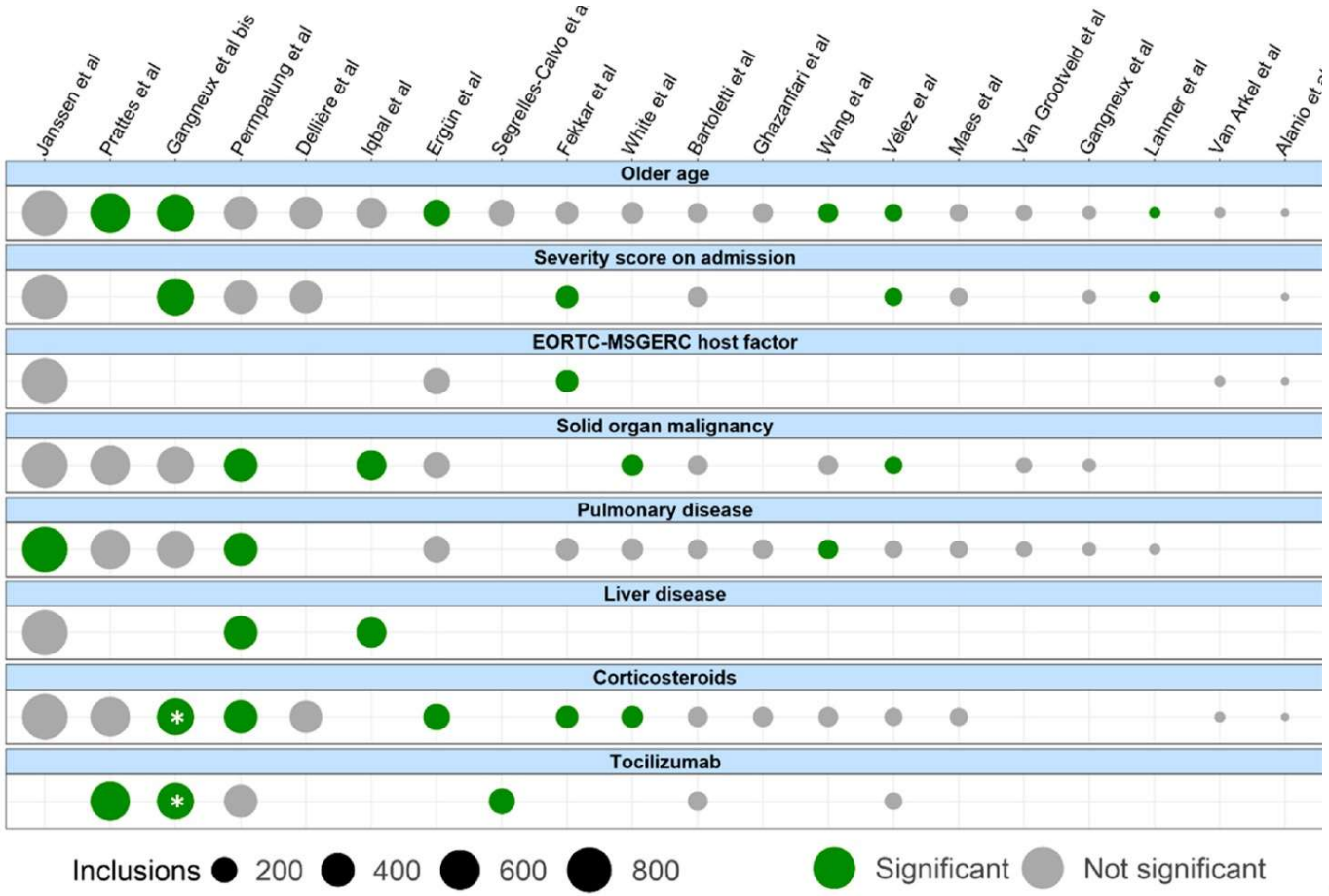


- Jan 8
  - Sputum sample grows *Aspergillus fumigatus*
  - Bronchoscopy shows ulcerative tracheobronchitis and copious secretions
  - BAL culture grows *A. fumigatus* and GM > 4.18
  - Blood GM is negative
  - Voriconazole 6mg/kg→4mg/kg started

