Prevention of Invasive Fungal Infection in SOT

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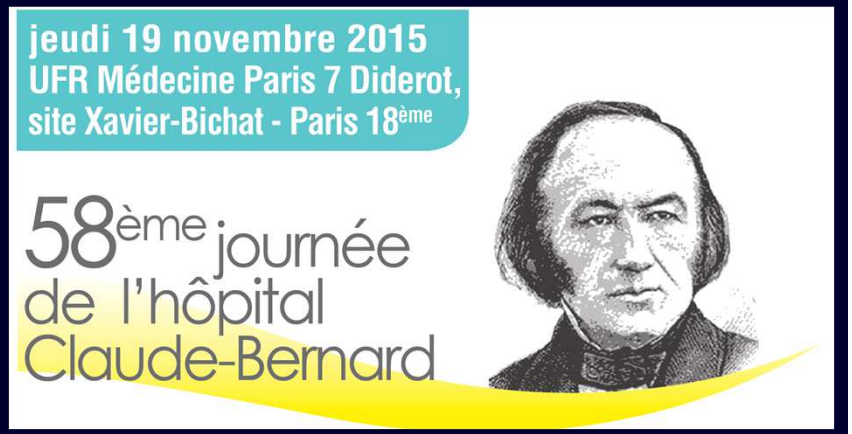

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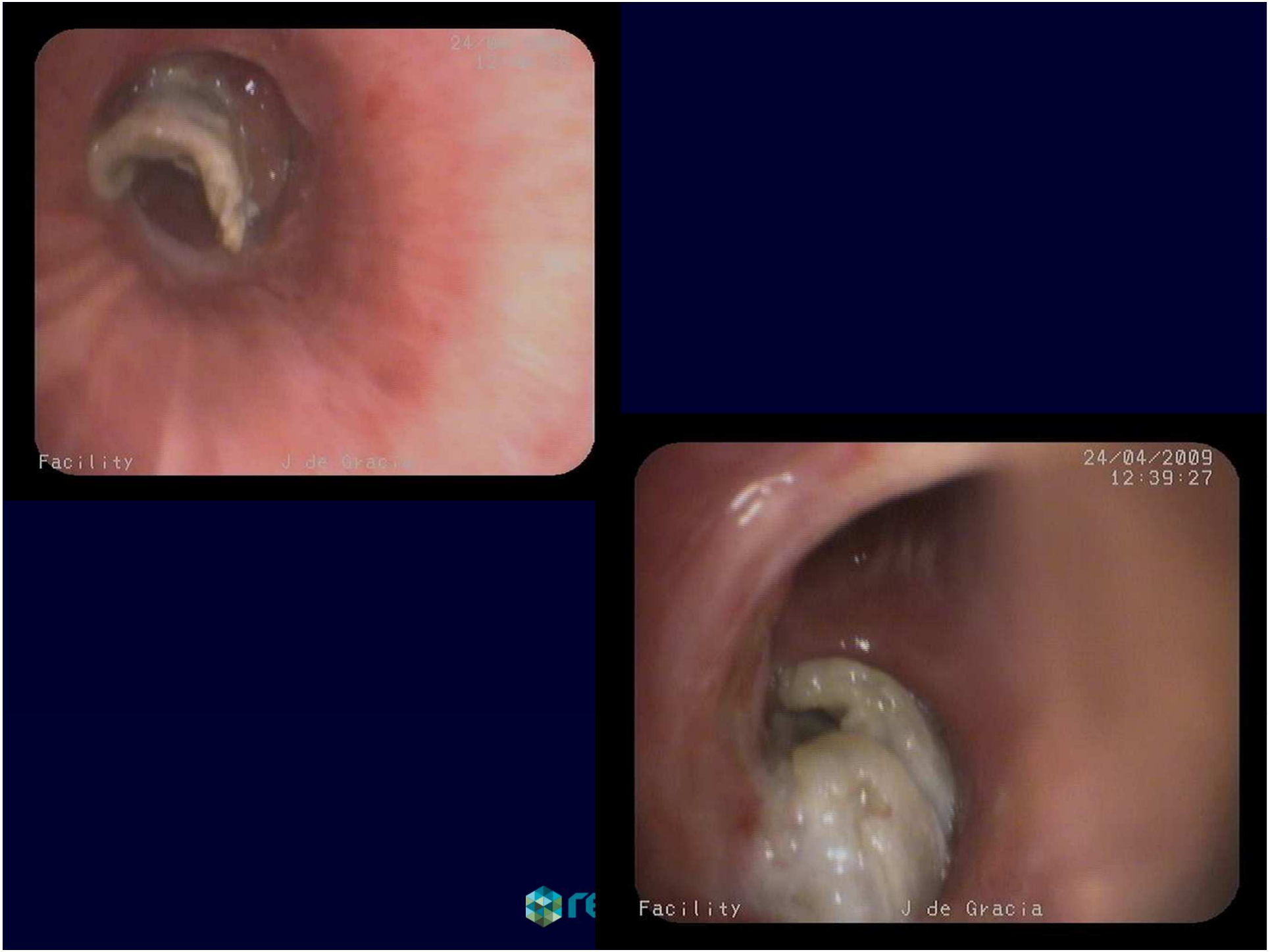
Transplant Recipient with great efforts dyspnea and a decrease of his PFT at m + 3.1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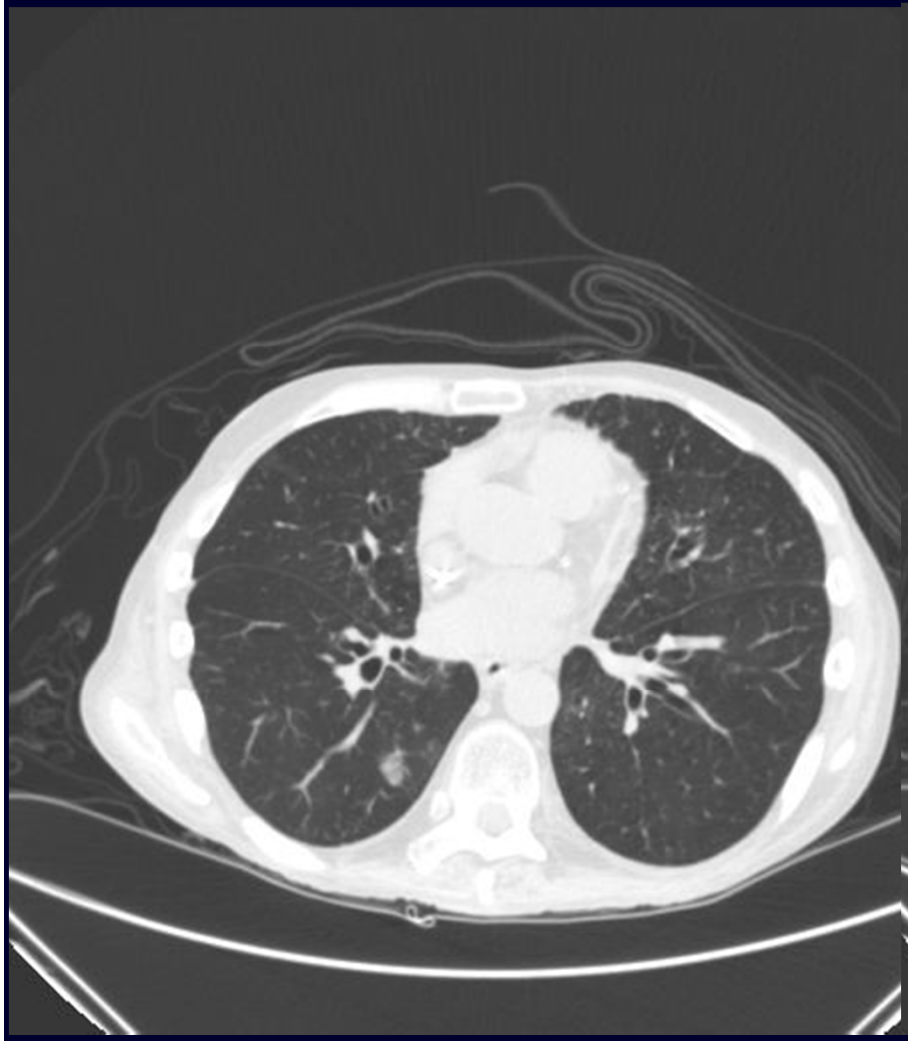

