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# Supplementary materials: Inhaled Antifungal Agents for Treatment and Prophylaxis of Bronchopulmonary Invasive Mold Infections

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## List of acronyms

\* p<0.05

+: plus

ABLC: amphotericin B lipid complex

AE: adverse event

ALL: acute lymphoblastic leukemia

AmBd: amphotericin B deoxycholate

AmBLF: amphotericin B lipid formulation

AML: acute myeloid leukemia

BID: two times a day

CLL: chronic lymphocytic leukemia

COPD: chronic obstructive pulmonary disease

D: day

FEV1: forced expiratory volume in one second

FLU: fluconazole

IA: invasive aspergillosis

IFD: invasive fungal disease

IPA: invasive pulmonary aspergillosis

ISC: isavuconazole

ITR: itraconazole

L-AmB: liposomal amphotericin B

M: month

MDS: myelodysplastic syndrome

MICA: micafungin

MMAD: median mass aerodynamic diameter

N: number of patients

N-AmB: nebulized amphotericine B

NR: not reported

NS: non-significant

OID: once a day

PMN: polymorphonuclear neutrophils

PSC: posaconazole

REF: reference

SCT: stem cell transplantation

TBA: tracheobronchial aspergillosis

TID: three times a day

VORI: voriconazole

W: week

Y.: year

**Table S1.** Nebulized AmB used as curative treatment for invasive mold infections.

Ref	N	Comorbidity	Pathogen	Pathology	Drug and Dilution	Dose <sup>a</sup>	Nebulizer	Other treatments	Outcome <sup>b</sup>
Birsan 1998 (1)	1	NR	<i>Aspergillus</i> sp.	TBA	AmBd, dilution n.d.	10 mg t.i.d., 6-8 w.	NR	Itraconazole PO	Cured
Zhou 2017 (2)	1	42y., None except influenzae infection	<i>Aspergillus</i> sp.	IPA	AmBd 25mg in 15mL of water for injection	12.5mg ×2/d, 3w.	NR	Voriconazole 16 w.	Clinical and Radiological cure
Huang 2012 (3)	11	Cancer (n=10, 5 lung cancer, 3 trachea), lung transplant and COPD (n=1)	<i>Aspergillus</i> sp.	TBA (necrotizing)	AmBd 12.5mg in 3 5mL of normal saline	12.5 mg/d., 15w. to 1y. <sup>c</sup>	NR	various systemic antifungal agents and eventually topical instillation of AmB	36% cured or improved
Wu 2010 (4)	12	Cancer (n=8, 5 lung, 1 trachea), lymphoma (n=1), none (n=2), tracheostenosis (n=1)	<i>Aspergillus</i> sp.	TBA (invasive : ulcer or necrosis or pseudomembranes)	AmBd dilution n.d.	5-10 mg ×2/d, 8 to 47d. <sup>d</sup>	NR	Various systemic antifungal agents and eventually interventional bronchoscopic treatment and eventually topical instillation of AmB	67% cured

Dal Conte 1996 (5)	1	33y., AIDS	<i>Aspergillus</i> sp.	TBA (invasive : positive biopsies and alveolar infiltrates)	AmBd 10 then 20 mg in 10mL of sterile water	10 then 20 mg/d, 45d.	Respi-guard II	Itraconazole 400mg/d, flucytosine 21d.	Clinical and radiological improvement, negative culture, patient died 2w. after discharge from <i>P.aeruginosa</i> pneumonia. Good tolerance.
Boots 1999 (6)	1	35y., none except <i>influenzae</i> infection	<i>Aspergillus</i> sp.	TBA (invasive: positive biopsies, necrosis, membranes)	AmBd, dilution n.d.	10mg ×2/d, 56d	NR	Various systemic antifungal agents	Cured
Roderhuis 1984 (7)	1	48y., alcohol abuse and asthma	<i>Aspergillus</i> sp.	IPA	AmBd in 3mL of 5% dextrose	from 1.25mg ×4/d to 25mg ×4/d, 8w.	Hudson 1720 Up-draft	Flucytosine PO 150mg/d and AmBd 50mg/d IV, 8w.	Clinical cure and radiological improvement
Boettcher 2000 (8)	3	Lung transplant (n=3)	<i>Aspergillus</i> sp.	TBA (ulcerative)	AmBd (n=1) 10mg b.i.d	50mg t.i.d, Duration:	NR	IV L-AmB 150-200mg/d and IV flucytosine 2.5mg t.i.d or q.i.d + secondary adjunction of topical instillation of AmBd or L-AmB and eventually interventional bronchoscopy	1 died (AmBd) from arterio-bronchic
Furco 2001 (9)	1	66y., diabetes	<i>Mucorales</i> hyphae (culture not performed)	Pulmonary mucormycosis	AmBd 30mg in 5mL of saline serum	30mg ×3/w, for 3 months	Europe Médical, O2 IV L-AmB 150mg/d 5L/min		Fistula 2 cured (seque- lary anasto- and eventually motic steno- sis)
Alfageme 2009 (10)	1	21y., induction treatment for ALL	<i>Mucor</i> sp.	Pulmonary mucormycosis	AmBd	n.d.	NR	IV L-AmB, adjunction of topical instillation of AmBd, adjunction of posaconazole, surgical treatment	Radiological improvement after topical instillations of AmBd, cure after surgical treatment
McGuire 2007 (11)	1	Bilateral lung transplant	<i>Rhizomucor</i> sp.	Mucormycosis of the bronchial anastomosis	AmBd	6mg t.i.d, indefinitely	NR	IV AmBd for 4 months + interventional bronchoscopic treatment	Clinical cure and normalized pulmonary function tests. Seque- lary anasto- motic stenosis dilatated.
Safdar 2004 (12)	1	61y., allogenic stem cell transplant	<i>Pseudalleschiera boydii</i> and <i>Rhizomucor</i> sp.	Pulmonary IFD	ABLC	50mg/d for 5 months	Respiguard II	Caspofungine 50mg/d	Clinical and radiological cure.