- Pt continues to deteriorate
- All cultures grow *A. fumigatus*
- BAL GM greater than 5
- Caspofungin was added to Voriconazole
- Pt is put on ECMO on Jan 15
- Goals of care discussed with family and care is withdrawn



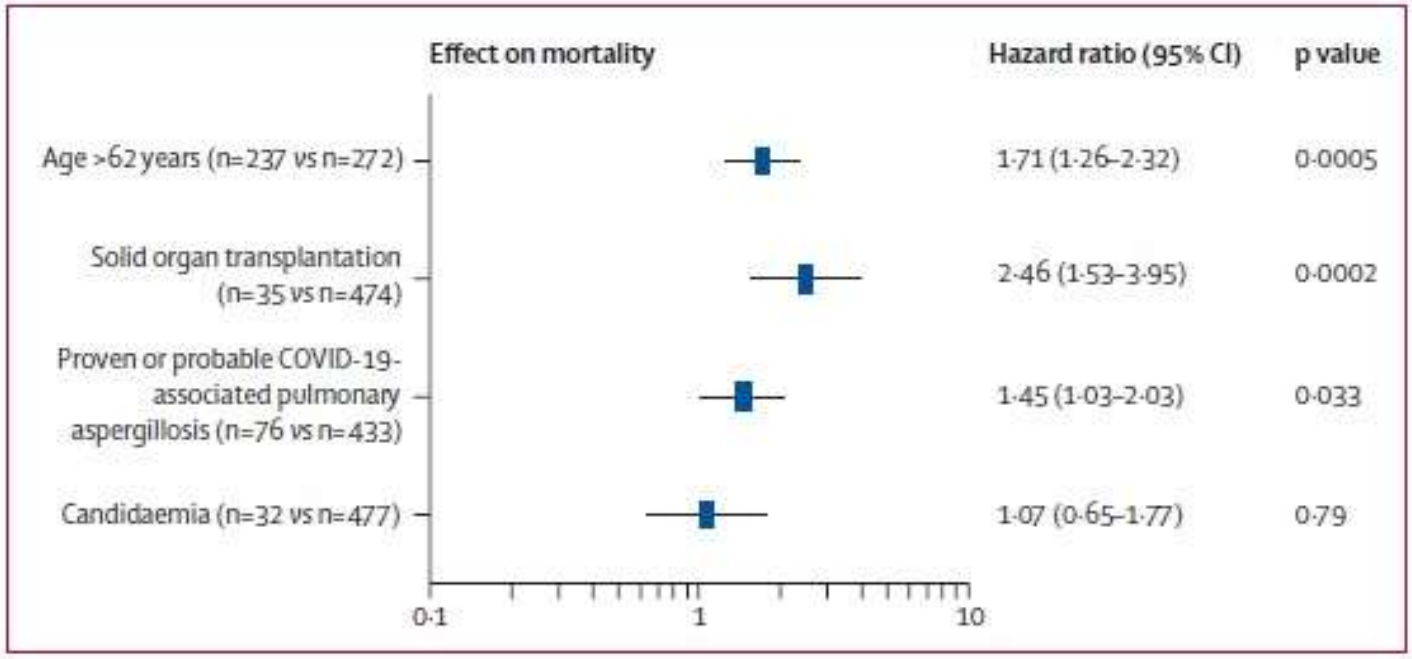
Risk factors of CAPA Studied



J. Fungi 2021, 7, 1067.