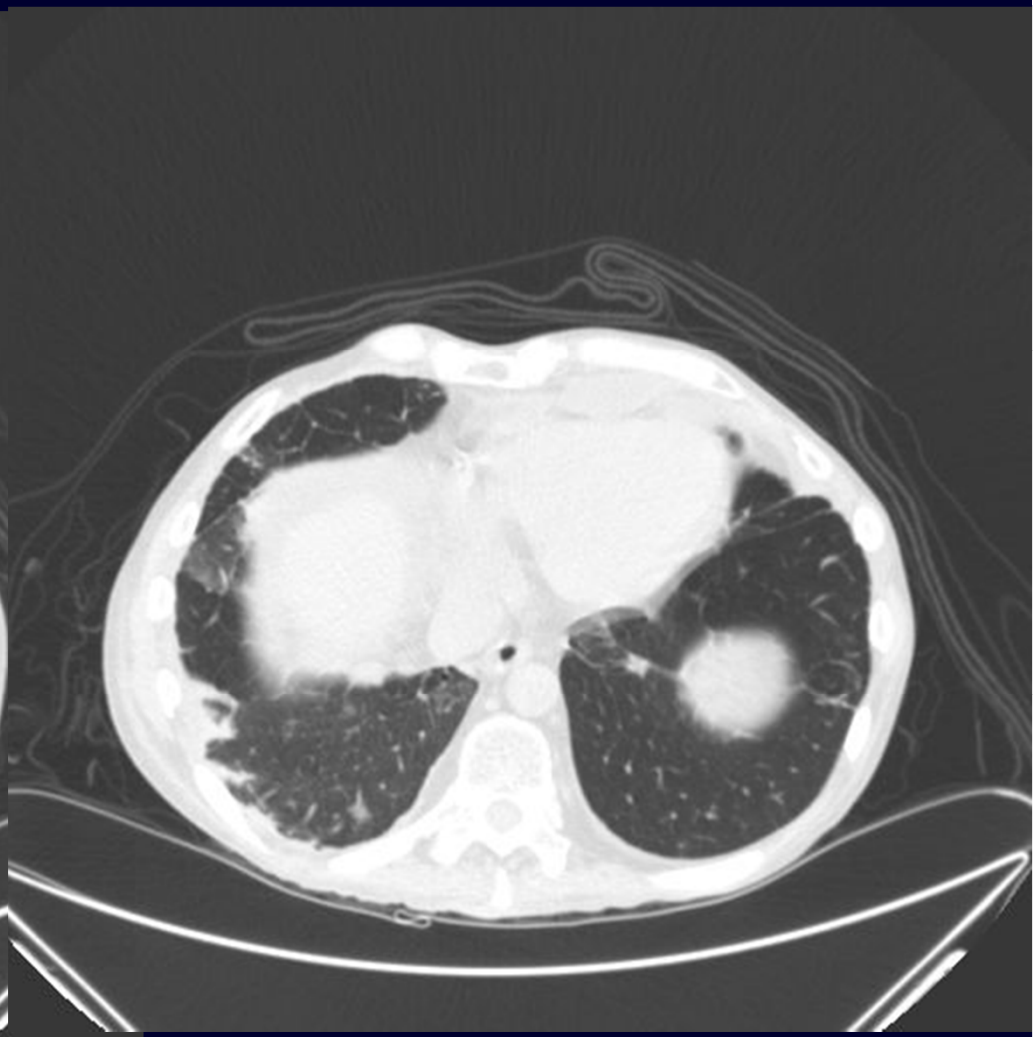

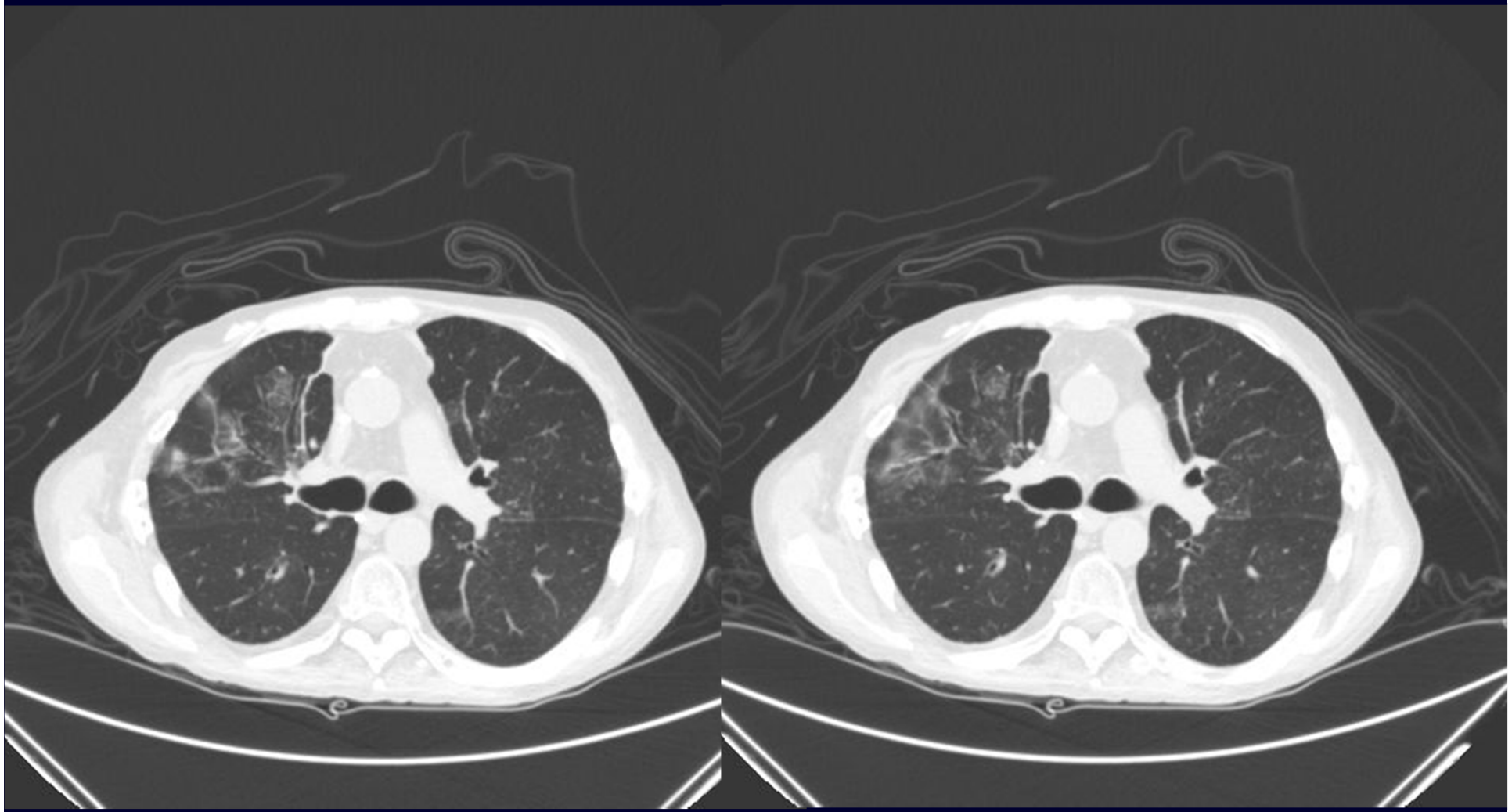

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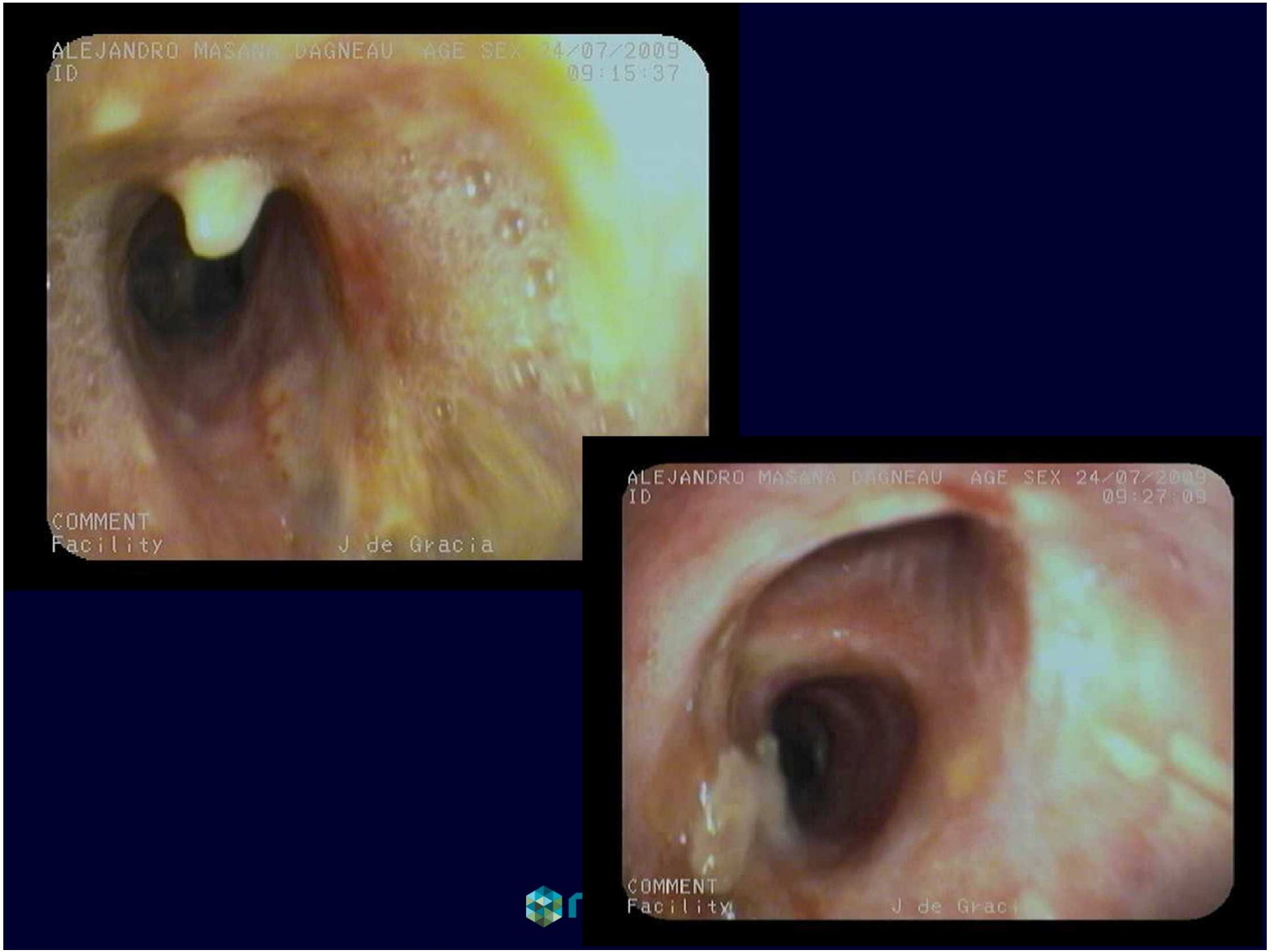
- Diagnosis:
  - Invasive Aspergillosis
    - Nodular Traqueobronchitis due to *Aspergillus fumigatus*
    - Invasive Pulmonary Aspergillosis
  - A3 Acute Rejection