								Good tolerance.
Godet 2017 (13)	1	36y., allogenic stem cell transplant	<i>Hormographella aspergil-lata</i>	Pulmonary IFD	L-AmB	25mg x3/w	NR	L-AmB 3mg/kg/D
Castagnolla 2007 (14)	1	8y., allogenic stem cell transplant	<i>Aspergillus sp.</i>	Refractory IPA	L-AmB	20mg x2/d for 3d., then 15mg x2/d. Stopped after 8 days because of neurological AE.	NR	L-AmB IV 10mg/kg/d + Caspofungine IV 100mg/m <sup>2</sup>
Canetti 2015 (15)	1	67y., transplant kidney	<i>Aspergillus sp</i>	IPA	ABLC	50mg/d monotherapy after voriconazole suspension. Gradually reduced and suspended after 13 months	Mede jet (Medel PRO®) nebulizer	Voriconazole 200mg x2/d stopped after 50d. due to liver toxicity No AE.
Venanzini 2019 (16)	5	2 allo SCT, 1 AML, 2 cancer and COPD	<i>Aspergillus sp</i>	IPA	ABLC	50mg/d (5mg/ml), sequen-tially re-duced to 50mg x3/w, 50 mg x2/w, and eFlow 50 mg /w in rapid nebu-patients with a fa-vorable outcome.	PARI BOY SX nebuliz-ers (PARI GmbH, Germany) eFlow (PARI with a fa-vorable Germany)	Systemic voriconazole or L-AmB or Caspofungin 3 complete response, 2 deaths not related. No AE
Safdar et Rodri-guez 2013 (17)	32	Allogenic stem cell transplant (56%), acute leukemia (69%), severe neutropenia (63%)	<i>Aspergillus</i> sp. (n=7), <i>Fusarium</i> sp. (n=2), <i>Rhizmucor</i> sp., <i>Scedosporium</i> sp., <i>Basidio-mycete</i> sp. (n=1 each)	Possible, probable or definite IFD	ABLC 50mg in 10mL of sa-line serum	50mg x2/d (78%) or 1x/d (22%) Median du-ration : 28 d	Small-vol-ume jet-nebulizers yielding 80% drug with less than 5-μm particle size. Were used, preceeded by 1 dose of SABA	Various systemic antifungal agents Complete or partial clinical and radiographic resolution in 50%. No serious adverse effect
Morales 2009 (18)	1	33y., bilateral lung transplant with endobronchial prothesis	<i>Aspergillus</i> sp., <i>Scedosporium</i> sp.	TBA / infec-tion of endo-bronchial prothesis	ABLC	25mg o.i.d	NR	Voriconazole 400mg/d + interven-tional broncho-scopy treatment + Clinical and microbiologi-cal cure (only