CAPA in SOT

565 mechanically ventilated patients ; 35 SOT



Gangneux JP Lancet Respiratory Disease Nov 2021

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Newer Antifungals

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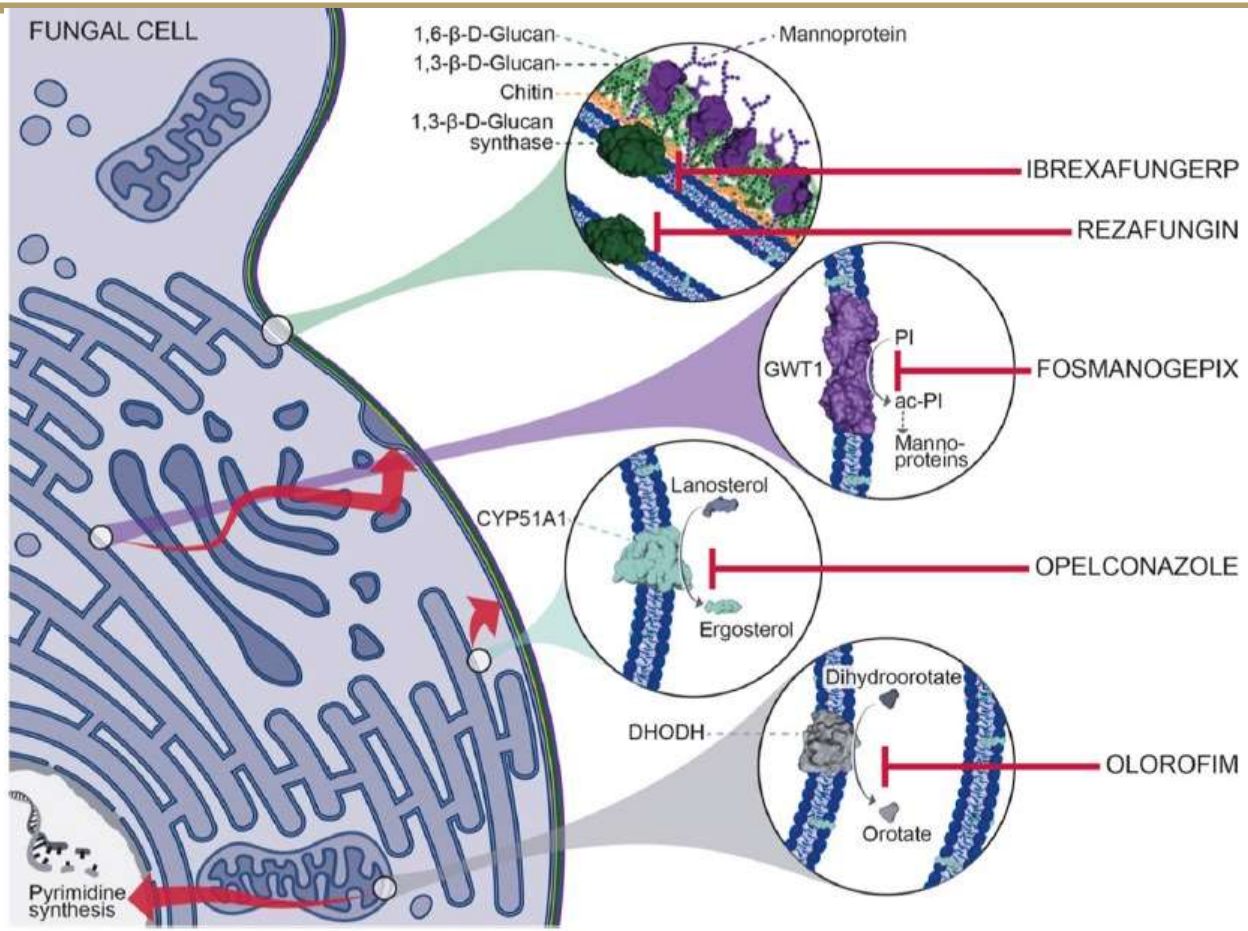
Newer Antifungals