- Treatment:
  - Excision by Rigid Bronchoscopy placing a small net distally to the fungal ball to prevent the dissemination to the graft.
  - Voriconazole + anidulafungin
  - Methylprednisolone 3 pulses of 500 mg daily
  - Nebulized Ambisome 25 mg q24h
  - Valganciclovir 900 mg q24h PO

- Transplant Medicine: Interdisciplinary Approach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Invasive Fungal Infections in SOT Recipients

Transplant patients have a significant risk of invasive fungal diseases (IFD

Caused mainly by *Candida* spp., *Aspergillus* spp., and to a lesser extent, *Cryptococcus* spp. and fungi belonging to the Mucorales order

Invasive Candidiasis SOT

- Most frequent agent of IFD
- Accounting for half of all IFDs
- Rate varies according to the organ transplanted, being particularly high in abdominal SOT
- First months after the surgery
- Candidemia peritonitis, UTI, wound or surgical anastomoses infection or esophagitis
- Overall survival up 60%

Invasive Aspergillosis SOT

- Incidence ranges from 0.1 - 2.4%
- IPA: Most common clinical form
- More frequent Thoracic SOT
- Lung transplant: Invasive Traqueobronchitis as single, ulcerative or nodular form
- Mortality:
  - > 60-70%
  - Lung Tx: depends on the clinical presentation
  - UT around 25 % / IPA 67-82%

IN … OT

MAJOR ARTICLE

Risk Factors for Invasive Aspergillosis in Solid-Organ Transplant Recipients: A Case-Control Study

J. Gavalda,[1] O. Len,[1] R. San Juan,[1] J. M. Aguado,[1] J. Fortun,[1] C. Lumbreras,[1] A. Moreno,[2] P. Munoz,[2] M. Blanes,[10] A. Ramos,[8] G. Rufi,[3] M. Gurgui,[4] J. Torre-Cisneros,[11] M. Montejo,[12] M. Cuenca-Estrella,[9] J. L. Rodriguez-Tudela,[9] and A. Pahissa,[1] for RESITRA (Spanish Network for Research on Infection in Transplantation)

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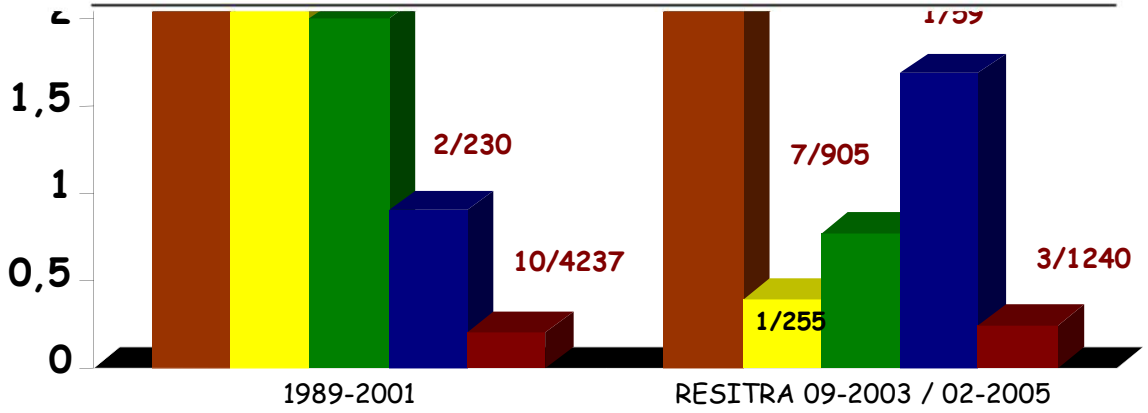

	1989-2001	RESITRA 09-2003 / 02-2005
Lung	3	3,87
Heart	2,4	0,39
Liver	2	0,77
Pancreas	0,9	1,69
Kidney	0,2	0,24

Resitra

IFI Lung Transplant. Epidemiology

- Incidence between 3 and 10%
- Prognosis seems to be better in the last decades
- Type disease:
  - Colonization
  - Traqueobronchitis simple, ulcerative or nodular
  - Invasive disease
  - Invasive disease Native lung
- As CMV, other herpes virus, respiratory virus and the colonization due to *P.aeruginosa,* the infection due to *Aspergillus* spp. May be a risk factor to the development of chronic rejection in the recipients of a lung allograft.

American Journal of Transplantation 2009; 9: 1–9
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2009.02635.x

Aspergillus Colonization of the Lung Allograft Is a Risk Factor for Bronchiolitis Obliterans Syndrome

S. S. Weigt[a,*], R. M. Elashoff[b], C. Huang[a], A. Ardehali[c], A. L. Gregson[d], B. Kubak[d], M. C. Fishbein[e], R. Saggar[a], M. P. Keane[f], R. Saggar[a], J. P. Lynch III[a], D. A. Zisman[a], D. J. Ross[a] and J. A. Belperio[a]

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Key words: Aspergillus, bronchiolitis obliterans syndrome, chronic rejection, fungal infection, lung transplantation, rejection

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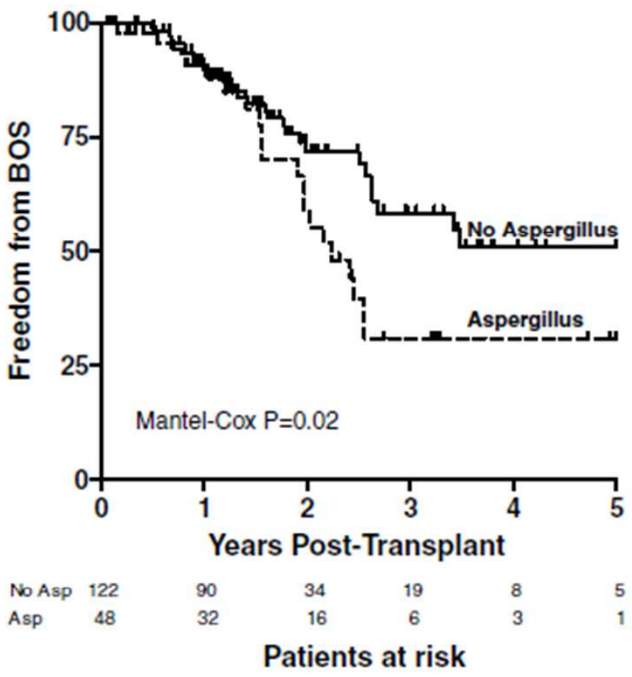

Figure 2: Kaplan–Meier representation of Freedom from BOS. Freedom from BOS after lung transplantation is reduced in the pre-BOS Aspergillus colonization group compared to the group without pre-BOS Aspergillus.

Table 3: Univariate Cox regression for risk factors of BOS

	BOS	
Variable	Hazard ratio (95% CI)	p-Value
Time-independent		
Female	1.11 (0.84–1.46)	0.45
Recipient age (per decade)	0.80 (0.63–1.03)	0.08
Pretransplant Aspergillus	0.98 (0.64–1.67)	0.95
Pretransplant diagnoses		0.13
COPD/ α_1-AT	1.00	
CF/bronchiectasis	0.76 (0.26–1.63)	
IPF	0.67 (0.38–1.15)	
Other	1.42 (0.81–2.44)	
Ischemia-time (h)	1.14 (0.90–1.44)	0.28
Type of transplant		0.12
Bilateral (or heart–lung)	1.00	
Single	0.79 (0.57–1.06)	
Induction agent		0.50
Basiliximab	1.00	
ATG	1.11 (0.82–1.56)	
Cumulative AR score	1.20 (1.07–1.34)	0.002
Time-dependent		
Aspergillus colonization	3.02 (1.73–5.27)	0.0001

Table 4: Multivariate Cox regression for risk factors of BOS

Variable	Hazard ratio (95% CI)	p-Value
Aspergillus colonization	1.81 (1.03–3.19)	0.02
Cumulative AR score	1.17 (1.04–1.31)	0.007

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Prevention

EDITORIAL 10.1111/1469-0691.12658

A special issue on infections in solid organ transplant recipients

J. Gavaldà[1], J. M. Aguado[2], O. Manuel[3], P. Grossi[4], H. H. Hirsch[5] on behalf of the ESCMID Study Group of Infection in Compromised Hosts (ESGICH)