			(with local laceration)			adjunction of topical instillation of AmBd or AmBLF	after instillations were added)
Al Yazidi 2019 (19)	1	13y., bilateral lung transplant	<i>Fusarium</i> sp.	Infection of the bronchial anastomosis (pseudomembranes)	L-AmB	25mg x3/w, indefinitely	NR
Peghin 2016 (20)	22	Lung transplant	<i>Aspergillus</i> sp.	IPA (n=15), ulcerative TBA (n=7)	L-AmB 50mg in 12 mL of sterile water	NR	Mainly jet nebulizer (Vent-streamor® Side-stream®, Phillips Resironics, with a CR60 compressor (air pressure, 27.2 psi; flow, 7.3 L/min; Phillips Respi-ronics) equipped with a disposable bacterial ex-hale filter
Taton 2018 (21)	1	60y., bilateral lung transplant	<i>Microascus</i> sp.	Bronchial IFD	Voriconazole And ABLC	40mg b.i.d and 100mg o.i.d; duration: 7w.	NR
Trujillo 2021 (22)	1	Kidney transplant, severe COVID-19	<i>A. fumigatus</i>	IPA	n-AmBL	25 mg [6 mL] thrice weekly	NR
							Systemic voriconazole and/or caspofungin and/or L-AmB
							Successfull therapy in 55%
							Combination of IV voriconazole, caspofungin and terbinafine + interventional bronchoscopic treatment
							Clinical and broncho-scopic cure
							Evolution was favorable

<sup>a</sup> including treatment duration when notified in the article, <sup>b</sup> including toxicity data when available, <sup>c</sup> mean duration of treatment was 3.5 months in responsive patients, <sup>d</sup> mean duration of treatment was 25 days, NR: not reported.

**Table S2.** Nebulized AmBd as prophylaxis in hematological patients.

Ref.	Study design	Comorbidities	Dose, Nebulizer	Adverse events / severe AE / treatment-limiting AE / type of AE	Outcome
Conneally 1990 (23)	Prospective, N=34 (vs 123 historical control)	Neutropenic oncology, SCT, hematological malignancies	AmBd 5mg bid	NR	0 vs 11.4% of IA over 1 year
Jeffery 1991 (24)	Retrospective, N=130.	Acute leukemia 57%, SCT 27%	AmBd 5mg/d, 1mg/ml, De Vilbiss atomizer	No AE noted	11.2% of proven IA over 11 years. 0 IFD over the 3 last

	AmBd prophylaxis (1986-1988) vs historical control (no prophylaxis:1977-1986)	(model 251 atomizer - De Vilbiss, Somerset, Pennsylvania)		years period when AmBd prophylaxis was used.
Myers 1992 (25)	Non comparative, N=26	SCT (69%), leukemia (31%)	5mg bid to 20mg bid (5mg/ml); "Airlife" Misty Neb Medication System	3.8% (bronchospasm) / 0 / 3.8% No IA over a 4 months period
Gryn 1993 (26)	Non comparative, N=29	Leukemia or SCT	30mg oid (10mg/ml), Misty Neb (Baxter Healthcare)	AEs: Coughing and dysgeusia (100%), nausea (69%), wheezing (17%), dysphagia (14%) NR (toxicity study)
Beyer 1993 (27)	Prospective non comparative N=40	Auto-SCT or high dose chemotherapy for germ cell tumors	AmBd 10mg bid; RespirGard II nebulizer and the Lifetec Jetair 10 compressor	2mg/ml; AEs: Dysgeusia, mild nausea, discomfort 5% of probable/proven IPA
Heinemann 1994 (28)	Prospective non comparative, N=22	AML 77%	10mg t.i.d, 5mg/ml	Treatment was well tolerated, and compliance was generally good. Apart from a slight bronchial irritation during deep inhalation, toxic pulmonary AEs were not observed. Median creatinine values unchanged. No serum AmB detected (n=10) No positive <i>Aspergillus</i> culture from weekly performed (nose, throat, sputum) analysis
Hertenstein 1994 (29)	Prospective non comparative, N=303	55% AML, 26% CML, 19% other 89% alloSCT, 9% autoSCT	10mg bid	Non limiting occasional mild cough and dysgeusia 3.6% proven IFD over a 120 days period
Behre 1995 (30)	Randomized, 65 (AmBd prophylaxis) vs 50 (no prophylaxis )	AML 58%, solid tumor hd chemotherapy (34%)	10mg bid (2mg/ml); Respigard II	54% / 0 / 23% AEs: Cough (54%), dysgeusia (51%), nausea (37%) 5% vs 12% of possible/probable/proven IA (NS)
Dubois 1995 (31)	Prospective non comparative, N=18	SCT 89%, leukemia induction chemotherapy 11%	30mg/d, 10mg/mL, Respigard II	33% / NR / 22% AEs: dyspnea 33%, vomiting 22%, cough 17%, decrease of peakflow >20% in 50% NR
De Laurenzi 1996 (32)	Retrospective, historical control N=48 (AmBd) vs historical control (N=107 and N=228 with combination of oral AmB and another systemic antifungal agent as prophylaxis)	SCT 81%	Oral AmB + IV AmB + nebulized AmBd 10 mg/d, 1 mg/ml, with "ACORN" II nebulizer system with adult aerosol MASK (MARQUEST Medical Products - USA)	Good tolerance 0 IFD vs 12.1% in the group oral AmB + azole and 1.6% in the group oral AmB + nystatin (no statistical comparison)
Erjavec 1997 (33)	Prospective non comparative, n= 42	52% AML, 41% ALL,	10mg tid (5 mg/ml), ParInhalerBoy (Pari-	54.8% / 35.7 / 11.9% (21.4% dose reduction) 28% of probable/proven IFD