Drugs (2021) 81:1703–1729 ;https://doi.org/10.1007/s40265-021-01611-0

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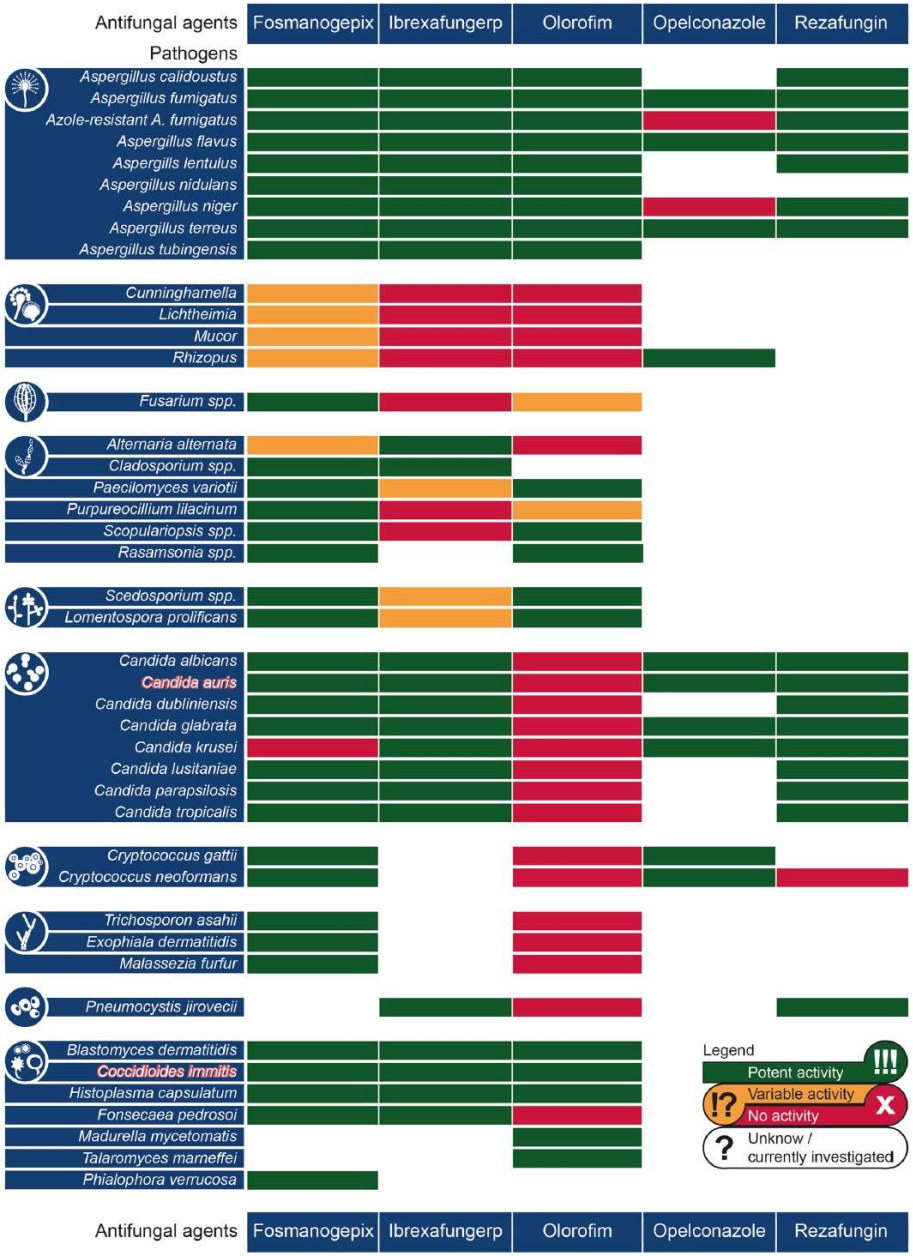


Drugs (2021) 81:1703–1729
https://doi.org/10.1007/s40265-021-01611-0

60 Year-old Woman with Progressive Anastomotic Site Disease after Lung Transplantation

- Undergoes left lung transplantation 2018
  - CMV D+/R+, EBV R+/D+, Toxo R-/D-
  - Prednisone , tacrolimus, MMF – no rejection

- Allograft airway edematous one month after transplantation
  - ***Scopulariopsis* sp.** grows from surveillance BAL 06 December 2018
  - No parenchymal disease
  - Inhaled amphotericin B