1) Infectious Diseases Department, Hospital Vall d'Hebron, Vall d'Hebron Research Institute VHIR, Barcelona, 2) Hospital Universitario 12 de Octubre, Madrid

TABLE 1. Summary and index of authors of the supplement: 'Recommendations for the Prevention and Management of Infections in Solid Organ Transplantation. A European Perspective'

Prevention IFD SOT

- Absence of clinical trials and the epidemiological differences in IFDs between different transplant programs lead to lack of definitive recommendations for the prevention of IFD in SOT
- TID Experience based Medicine NOT Evidence based Medicine
- Reduction in the incidence needs to be analyzed together with other types of measures more important than antifungal prophylaxis
  - optimization of surgical procedures
  - proper handling of immunosuppression
  - environmental control of certain filamentous fungi

Prevention IFD SOT

The correct identification of patients at increased risk of fungal infection is the main goal for a proper IFD prevention

The election of general prophylaxis versus targeted prophylaxis is based on the type of transplant and clinical risk factors

Appropriate prophylaxis consider the effectiveness, safety, minimal side effects and drug interactions

Risk Factors Invasive Candidiasis in SOT

Poor Pre Transplant health condition

Retransplantation

Complicated Surgery

Renal failure Hemodialysis

Complicated Immediate Post Transplant

OverImmunossupression

Risk Factors Invasive Candidiasis in SOT

Transplant type	Target Population
Liver	**High-Risk Liver Transplant Recipients:** ***Major:*** Retransplantation, fulminant hepatic failure, Split, Living-donor renal failure requiring replacement therapy, ***Minor:*** MELD score > 20 > 40 transfusion blood products, choledochojejunostomy (Roux-en-Y), renal failure not requiring replacement therapy (CrCl <50 mL/min), early reintervention, multifocal colonization/infection by *Candida* spp. choledocho-jejunostomy, , high transfusion requirement (≥40 units of cellular blood products
Pancreas	Postperfusion pancreatitis, Acute Rejection and poor initial allograft function, Vascular thrombosis, Enteric drainage, anastomotic problems, haemodialysis, laparotomy after transplantation, bacterial or CMV co-infection
Intestinal	Acute Rejection and poor initial allograft function, haemodialysis, laparotomy after transplantation, bacterial or CMV co-infection, anastomotic problems. overimmunosuppression
Heart	Acute Rejection Hemodialysis, re-exploration after transplantation, CMV disease, .

Risk Factors IA in SOT

	Early AI	Late AI (> 3 months posttransplant)
Liver Transplant	Retransplantation Kidney failure, especially posttransplant hemodialysis Fulminant hepatic failure as transplantation cause Complicated surgery or reoperation	More than 6 g of prednisone in the third month after transplantation Posttransplant renal failure Posttransplant haemodialysis Leukopenia (<500/mm3) Chronic Graft dysfunction
Lung Transplant	Bronchial anastomotic ischemia or bronchial stent placement Acute rejection Single-lung transplant *Aspergillus* spp. colonization PRE or during first year POST	Chronic Graft dysfunction
Heart Transplant	*Aspergillus* spp. colonization of the respiratory tract Reoperation Posttransplant hemodialysis Hipogammaglobulinemia (IgG < 400 mg/dl)	ICU readmission Kidney transplant > 2 Acute Rejection episodes
Kidney Transplant	Graft lost and hemodialysis Hemodialysis Prolonged high corticosteroids doses	
	CMV Infection **Overimmunosuppression**	

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Wiley Periodicals Inc.

doi: 10.1111/ajt.12114

Special Article

Candida Infections in Solid Organ Transplantation

F. P. Silveira[a,*], S. Kusne[b] and the AST Infectious Diseases Community of Practice

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**Corresponding author: Fernanda P. Silveira silveirafd@upmc.edu*

guilliermondii, an important pathogen in neutropenic hosts, are more common among stem cell transplant recipients, but far less common among organ transplant recipients (9), and may vary according to institution and geographic location.

Established risk factors for invasive candidiasis in the general population include age, broad spectrum antibiotic therapy, use of central venous catheter, receipt of parenteral

Table 3: Risk factors for *Candida* infection and recommended prophylactic strategies

Organ	Risk factors	Antifungal prophylaxis	Duration
Liver	Prolonged or repeat operation Retransplantation Renal failure Choledocho-jejunostomy *Candida* colonization High transfusion requirement	Fluconazole 400 mg/day LFAmB 3–5 mg/kg/day[1]	Up to 4 weeks or Until resolution of risk factors
Small bowel	Graft rejection/dysfunction Enhanced immunosuppression Anastomotic dysruption Abdominal reoperation Multivisceral transplantation	Fluconazole 400 mg/day LFAmB 3–5 mg/kg/day[1]	At least 4 weeks Until healing of anastomosis and absence of rejection
Pancreas	Enteric drainage Vascular thrombosis Postperfusion pancreatitis	Fluconazole 400 mg/day LFAmB 3–5 mg/kg/day[1]	At least 4 weeks

[1]If high rates of non-*albicans* spp or risk factors for *Aspergillus*.

Prevention Invasive Candidiasis SOT

Transplant type	Target Population	Antifungal Drug Election Alternative	Duration
Kidney – Lung - Heart	**No prophylaxis (B-III)**		
Pancreas Pancreas-kidney	**All recipients**	**Fluconazole (B-II)**	1-2 weeks
	High-Risk Pancreas Transplant Recipients: Limitation problems with the use of fluconazole Enteric drainage, anastomotic problems Postperfusion pancreatitis. laparotomy after transplantation, Vascular thrombosis haemodialysis, Cr CL<50ml/min, Acute Rejection and poor initial allograft function, **Overimmunosuppression** bacterial or CMV co-infection	**Caspofungin (A-III)** **Micafungin (A-III)** **Anidulafungin (A-III)** **Lip-AB IV (A-III)** **AB lipid complex IV**	Determined by the presence of risk factor
Intestinal	**All recipients**	**Fluconazole (B-II)**	3–4 weeks Until healing of anastomosis and absence of rejection
	High-Risk Intestinal Transplant Recipients: Limitation problems with the use of fluconazole Laparotomy after transplantation, anastomotic problems. haemodialysis, Acute Rejection and poor initial allograft function, **Overimmunosuppression** bacterial or CMV co-infection,	**Lip-AB IV (A-III)** **Caspofungin (A-III)** **Micafungin (A-III)** **Anidulafungin (A-III)** **AB lipid complex IV (A-III)**	Determined by the presence of risk factor Until healing of anastomosis and absence of rejection

Prevention IFD in Liver Transplantation

Transplant type	Target Population	Antifungal Drug Election Alternative
Liver	**High-Risk Liver Transplant Recipients:** ***Major:*** Retransplantation, fulminant hepatic failure, MELD ≥ 30 Renal failure requiring replacement therapy ***Minor:*** MELD score 20-30, Split, Living-donor, choledochojejunostomy (Roux-en-Y), High transfusion requirement (≥40 units of cellular blood products), Renal failure not requiring replacement therapy (CrCl <50 mL/min), Early reintervention, multifocal colonization/infection by *Candida* spp.	**If one major or two minor criteria:** **Micafungin (A-II)** **Caspofungin (A-II)** **Lip-AB IV (A-II)** **AB lipid complex IV (A-II)** **Anidulafungin (B-III)**

Duration 2- 4 w or end risk factors

Prevention IFD in Liver Transplantation

Transplant type	Target Population	Antifungal Drug Election Alternative	Duration
Heart	**No prophylaxis**		
	High-Risk Heart Transplant Recipients: Acute Rejection Hemodialysis, Re-exploration after transplantation, *Aspergillus* spp. heavy colonization of air.	**Itraconazole (A-II)** **Voriconazole (B-III)** **Posaconazole (B-III)** **Equinocandins (B-III)**	At least 3 months
Late Invasive Aspergillosis	**High-Risk Late Invasive Aspergillosis** Chronic rejection, allograft dysfunction due to VHC (liver transplant), hemodialysis	**Nebulized Lip-AB B (A-III)** Load 25 mg 3 times a wk for 2 weeks, then once a wk	Determined by the presence of risk factors
		Nebulized Amphotericin B lipid complex (B-III) Load once every 2 days for 2 weeks, then 50 mg once a week	Determined by the presence of risk factors

Prevention IFD in Liver Transplantation

Transplant type	Target Population	Antifungal Drug Election Alternative	Duration
Lung/ Lung-heart	**All recipients** Recommended strategy **OR** **Guided Prophylaxis** Induction with Alemtuzumab or Thymoglobulin Acute rejection Single-lung transplant *Aspergillus* spp. Colonization PRE or during first year POST transplant Acquired hypogammaglobulinemia (IgG < 400 mg/dL)	**Nebulized Lip-AB 25mg (A-II)** Until resolution of bronchial suture: 3 times a week 2 to 6 month: once a week > 6 month: once every 2 weeks **Guided Prophylaxis:** Load 25 mg 3 times a week for 2 weeks, then once a week.	Indefinite or for a minimum of 12 m
		Nebulized Amphotericin B lipid complex 50mg (B-II)# Load once every 2 days for 2 weeks, then 50 mg once a week	A minimum of 12 m
		Voriconazole (B-II) PO. Load 400 mg q12h, then 200 mg q12h	Determined by the presence of risk factors, minimum 4 m