		7% other haematological diseases	Werk GmbH, Germany)	AEs: coughing, signs of bronchial obstruction, and nausea or vomiting Note: Higher concentration than other studies (5 mg/ml)	
Schwartz 1999 (34)	Randomized, multi-center; n=227 AmBd vs 155 without prophylaxis	74% AML, 9% ALL/NHL relapse, 17% autoSCT	10mg bid	NR	4.4% vs 5.0% of possible/probable/proven IA (NS)
Morello 2011 (35)	Prospective, non comparative N=102	alloSCT	AmBd 15mg bid (3mg/ml) + systemic antifungal agent (fluconazole 72.5%) ; Airlife Misty-Neb Nebulizer with Aerosol Mask and 213 cm Oxygen Tubing; Cardinal Health Inc., McGaw Park, IL, USA)	89% / 1% / 1% (bronchospasm) AEs: dysgeusia 89%, mild cough 85%, nausea No renal failure	5.0% of possible/probable/proven IFD at day 120. 3/16 in the group of inadequate AmBd (<7days) vs 2/85 in the group of adequate AmBd* (>7days of treatment)
Nihtinen 2012 (36)	Retrospective, historical control N=354 (AmBd) vs 257 (no antifungal prophylaxis)	alloSCT	AmBd 25mg/d for 2-3 months, 5mg/ml, with pre-administration of salbutamol	No discontinuation due to treatment	2.5% vs 6.6%* of probable or proven IA over a 5-years period

\*: significantly different with p<0.05, NR: not reported.

**Table S3.** Nebulized lipid formulations of AmB (L-AmB or ABLC) as prophylaxis hematological patients.

Ref	Study design	Comorbidities	Dose, Nebulizer	Adverse events / severe AE / treatment-limiting AE / type of AE	Outcome
Alexander 2006 (37)	Prospective, open-label, non comparative, N=40	100% alloSCT	ABLC 50 mg/d d1-4, then o.i.w 13w. + FLU p.o./i.v. day 1 to day 100	7.5 % / 0 / 0 AEs: cough, dysgeusia, nausea, vomiting; decrease of FEV1>20% in 5.2% ; no wheezing nor dyspnea	7.5% probable/proven IFD during the study period (13w)
Rijnders 2008 (38)	Randomised, double blinded, versus placebo N= 139 (L-AmB) vs 132 (placebo)	49% AML/MD S, 21% au-toSCT, 11% al-loSCT	L-AmB 12.5 mg x2/w until PNN>300 + FLU (dose NR) placebo inh. + FLU (dose NR) adaptive aerosol-delivery system (Halolite or ProDose AAD; Ro-medic/Medic-Aid; Meerssen, The Netherlands) MMAD=1.9uM	11.5% vs 0.8%* / 0 / 45% vs 30%* AEs: Cough (11.5% vs 0.8%*)	4.3% vs 13.6% of proven/probable IPA*
Slobbe 2008 (39)	Randomised, double blinded, versus placebo N=38 (L-AmB) vs 39 (placebo)	AML-SMD 35%, SCT 48%, Intensive chemotherapy	L-AmB 12.5mg/d x2/w (5mg/ml) adaptive aerosol-delivery system (Halolite or	32% vs 21% of decline of FEV1>20% (NS) AEs: cough (74% vs 26%*), dysgeusia 37% vs 62% *, nausea or vomiting 13% vs 25%. No creatinine elevation.	NR