Hope WW et al. mBio 2017;8:e01157-17 | Buil JB et al. JAC 2017;72:2548 - 52 | Wiederhold NP et al. JAC 2017;72:1977 – 80 | Oliver JD et al. PNAS 2016; doi /10.1073/pnas.1608304113

60 Year-old Woman with Progressive Anastomotic Site Disease after Lung Transplantation

- Started treatment with

Olorofim on 04 Feb. 2019

- Cultures sterilized,

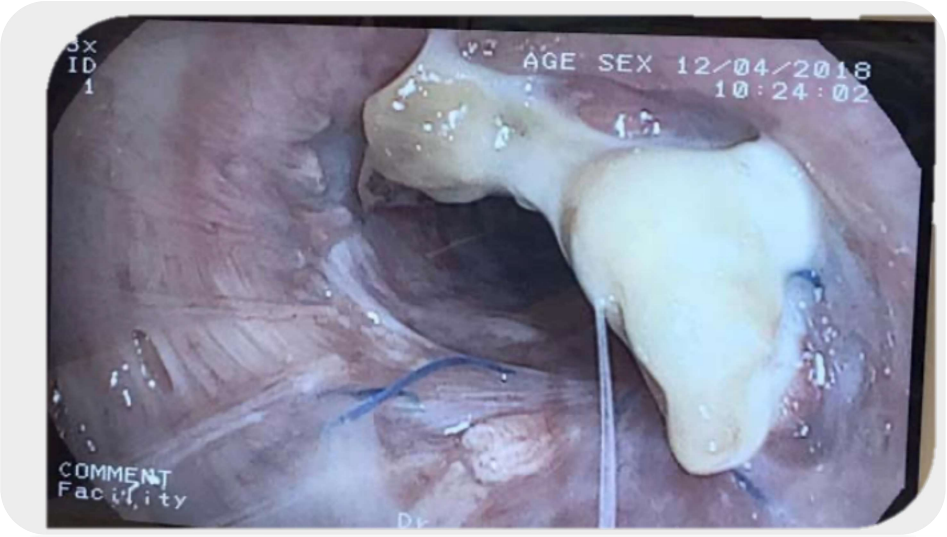
Steady improvement

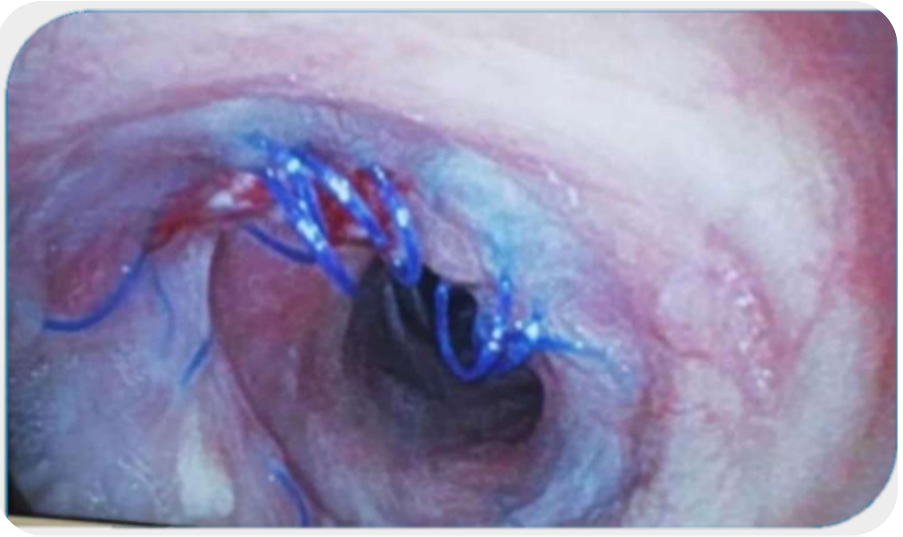
- Completed 12 weeks of treatment
- Required stenting for airway patency, done after completion of treatment