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Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2006.01548.x

Voriconazole Prophylaxis in Lung Transplant Recipients

S. Husain[a], D. L. Paterson[a], S. Studer[d], J. Pilewski[d], M. Crespo[d], D. Zaldonis[c], K. Shutt[a], D. L. Pakstis[a], A. Zeevi[b], B. Johnson[d], E. J. Kwak[a] and K. R. McCurry[b,c,*]

Introduction

Lung transplant recipients suffer from a high rate of infectious complications including a high rate of invasive aspergillosis (IA) (1–3). Aggressive immunosuppression as

	Voriconazole	Targeted Itraconazole/ inhaled Ab	p - value
n IFI	1/65 (1.5%)	7/30 (23%)	0.001
n non Aspergillus infections at one y	2/65 (3%)	7/30 (23%)	0.004

- Voriconazole: 200 mg bid minimum 4 m (n = 65)
- Targeted: *Aspergillus* spp Pre or post: Itraconazole 200 mg bid ± Ab nebulized 4-6 post Tx (n = 30)

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IFI Lung Transplantation
Use of voriconazole

Risk of Liver Toxicity

Drug interactions

Need to TDM

Risk of skin cancer

American Journal of Transplantation 2006; 6: 3008–3016
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2006.01548.x

Voriconazole Prophylaxis in Lung Transplant Recipients

S. Husain[a], D. L. Paterson[a], S. Studer[d], J. Pilewski[d], M. Crespo[d], D. Zaldonis[c], K. Shutt[a], D. L. Pakstis[a], A. Zeevi[b], B. Johnson[d], E. J. Kwak[a] and K. R. McCurry[b,c,*]

Introduction

Lung transplant recipients suffer from a high rate of infectious complications including a high rate of invasive aspergillosis (IA) (1–3). Aggressive immunosuppression as

Table 4: Comparison of the rate of elevated liver enzymes (≥3 times upper limit of normal) between targeted prophylaxis group and voriconazole group

	Voriconazole prophylaxis group %(n) (n = 65)	Targeted prophylaxis group %(n) (n = 27)	p values
GGTP[1]	60% (39/65)	41% (11/27)	0.07
ALT[2]	45% (29/65)	15% (4/27)	0.005
AST[3]	37% (25/65)	15% (4/27)	0.02

[1] Gammaglutamyl transpeptidase.
[2] Alanine aminotransferase.
[3] Aspartate aminotransferase.

Table 1. Risk Factors for Skin Cancer Development in Organ Transplant Recipients

Fitzpatrick skin type I to III
Increasing age at transplantation
Duration and level of immunosuppression
Type of organ transplant (heart/lung > kidney > liver)
Previous transplant
Squamous cell carcinoma before transplant
History of lymphoma pretransplant/posttransplant
Pretransplant end organ disease (eg, rheumatoid arthritis, systemic lupus erythematosus, or autoimmune hepatitis)
Liver transplant recipients with psoriasis on previous biological therapy/psoralen plus ultraviolet A light phototherapy

From Zwald FO and Brown M. J Am Acad Dermatol. 2011 Aug; 65(2):253–61; quiz 262. doi: 10.1016/j.jaad.2010.11.062.

Author	Study Design	Population Studied	Outcome Measure	Results
Feist et al [24]	Retrospective cohort	120 lung transplant recipients: cases (n = 32), controls (n = 88)	Incidence of SCC	• SCC developed in 39.5% of patients who received voriconazole compared with 19.5% of patients who did not receive voriconazole (P = .03)· Older age at time of transplant, skin cancer pretransplant, and longer voriconazole therapy were independent risk factors for skin cancer development
Singer et al [26]	Retrospective cohort	327 lung transplant recipients: cases (n = 50), controls (n = 277)	Time to first SCC after transplantation	• Exposure to voriconazole was associated with a 2.6-fold increased hazard for SCC (P = .014) • Hazard of SCC increased by 5.6% with each 60-day exposure at a standard dose of 200 mg twice daily (P = .006) • Significant covariates include white race, older age at transplantation, skin cancer pretransplant, use of voriconazole therapy, voriconazole cumulative dose, and voriconazole duration of therapy
Vadnerkar et al [25]	Retrospective case control	68 lung transplant recipients selected from a cohort of 543 patients: cases (n = 17), controls (n = 51)	Incidence of SCC	• 3.1% of study population developed SCC during a 6-year period; patients received voriconazole for a significantly longer duration compared with controls (P = .03) • Duration of voriconazole use (P = .04) and residence in locations with high levels of sun exposure (P = .0004) were independent risk factors for SCC
Zwald et al [28]	Retrospective cohort	91 lung transplant recipients: cases (n = 28), controls (n = 63)	Number of nonmelanoma skin cancers after lung transplantation	• Number of months on voriconazole was found to be significantly associated with number of NMSC (P = .007) • Time since transplantation, age, skin type I or II, and months of exposure to voriconazole were found to be independent risk factors for number of skin cancers posttransplantation

Azoles Drug A (FLU, ITRA, VOR, POS) Drug B	Effect	Recommendation
Antacid **H2 antagonist** Cimetidine Famotidine Ranitidine	↓↓ **ITRA** conc **Cimetidine VOR** ↓↓ conc	**Avoid/ Use Alternative ITRA** **Avoid/ Use Alternative combination Cimetidine /VOR**
Antiepileptic drugs Carbamazepine Fosphenytoin Oxcarbazepine Phenytoin	↓↓ **A** conc ↑↑ **B** conc **A, B;** increase ++ metabolism CYP3A4 ↓↓ CNI, mTOR inhibitors conc [a]	**Avoid/ Use Alternative** Consider use other non-azole antifungal drug Partial Seizures: Consider Valproic acid, Gabapentin, Pregabalin, Lacosamide Acute repetitive seizures or status epilepticus: Consider IV **Lorazepam**
Barbiturates Secobarbital Pentobarbital Phenobarbital	↓↓ **A** concentration **B** increase ++ metabolism CYP3A4 ↓↓ CNI, mTOR inhibitors conc [a]	**Avoid/ Use Alternative**
Benzodiazepines Alprazolam Bromazepam Chlordiazepoxide Clobazam Clonazepam Clorazepate Diazepam Estazolam Flurazepam Midazolam Nitrazepam Triazolam	↑ **B** conc	**Avoid/Use Alternative or Consider therapy modification** Consider **Lorazepam, Oxazepam, or Temazepam** or **Decrease benzodiazepine dose**
Calcium Channel Blockers (CCB) Amlodipine Diltiazem Felodipine Isradipine Nicardipine Nifedipine Nisolpidine Verapamil	↑ **B** conc Verapamil, diltiazem, nicardipine, and amlodipine: **B, A; inhibition** metabolism CYP3A4: ↑ CNI, mTOR inhibitors conc [b] **Nifedipine, isradipine** No effect metabolism CYP3A4	**Consider Avoid/ Use Alternative** **If clearly indicated:** Consider use other non-azole antifungal drug CCB dose reduction is needed Monitor toxic effects CCB Consider avoid mTOR inhibitors **or** **Consider Nifedipine, isradipine** TDM CNI closely
Clopidogrel	↓ **B** efficacy VOR, FLU	**Avoid VOR, FLU / Use Alternative**
Cyclosporine	↑ **B** conc	**Consider therapy modification** **Reduce B dose mandatory:** FLU: Dose dependent. By 20-50%; VORI: by ½; POS: by ¼. Monitor TDM Cyclosporine closely
Digoxin	**ITRA, POSA** ↑ **B** conc	Monitor for increased serum
Ergot alkaloids dihydroergotamine, ergonovine, ergotamine, methylergonovine	↑ **B** conc	**Avoid ITR, VOR, POS / Use Alternative** Consider use other non-azole antifungal drug **FLU: Decrease doses of** Ergot alkaloids. Monitor for increased toxicity
Fentanyl	↑ **B** conc Cyclosporine ↑ **B** concentration	**Avoid VOR, POS, ITRA / Use Alternative** **Consider therapy modification** FLU, ITRA, Decrease dose fentanyl Monitor adverse events fentanyl
Herbal Product: St. John's Wort (hypericum perforatum)	↓ **VOR**	**Avoid** Should be avoided due to the risk for voriconazole treatment failure.
Herbal Product: Red Yeast Rice	**ITRA, VORI, POSA** ↑ **B** conc	**Avoid** Concentrations of lovastatin and related compounds found in Red Yeast Rice may be increased. Potential for myopathy
Highest Risk QTc-Prolonging Agents / QTc-Prolonging Agents Amiodarone Artemether Astemizole Cisapride Citalopram Disopyramide Dronedarone Escitalopram Flupentixol Halofantrine Procainamide Quinidine Quinine Saquinavir Sotalol Sparfloxacin Telithromycin Terfenadine	**A** Enhance the QTc-prolonging effect of **B** **CNI** Enhance the QTc-prolonging effect of **B**	**Consider Avoid Combination/ Use Alternative** Risk of torsades de pointes or potentially life-threatening ventricular tachyarrhythmias Consider use other non-azole antifungal drug Combinations should only be undertaken with caution and should be avoided when possible
Macrolides Erythromycin Clarithromycin Azithromycin	↑ **A** concentration ↑ **B** concentration A,B Synergism inhibition metabolism CYP3A4: ↑↑ CNI, mTOR concentrations [b]	**Avoid Erythromycin/Use Alternative** Consider therapy modification **Use ONLY if Clearly Indicated** Consider use **azithromycin** Consider use other non-azole antifungal
mTOR Sirolimus	↑ mTOR conc [b]	**Avoid Combination VOR, POS/ Use Alternative**