			ProDose AAD; Ro- medic/Medic-Aid; Meerssen, The Netherlands)		
Hullard- Pulstinger 2011 (40)	Prospective, comparative N=96 (L-AmB) vs 105 (Historical con- trol)	67% AML, MDS, AL, 13% ALL, 11% NHL/HD/MM , 7% MPD, 1% AA, PNH, 34% alloSCT	L-AmB 12.5mg + FLU 400 mg vs FLU 400 mg. C= undiluted; 12.5mg/d 36.5% / 0 / 42.7% stopped treatment 4 days then ×2/week, mainly due to incomfort until PNN>500; AEs: Cough > incomfort > bad taste > nausea/vomiting	stream nebulizers (LC Star, Pari, Starnberg, Germany)	2.1% vs 3.8% of proba- ble/proven IPA (NS)
Chong 2015 (41)	Prospective, comparative N= 127 vs 108 (Historical con- trol)	86% AML 13% MDS < 1% CML	L-AmB 12.5 mg ×2/w until PNN>500 + FLU 400 mg po vs FLU 400mg	Prodose® AAD nebu- liser from 2008 to 2011; Akita® AAD nebuliser from 2011; Romedic, Meerssen, The Netherlands)	No serious AEs. 9.5% vs 23.4% of proba- ble/proven IPA* until 28 days after neutrophil re- covery

\*: significantly different with p<0.05, NR: not reported.

**Table S4.** Nebulized AmBd as prophylaxis in lung transplant recipients.

Ref	Study design	Comorbidities	Dose, Nebulizer	Adverse events / severe AE / treatment– limiting AE / type of AE	Outcome
Reichenspur- ner 1997 (42)	Prospective, histori- cal control. N=126 vs 101 without prophylaxis	Hearttransplant 60%, lung trans- plant 17%, heart-lung trans- plant 21%	5mg t.i.d increased to 20mg t.i.d in 5 days postop	7.9% (nausea) / 0 / 1.6%	4% vs 7% of fungal infec- tions* (1 year post-op) 2% vs 12% of <i>Aspergillus</i> infections
Calvo 1999 (43)	Prospective histori- cal control. N = 52 vs 13 without prophylaxis	Lung trans- planted recipi- ents	AmBd 0.2 mg/kg every 8 hours + FLU 200 mg PO BID	NR	0% vs 23% of IFD
Monforte 2001 (44)	Prospective, histori- cal control N=44 vs 11 without prophy- laxis	Lung trans- planted recipi- ents	6mgq8h from d1 to d120 postop, then 6mg o.i.d. 1 mg/mL.	32% / NR / 2.3% (bron- chospasm) AEs: Cough, 32%; mild bron- chospasm, 9%; nausea, 7%	22.7% vs 72.7% of <i>Asper- gillus</i> infection (TBA or IPA) (OR=0.13* in multi- variate analysis)
Minari 2002 (45)	Retrospective with historical control. N= 81 vs 88 without prophylaxis	Lung trans- planted recipi- ents	AmBd 5-10 mg BID in the immediate postop phase, then switched to itraconazole PO. Up to 2 weeks of overlap	NR	4.9% (AmBd) vs 18.2% (no AmBd) of proba- ble/proven IPA*
Cadena 2009 (46)	Retrospective N=35 (n-AmBd + voriconazole) vs N=32 historical con- trol (itraconazole)	Lung trans- planted recipi- ents	AmBd 10 mg BID for 2w + voriconazole 200 mg PO BID for 3 months; Itraconazole 200 mg PO bid for 3months	34% hepatotoxicity (voricon- azole) vs 0% (itraconazole)*	2.9% definite IFD vs 12.5% (no stat)