Hope WW et al. mBio 2017;8:e01157-17 | Buil JB et al. JAC 2017;72:2548 - 52 | Wiederhold NP et al. JAC 2017;72:1977 – 80 | Oliver JD et al. PNAS 2016; doi /10.1073/pnas.1608304113

UK Special Needs program requests for PC-945 for patients with no other treatment options

Type	# of Patients	Prior Antifungal Treatment	Clinical Effect with PC495 at 3 Months
Treatment			
Lung transplants (CF, α1-antitrypsis deficiency, IPF, hypersensitivity, pneumonitis)	7	≥ 2.5 months to > 2 years (multiple azoles, caspofungin, neb amph B, terbinafine	Favorable response in 6 patients, Stable disease in 1 patient (infection unconfirmed)
Critical Care (lupus-related hemophagocytic syndrome)	1	1 month (IV isavuconazole, IV voriconazole, caspofungin, IV amph B, neb amph B)	Favorable response (treated for 6 weeks)
ABPA	1	> 12 years (azole, caspofungin, neb amph B, IV amph B)	Favorable response
Secondary Prophylaxis			
Lung transplant (Aspergilloma)	1	Surgical removal, multiple azoles, caspogungin, amph B contraindicated	Follow-up information pending





- 29 year old female with CF developed invasive Aspergillus 1-month post bilateral lung transplant
- Infection not responding to 2+ months on multiple antifungal treatments
- Azoles, caspofungin, terbinafine & neb amphotericin B

Courtesy : Dr. Anna Reed, London

- After 2 weeks of pC945 inhalation, the effects began to clear
- At 2 months no fungus was visible at site of infection, and airway had healed (shown above)
- Treated with PC945 for 3 months
- Complete response

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Phage Therapy of *Mycobacterium* Infections: Compassionate Use of Phages in 20 Patients With Drug-Resistant Mycobacterial Disease

- 20 patients on a compassionate use basis, and patients were monitored for adverse reactions, clinical and microbiologic responses, the emergence of phage resistance, and phage neutralization in serum, sputum, or bronchoalveolar lavage fluid.
- No adverse reactions attributed to therapy were seen in any patient regardless of the pathogen, phages administered, or the route of delivery.
- Favourable clinical or microbiological responses were observed in 11 patients.
- Neutralizing antibodies were identified in serum after initiation of phage delivery intravenously in 8 patients, potentially contributing to lack of treatment response in 4 cases.
- Eleven patients were treated with only a single phage, and no phage resistance was observed in any of these.
- 2 lung transplant recipients both became negative

Clinical Infectious Diseases® 2023;76(1):103–12

Hyperammonemia Syndrome post-Lung Transplantation

Age at transplant	55.2 (±9.7)
Male	66.6% (*n* = 28)
Cause of ESLD	
Idiopathic pulmonary fibrosis	34.9% (*n* = 15)
Chronic obstructive lung disease	23.2% (*n* = 10)
Bilateral sequential lung transplant	85.4% (*n* = 41)
Time of HS presentation	11.0 (±7.7) days
Clinical presentation	
Decreased level of consciousness	11.9% (*n* = 5)
Lethargy and somnolence	11.9% (*n* = 5)
Cerebral edema	36.6% (*n* = 11)
Ammonia level at diagnosis	326 (±317.4) μmol/L
Microbiology findings	88.8% (*n* = 16)
Ureaplasma urealyticum	56% (*n* = 9)
Ureaplasma parvum	31.2% (*n* = 5)
Mycoplasma hominis	31.2% (*n* = 5)
Co-infection rate	18.7% (*n* = 3)
Therapy during HS	
Use of antimicrobials in HS	41.6% (*n* = 15)
Renal replacement therapy	77.5% (*n* = 38)
Bowel decontamination	75.5% (*n* = 37)
Nitrogen scavenging therapy	53.0% (*n* = 26)
Dietary modifications	26.5% (*n* = 13)
Overall fatality rate	59.1% (*n* = 29)

Transpl Infect Dis. 2022;24:e13940.