Nebulized Amphotericin B The Vall d'Hebron Experience

reipi RED ESPAÑOLA DE INVESTIGACIÓN EN PATOLOGÍA INFECCIOSA
Vall d'Hebron Institut de Recerca VHIR

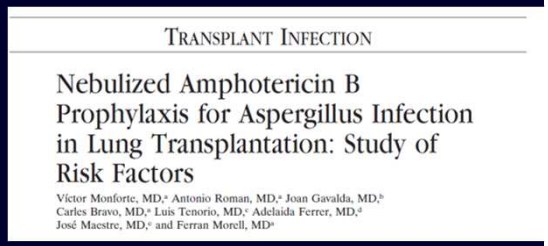
Lung Transplantation: Prophylaxis Nebulized CAB *Aspergillus* Infection

	n	Median (range) Follow-up (mo)	*Candida* Mucositis n (%)	*Aspergillus* Infection n (%)	Median (range) Time to Tx (mo)	Death Related to *Aspergillus* Infection, n (%)
No prophylaxis	13	27.5 (4-56)	8 (61.5 %)	7 (53.8 %) 3 IPA 2 UT - 2 T	11.6 (0.3-41)	3 (23.1%)
Prohylaxis (intent to treat)	280	20.9 (0.7-48)	0	17 (6%) 2 IPA 3 UT - 12 T	6 (0.5-27.6)	2 (0.7 %)
Compliance	177			11 (6.2%)		1 (0.5%)
No compliance	18			5 (27.7 %)		1 (5%)

Monforte V, et al. *J Heart Lung Transplant*. 2001;20:1274-1281.

Lung Transplantation: Prophylaxis Nebulized CAB *Aspergillus* Infection

Risk Factors


TRANSPLANT INFECTION

Nebulized Amphotericin B Prophylaxis for Aspergillus Infection in Lung Transplantation: Study of Risk Factors

Víctor Monforte, MD,[a] Antonio Roman, MD,[a] Joan Gavalda, MD,[b] Carles Bravo, MD,[a] Luis Tenorio, MD,[c] Adelaida Ferrer, MD,[a] José Maestre, MD,[c] and Ferran Morell, MD[b]

- Nebulized CAB independent factor to decrease *Aspergillus* infection
  - Odds ratio: 0.13; 95% CI 0.02-0.69; *P*<0.05
- CMV disease independent risk factor
  - Odds ratio: 5.1; 95% CI 1.35-19.17; *P*<0.05

Monforte V, et al. *J Heart Lung Transplant*. 2001;20:1274-1281.

Lung Transplantation: PK and Distribution of Nebulized CAB

- BL and BAL were obtained from 115 consecutive bronchoscopies in 39 patients
- Procedures at 4, 12, 24, and 48 hours and 7 days postnebulization of 6 mg CAB
- HPLC was used to measure concentrations (µg/mL)
- Results were provided as mean (95% CI of the mean)

Monforte V, et al. *Transplantation. 75(9):1571-1574, May 15, 2003*.

Lung Transplantation: PK of Nebulized CAB

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TRANSPLANTATION
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Vol. 75, 1571–1574, No. 9, May 15, 2003
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NEBULIZED AMPHOTERICIN B CONCENTRATION AND DISTRIBUTION IN THE RESPIRATORY TRACT OF LUNG-TRANSPLANTED PATIENTS

VÍCTOR MONFORTE,[1] ANTONIO ROMAN,[1,5] JOAN GAVALDÁ,[2] ROSA LÓPEZ,[3] LEONOR POU,[3] MARC SIMÓ,[4] SANTIAGO AGUADÉ,[4] BERNAT SORIANO,[4] CARLES BRAVO,[1] AND FERRAN MORELL[1]

	n	BL (µg/mL)	BAL (µg/mL)
4 h*	30	3.0 (1.6-4.4)	15.8 (11-20.6)
12 h	32	2.2 (1.1-3.3)	13.7 (9.5-17.8)
24 h	25	2.1 (1-3.2)	11 (7-15.1)
48 h	15	1.6 (0.8-2.4)	10.6 (6.7-14.7)
7 d	4	ND	ND

*In 5 patients, **no** serum levels of CAB were detected.

Monforte V, et al. ***Transplantation. 75(9):1571-1574, May 15, 2003.***

Lung Transplantation: Nebulized CAB Distribution


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- Distribution studies in 17 lung transplant recipients
- Amphotericin B 25 mg labeled with SnCl + 600 MBq of 99m technetium (Tc)
- Inhalation—deposition images by scintigraphy; 6 standard projections
- 250 MBq of 99mTc-labeled macroaggregates; IV + comparative perfusion projection

Monforte V, et al. ***Transplantation. 75(9):1571-1574, May 15, 2003.***

Lung Transplantation: Nebulized CAB Distribution

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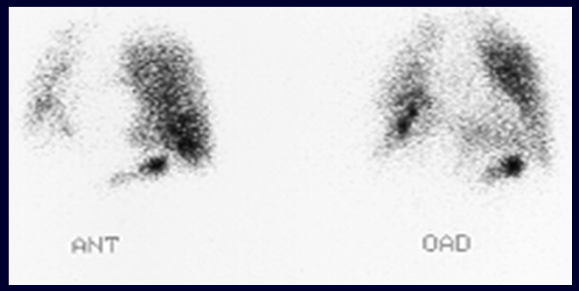
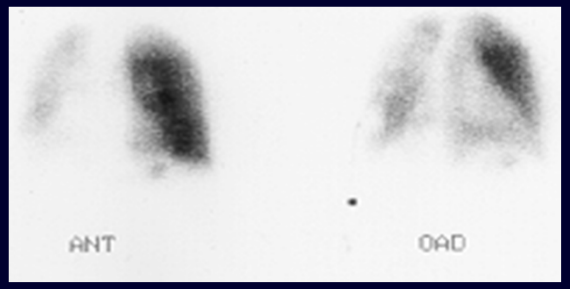
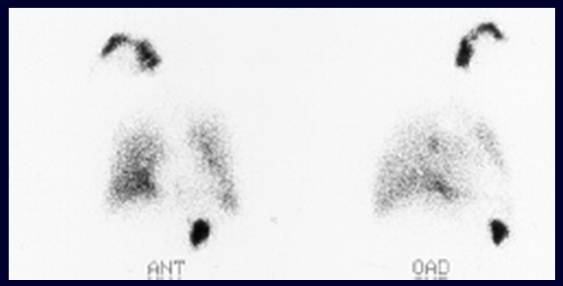
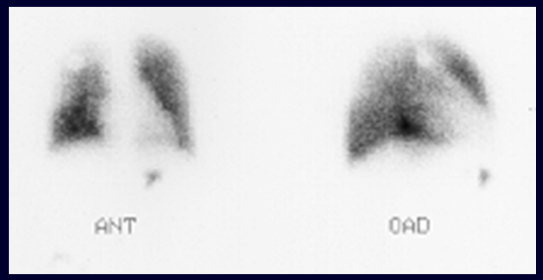


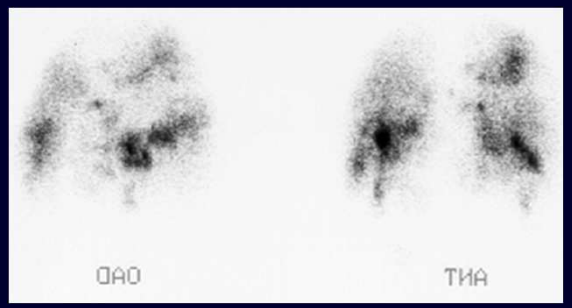


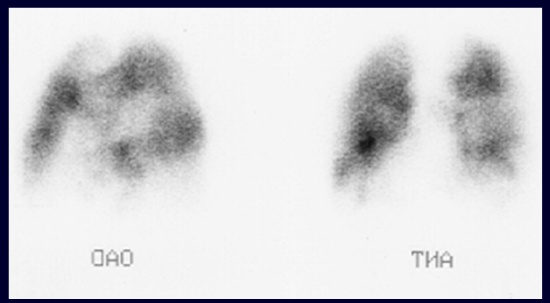
Single Lung Transplant





Double Lung Transplant





Chronic Rejection

Ventilation Perfusion

Monforte V, et al. *Transplantation. 75(9):1571-1574, May 15, 2003*.

Can We Use Nebulized LAb as Prophylaxis?

Higher amphotericin B BAL concentrations?

Alveolar macrophage uptake?

Does interval dosing promote better compliance?

TRANSPLANTATION INFECTION

Nebulized Liposomal Amphotericin B Prophylaxis for *Aspergillus* Infection in Lung Transplantation: Pharmacokinetics and Safety

Víctor Monforte, MD,[a,e] Piedad Ussetti, MD,[b] Rosa López, MD,[c] Joan Gavaldà, MD,[d] Carles Bravo, MD,[a,e] Alicia de Pablo, MD,[b] Leonor Pou, MD,[c] Albert Pahissa, MD,[d] Ferran Morell, MD,[a,e] and Antonio Román, MD[a,e]

J Heart Lung Transplant 2009;28:170–5.

ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

Feasibility, tolerability, and outcomes of nebulized liposomal amphotericin B for *Aspergillus* infection prevention in lung transplantation

Víctor Monforte, MD,[a,f] Piedad Ussetti, MD,[b] Joan Gavaldà, MD,[c] Carles Bravo, MD,[a,f] Rosalia Laporta, MD,[b] Oscar Len, MD,[c] Cristina López García-Gallo, MD,[b] Lluís Tenorio, MD,[d] Joan Solé, MD,[e] and Antonio Román, MD[a,f]

[a]*From the Respiratory,*
[c]*Infectious Disease,*
[d]*Intensive Care, and*
[e]*Thoracic Surgery Departments, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona; the*
[b]*Respiratory Department, Hospital Universitario Puerta de Hierro, Madrid; and*
[f]*Ciber Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain.*

J Heart Lung Transplant 2010;29:523–530

RED ESPAÑOLA DE INVESTIGACIÓN EN PATOLOGÍA INFECCIOSA

Vall d'Hebron Institut de Recerca VHIR

PK and Efficacy of N-LAB in Lung Transplantation Methods

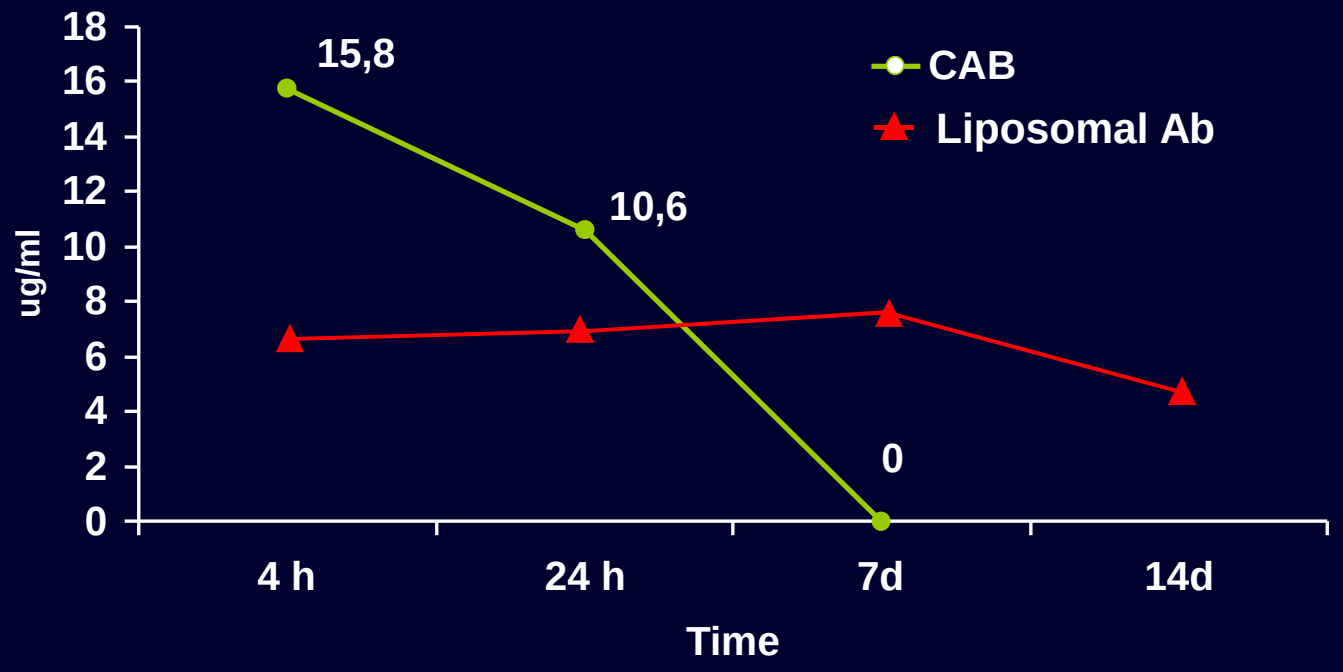
- AmBisome 50 mg + 12 ml Sterile Water (4 mg/ml solution)
  - 6 ml aliquot of the solution (24 mg) were nebulized
- Jet nebulizer (System 22 Acorn with a CR60 compressor)
- A trained nurse instructed patients to inhale through a mouthpiece and exhale through the nose, to protect the upper airways
- The procedure lasted 15 to 20 minutes

Lung Transplantation: Nebulized AmBisome Prophylaxis Dosing

- 25 mg of LAb
  - 30-60 days, 3 times a week
    - Healing bronchial anastomoses
  - 2-6 months, once a week
  - >6 months, once every 15 days

Lung Transplantation
Nebulized Ambisome PK

- Clinical assay similar to previous study with CAB
- Ambisome dose 25 mg



No drug levels in blood were seen.

TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

10 years of prophylaxis with nebulized liposomal amphotericin B and the changing epidemiology of *Aspergillus* spp. infection in lung transplantation

Maddalena Peghin,[1,2] Victor Monforte,[3,4] Maria-Teresa Martin-Gomez,[5] Isabel Ruiz-Camps,[1,2] Cristina Berastegui,[3,4] Berta Saez,[3,4] Jordi Riera,[6] Piedad Ussetti,[7] Juan Solé,[8] Joan Gavaldá[1,2] and Antonio Roman[3,4]

- 412 patients, mean follow-up 2.56 years (IQR 1.01–4.65)
- 22 patients Invasive Aspergillosis (22/412, 5.3%)
  - 1-year cumulative incidence of IA: 3.6%
  - IPA 15 (3.6%)
  - Ulcerative Tracheobronchitis 7 (1.7%)
- 31 NIA: Tb 23; Stent infections 6; native-lung aspergillomas 2

- Long term Prophylaxis: Safety
  - Mild adverse effects 12 (2.9%)
    - Mild, transitory breathing difficulty 8 (1.9%)
    - Nausea 3; dizziness in 1 (0.2%)
  - Discontinuation: 7 (1.7%) due secondary effects; 7 spontaneously

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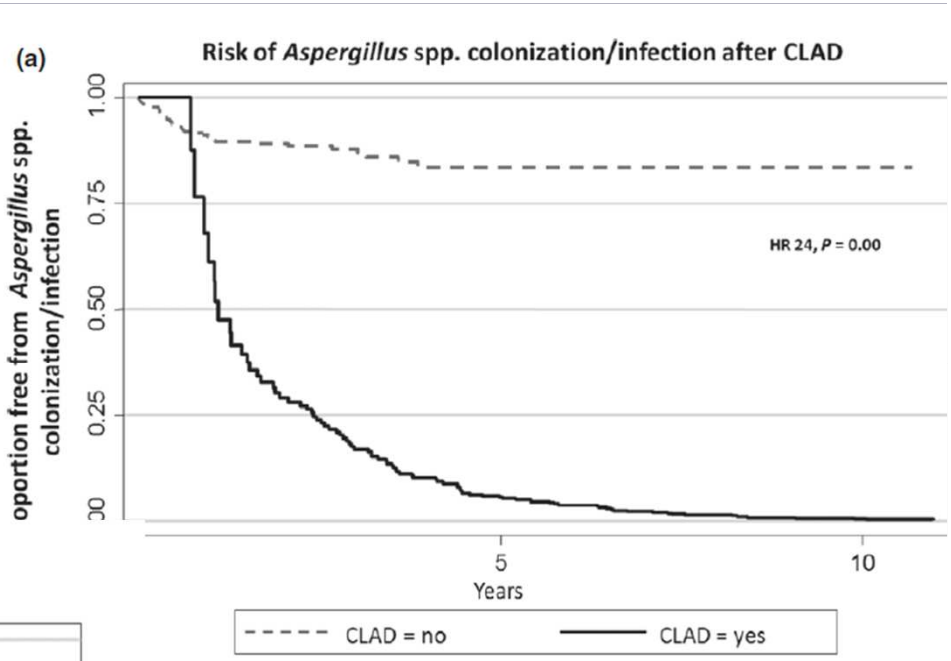