				AmBd vs ABLC : % of AEs:	
Drew 2004 (47)	Randomised, double blinded, single center N= 49 (AmBd) vs 51 (ABLC)	Lung transplanted recipients	AmBd 25-50 mg daily × 4 d, then weekly for 7w; ABLC 50-100 mg daily × 4 d, then weekly for 7w. Both 5mg/ml, Hudson RCI Up-Draft, Model No 1724	AEs: cough (10.6% vs 2.1%); dyspnea (19.9% vs 2.1%); nausea (8.5% vs 2.1%); wheezing 6.4% vs 4.2%; dysgeusia 10.6% vs 7.7%; decline in FEV>20%: 10.6% vs 11.1%; bronchospasm 25% vs 20.4% Discontinuation due to intolerance: 12.2% vs 5.9%	14.3% vs 11.8% of possible/probable/proven IFD during the 2 months of drug administration (NS)
Lowry 2007 (48)	Retrospective, comparative N=27 (AmBd) vs N = 18 (L-AmB)	Lung transplanted recipients	AmBd 10 mg BID L-AMB 20 mg BID	30% vs 30% (NS) (Ratio complaints/doses administered = 1.0% vs 1.2%) / 7% vs 6% (significant respiratory AE requiring treatment) / 0%	5.6% vs 0% of IA (no stat)
Monforte 2010 (49)	Comparative, prospective N=104 vs N=49 (historical control with AmBd)	Lung transplanted recipients	AmBd 6mg tid (day1-120), then 6mg/d lifelong; 1mg/ml 1-jet nebulizer (Ventstream® or Sidestream®, Phillips Respironics, Murrysville, PA), CR60 compressor	AEs (L-AmB vs AmBd): cough 20.2% vs 24.5% (NS); mild dyspnea 7.7% vs 8.2% (NS); nausea 7.7% vs 6.1% (NS); bronchospasm 1.9% vs 4.1% (NS)	IA 1.9% vs 4.1% (NS)
Eriksson 2010 (50)	Retrospective, non comparative N=76	Lung transplanted recipients	AmBd 25 mg twice daily (N = 15) or ABLC 50-100 mg daily × 4 d then once weekly from day 5 (N = 61) + Caspo IV in high risk patients and those delayed in inhalation prophylaxis + “occasional” fluconazole 100-200 mg/d during extended ICU stay or use of broad-spectrum antibiotics.	NR	Possible/probable/proven IA 3.9%
Koo 2012 (51)	Retrospective, non comparative N=82 (n-AmBd or n-L-AmB) vs N=83 (n-AmBd or n-L-AmB + micafungine + preemptive strategy)	Lung transplanted recipients	Universal (cohort 1) (N = 82) n-AmBd 25 mg BID OR n-L-AmB 20 mg BID during post-tx hospitalization Combination of strategies (cohort 2) (N = 83) universal n-AmBd 25 mg BID or n-L-AmB 20	No AE noted	35.4% probable/proven IFD vs 12% (no statistical analysis) 9.8% probable/proven IA vs 2.4%

			mg BID during post-tx hospitalization + MICA 100 mg IV daily during anesthesia and 7-10 d post-tx + Preemptive FLU or VORI (doses not specified) × 3-6 months		
Alissa 2021 (52)	Retrospective N=84 twice daily compared with 3 times daily	Lung transplant recipients	AmBd twice daily compared with 3 times daily	side effects were not significantly higher in the 3 times daily	Rate of Aspergillus infection 17% twice daily vs 4% three times daily twice daily

\*: significantly different with p<0.05, NR: not reported.

**Table S5.** Nebulized AmB lipid formulations as prophylaxis in lung transplant recipients.

Ref	Study design	Comorbidities	Dose, Nebulizer	Adverse events / severe AE / treatment-limiting AE / type of AE	Outcome
Drew 2004 (25)	Rd, db, single center N= 49 AmBd vs 51 ABLC	Lung transplanted recipients	AmBd 25-50 mg daily × 4 d, then weekly for 7w; ABLC 50-100 mg daily × 4 d, then weekly for 7w. Both 5mg/ml, Hudson RCI Up-Draft, Model No 1724	AEs: cough (10.6% vs 2.1%); dyspnea (19.9% vs 2.1%); nausea (8.5% vs 2.1%); wheezing 6.4% vs 4.2%; dysgeusia 10.6% vs 7.7%; decline in FEV>20%: 10.6% vs 11.1%; bronchospasm 25% vs 20.4%	14.3% vs 1.8% of possible/probable/proven IFI during the 2 months of drug administration (NS)
Lowry 2007 (48)	Retrospective, comparative N=27 (AmBd) vs N = 18 (L- Amb)	Lung transplanted recipients	AmBd 10 mg BID L-AMB 20 mg BID	discontinuation due to intolerance: 12.2% vs 5.9% 30% vs 30% (NS) (Ratio complaints/doses administered = 1.0% vs 1.2%) / 7% vs 6% (significant respiratory AE requiring treatment) / 0% AEs: dyspnea > cough > bronchospasm	5.6% vs 0% of IA (no stat)
Eriksson 2010 (50)	Retrospective, non comparative N=76	Lung transplanted recipients	AmBd 25 mg twice daily (N = 15) or ABLC 50-100 mg daily × 4 d then once weekly from day 5 (N = 61) + Caspo IV in high risk patients and those delayed in inhalation prophylaxis + “occasional” fluconazole 100-200 mg/d during extended ICU stay or use of broad-spectrum antibiotics.	NR	Possible/probable/proven IA 3.9%
Koo 2012 (51)	Retrospective, non comparative N=82 (n-AmBd or n-L-AmB) vs N=83 (n-	Lung transplanted recipients	Universal (cohort 1) (N = 82) n-AmBd 25 mg BID OR n-L-AmB 20 mg BID during post-tx hospitalization	No AE noted	35.4% probable/proven IFD vs 12% (no stat) 9.8% probable/proven IA vs 2.4%