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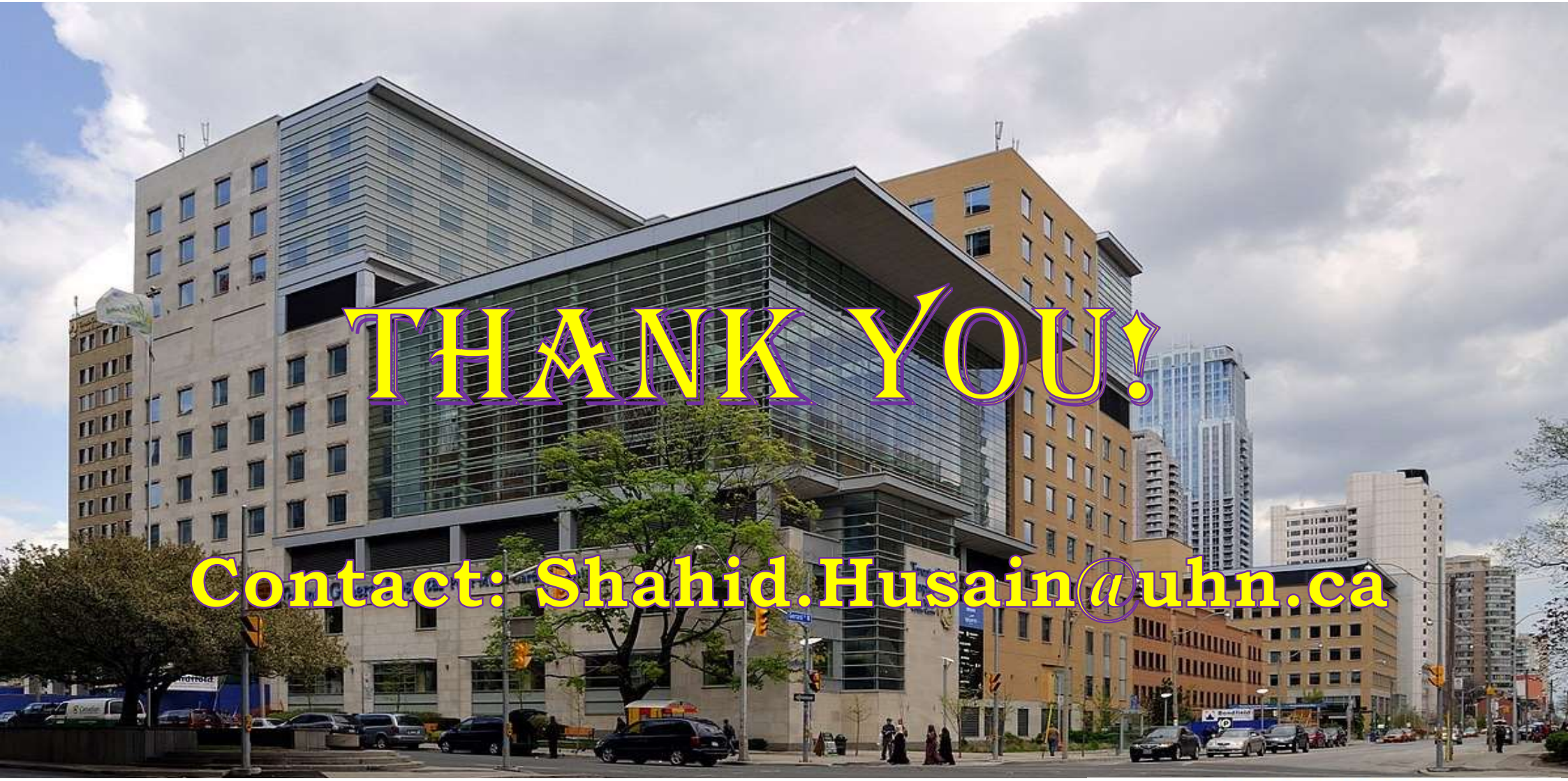

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