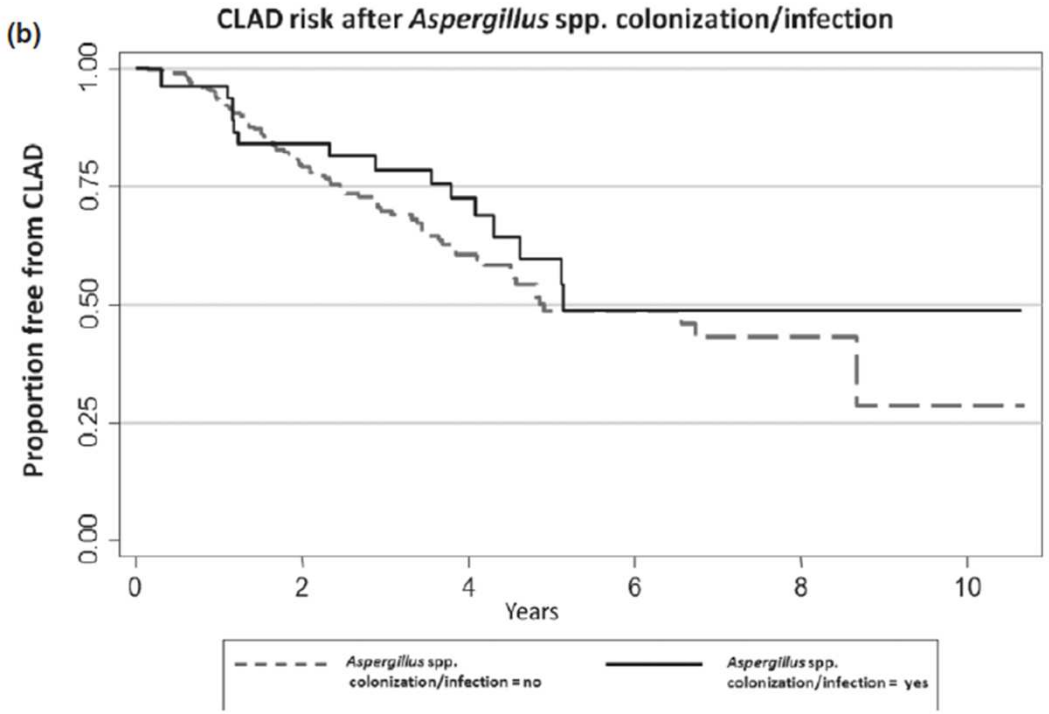

Figure 3 Time-dependent Cox-regression analysis: (a) development of *Aspergillus* spp. colonization or infection after chronic lung allograft dysfunction (CLAD); (b) Development of CLAD after *Aspergillus* spp. colonization or infection.

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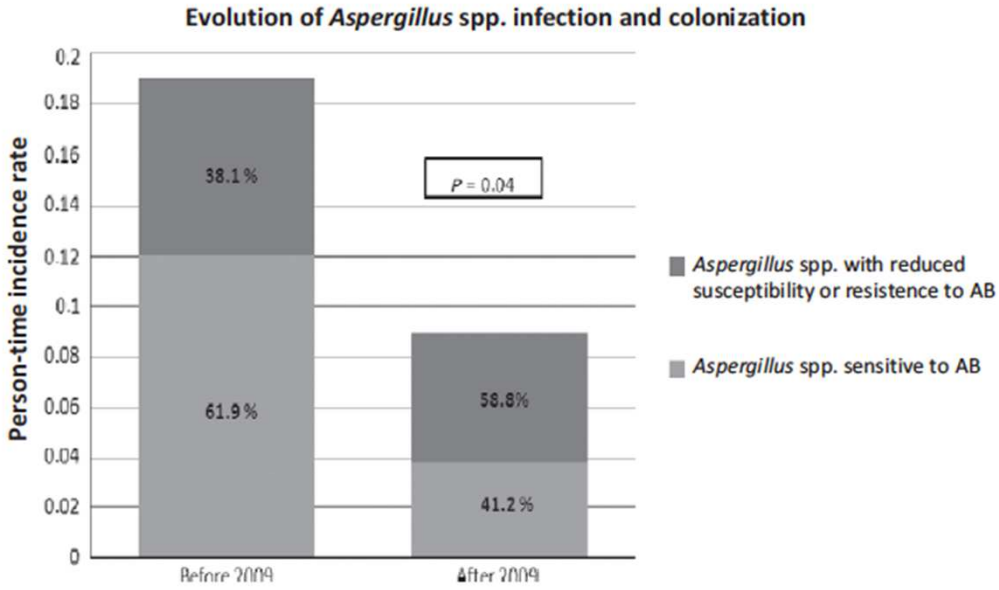
Table 5. Risk factors potentially associated with the development of 59 *Aspergillus* spp. infections in 53 lung transplant patients.

Risk factors	*Aspergillus* spp. infections *n* (%)
Chronic gram-negative bacterial colonization	38/59 (64.4)
Bronchial stenosis without stent	28/59 (47.5)
Chronic lung allograft dysfunction	21/59 (35.6)
Acute rejection	15/59 (25.4)
CMV disease	14/59 (23.7)
Bronchial stent	14/59 (23.7)
Pre-transplant *Aspergillus* spp. colonization	9/59 (15.2)
Massive inhalation	8/59 (13.6)
Overimmunosuppression	6/59 (10.2)
Abandonment of prophylaxis	4/59 (6.8)
Induction immunosuppression	3/59 (5.1)

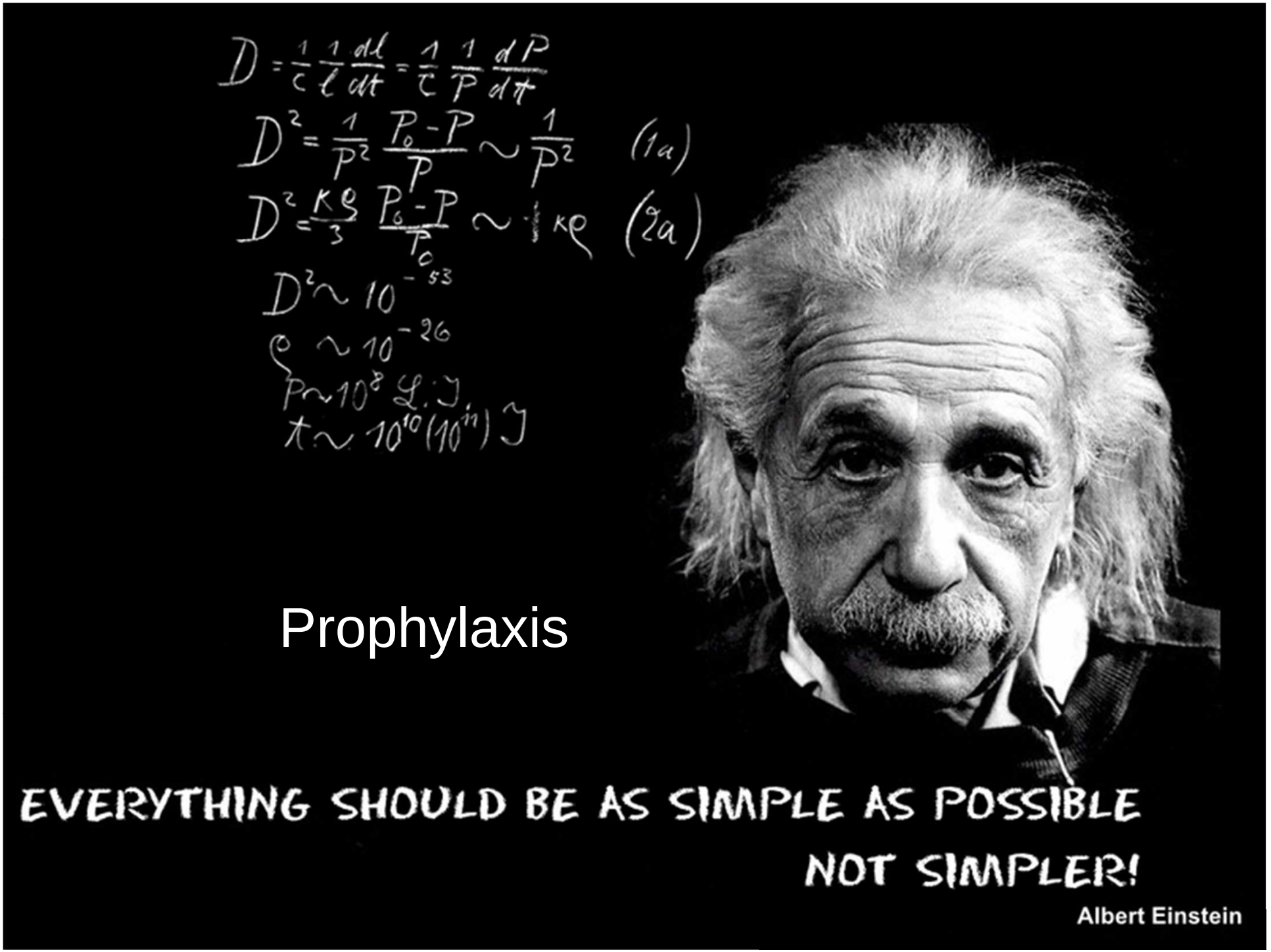
- No significant differences were observed between early and late IA episodes
- In late episodes greater frequency of association with bronchial stenosis (55.1% vs 10%, P = 0.13) and CLAD (42.9% vs 0%, p = 0.01)



Time/years	Person-time follow-up (days)	Rate	Incidence rate ratio	95% CI	P
2003–2008	214.53088	0.191	1.97	0.14-0.25	0.0003
2009–2014	857.06018	0.096	1.32	0.07-0.12	

Figure 2 Person-time incidence rates and incidence rate ratios of *Aspergillus* spp. infection and colonization, and evolution of *Aspergillus* spp. with reduced susceptibility or resistance (*A. flavus*, *A. terreus*, and *A. alliaceus*) to amphotericin from July 2003 to December 2008 (before 2009) and from January 2009 to July 2014 (after 2009). AB, amphotericin B.

- Mortality: 11 patients (11/412; 2.7%)
  - IPA 8 of 15 (53.3%)
  - UT 1 of 7 (14.3%)
  - Aspergilloma One patient


Prophylaxis
EVERYTHING SHOULD BE AS SIMPLE AS POSSIBLE
NOT SIMPLER!
Albert Einstein

Gràcies
Merçi