	AmBd or n-L- AmB and micafungine and preemptive strategy)	Combination of strategies (cohort 2) (N = 83) universal n-AmBd 25 mg BID  or n-L-AmB 20 mg BID during post-tx hospitalization + MICA 100 mg IV daily during anesthesia and 7-10 d post-tx + Preemptive FLU or VORI (doses not specified) × 3-6 months		
Palmer 2001 (53)	Prospective, non comparative, N=51	Lung (92%) or heart- lung (8%) transplant recipients	ABLC 50mg or 100mg (if ventilated)/d for 4 days, then o.i.w for 2 months 5mg/ml (Hudson RCI, Updraft, model 1724)	1.6% / NR / 2% AEs: nausea or vomiting, dysgueusia. Decrease of FEV1>20% in 5% No bronchospasm nor cough nor dyspnea.  4% of pulmonary fungal infections (proven or probable lung candida infection) 8% of extra-pulmonary fungal infection (candida)
Borro 2008 (54)	Retrospective, N=60	Lung transplanted recipients (1 heart-lung)	n-ABLC 50 mg (5mg/ml) once every 2 days for 2 wk, then once weekly for 13 wk and FLU 200 mg IV, then 200 mg PO BID for 3 wk Nebulizer (MMAD 3.0 to 4.5uM) with CR60 compressor	6.8% / 0 / 0 AE: Nausea, vomitting. No bronchospasm 1.7% possible IPA
Monforte 2010 (49)	Comparative, prospective N=104 vs N=49 (historical control with AmBd)		L-AmB 25mg 3×/week × 60 d, then 25 mg 1×/ wk × 120 d, then 25 mg every 2 wk, lifelong; 5mg/ml;	20.2 vs 24.5% / 0 / 2.9% vs 4.1% (NS) (bronchospasm> nausea)  IA 1.9% vs 4.1% (NS)
Monforte 2009 (55)	Prospective, non comparative N=27	Lung transplanted recipients	AmBd 6mg t.i.d (day1-120), then 6mg/d lifelong; 1mg/ml 1-jet nebulizer (Ventstream® or Sidestream®, Phillips Respironics, Murrysville, PA), CR60 compressor  L-AmB 25 mg (6 ml) 3 times per week up to Day 60	AEs (L-AmB vs AmBd): cough 20.2% vs 24.5% (NS); mild dyspnea 7.7% vs 8.2% (NS); nausea 7.7% vs 6.1% (NS); bronchospasm 1.9% vs 4.1% (NS)
Peghin 2016 (20)	Retrospective observational N=412	Lung transplanted recipients	post-transplantation, 25 mg once per week between Days 60 and 180, and 25 mg once every 2 weeks thereafter for life	no changes in the mean FEV1 value before and after n-LAB in 95%. 1 patient had a decrease of 14% (asymptomatic)  Safety and PK study  I.A 5.3% (3.6% 1-year cumulative incidence of IA)
			L-AmB 25mg ×3/w day 1-60, then 25mg 1x/w day 60-180, then 25mg every 2w. life-time	(especially hepatotoxicity)

Linder 2021 (56)	Retrospective N=105	Lung trans- planted recipi- ents	Universal antifungal prophylaxis (ITR 200 mg PO daily 6 months + n-AmBL 12.5 mg three times or ITR) vs (VOR or FLU or MIC)	Universal antifungal prophylaxis more effective than targeted anti-fungal prophylaxis
Baker 2020 (57)	Prospective N=815	Lung trans- planted recipi- ents	n-AmBC	
Ibáñez- Mar- tínez E 2021 (58)	Retrospective	Lung trans- planted recipi- ents	nebulized lipidic amphotericin B prophylaxis	
Samanta (59)	Retrospective N=200	Lung trans- planted recipi- ents	ISC + n-AmB vs VOR + n-AmB	

\*: significantly different with p<0.05, NR: not reported.

**Table S6.** Comparative studies of nebulized AmBd prophylaxis and nebulized lipid formulations of AmB prophylaxis.

Ref	Study design	Comorbi- ties	Dose, Nebulizer	Adverse events / severe AE / treat- ment-limiting AE / type of AE	Outcome
Drew 2004 (47)	Rd, db, single center N= 49 AmBd vs 51 ABLC	Lung trans- planted re- cipients	AmBd 25-50 mg daily × 4 d, then weekly for 7w; ABLC 50-100 mg daily × 4 d, then weekly for 7w. Both 5mg/ml, Hudson RCI Up-Draft, Model No 1724	AmBd vs ABLC :  cough (10.6% vs 2.1%); dyspnea (19.9% vs 2.1%); nausea (8.5% vs 2.1%); wheezing 6.4% vs 4.2%; dysgeusia 10.6% vs 7.7%; decline in FEV>20%: 10.6% vs 11.1%; bronchospasm 25% vs 20.4%	14.3% vs 11.8% of possi-ble/probable/proven IFI during the 2 months of drug adminstration (NS)
Lowry 2007 (48)	Retrospective, comparative N=27 (AmBd) vs N = 18 (L- AmB)	Lung trans- planted re- cipients	AmBd 10 mg bid L- AMB 20 mg bid	discontinuation due to intolerance: 12.2% vs 5.9%  30% vs 30% (NS) (Ratio com-plaints/doses administered = 1.0% vs 1.2%) / 7% vs 6% (significant respi- tory AE requiring treatment) / 0%	5.6% vs 0% of IA (no statisti- cal analysis)
Monforte 2010 (49)	Comparative, prospective N=104 vs N=49 (historical con- trol with AmBd)	Lung trans- planted re- cipients	L-AmB 25mg 3×/week × 60 d, then 25 mg 1×/ wk × 120 d, then 25 mg every 2 wk, lifelong; 5mg/ml; AmBd 6mg t.i.d (day1-120), then 6mg/d lifelong; 1mg/ml 1-jet nebulizer (Vent- stream® or Side- stream®, Phillips Respi- ronics, Murrysville, PA), CR60 compressor	Type of AE: dyspnea > cough > bron- chospasm  20.2 vs 24.5% / 0 / 2.9% vs 4.1% (NS) (bronchospasm> nausea)  AEs (L-AmB vs AmBd): cough 20.2% vs 24.5% (NS); mild dyspnea 7.7% vs 8.2% (NS); nausea 7.7% vs 6.1% (NS); bronchospasm 1.9% vs 4.1% (NS)	IA 1.9% vs 4.1% (NS)

**Table S7.** Studies of n-voriconazole used as curative treatment for invasive mold infections.

Ref	N	Comorbid- ity	Pathogen	Pathol- ogy	Dilution	Dose	Nebulizer	Other treatments	Outcome
Thanuk- rishnan 2019 (60)	1	27y., lung transplant (hyper- IgE syndrome)	<i>Aspergillus</i> sp.	IPA	Voricona- zole 10mg/ml in sterile wa- ter	40mg t.i.d 1w., then b.i.d 1w., then 40mg o.i.d on maintenance therapy	AeroEclipse II nebulizer with 8650D compressor operated at 40 psig	IV L-AmB 5mg/kg/d and caspofungin 50mg/d. (sys- temic voricona- zole induced liver toxicity)	Clinical improve- ment. Died from chronic lung graft dysfunction 3 years later
Hilberg 2012 (61)	3	(1) 66y., high- dose corticoster- oids  (2) 61y., bi- lateral lung transplant  (3) 37y. heart and bi- lateral lung transplant	<i>Aspergillus</i> sp. (n=3) (n=3)	IPA	Voricona- zole 200mg in 20mL of water	40mg (4mL) t.i.d for 2w., then b.i.d. Du- ration: 6months (1), maintenance therapy (2),	Jet nebuliser (Side- stream®; Philips Respironics), com- pressor (Portaneb; Medic-Aid); flow rate 8L/min, dur- ing 15min	0 (failure or tox- icity of systemic voriconazole)	1: Clinical and ra- diological cure (1) or improvement (2, 3). Patient (2) died 2 months later of graft dys- function. Good tolerance
Holle 2014 (62)	1	70y, cystic fi- brosis	<i>Scedosporiu- m apiosper- mum</i>	Pulmo- nary IFD	Voricona- zole 6.25mg/ml in sterile water	40mg o.i.d, for 3 months	NR	Systemic voricon- azole (8mg/kg/d) and L-AmB (3mg/kg/d)	Clinical cure and radiological im- provement. Good tolerance
Taton 2018 (21)	1	60y., bi- lateral lung transplant	<i>Microascus</i> sp.	Bron- chial IFD	Voricona- zole And ABLC	40mg bid and 100mg o.i.d ; duration: 7w.	NR	Combination of IV voriconazole, caspofungin and terbinafine and interventional bronchoscopic treatment	Clinical and bron- choscopy cure

\*: significantly different with p&lt;0.05, NR: not reported.

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