Overview of the Role of Inhaled Antifungals in Invasive Fungal Infections

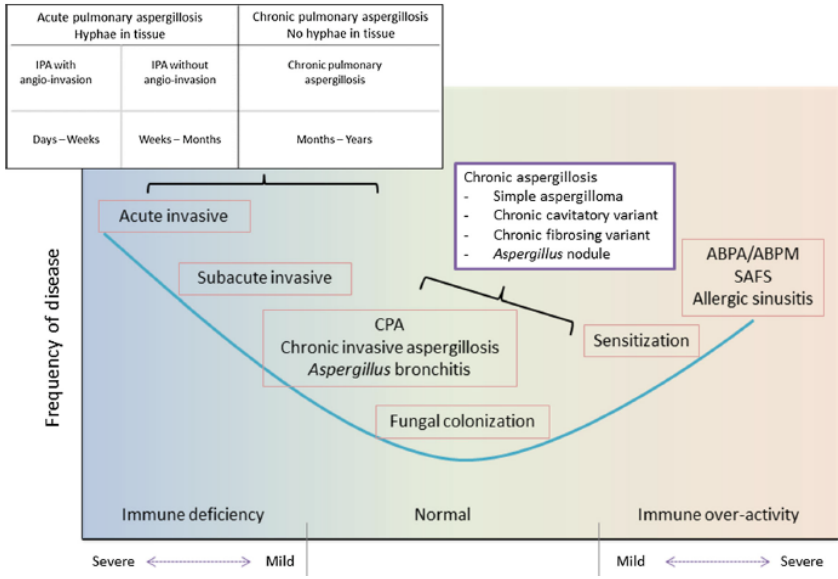
Kieren A. Marr MD, MBA
Professor of Medicine, Director Transplant and Oncology ID
Vice Chair of Medicine for Innovation
Johns Hopkins University

Outline

- Focus on pulmonary mold infections
- Infections: heterogeneity
- Risks and manifestations in specific patient populations
  - Hematologic malignancies
  - ICU (post-viral lung disease)
- Roles of inhaled antifungals
  - Prophylaxis, early prevention
  - Adjunctive therapy

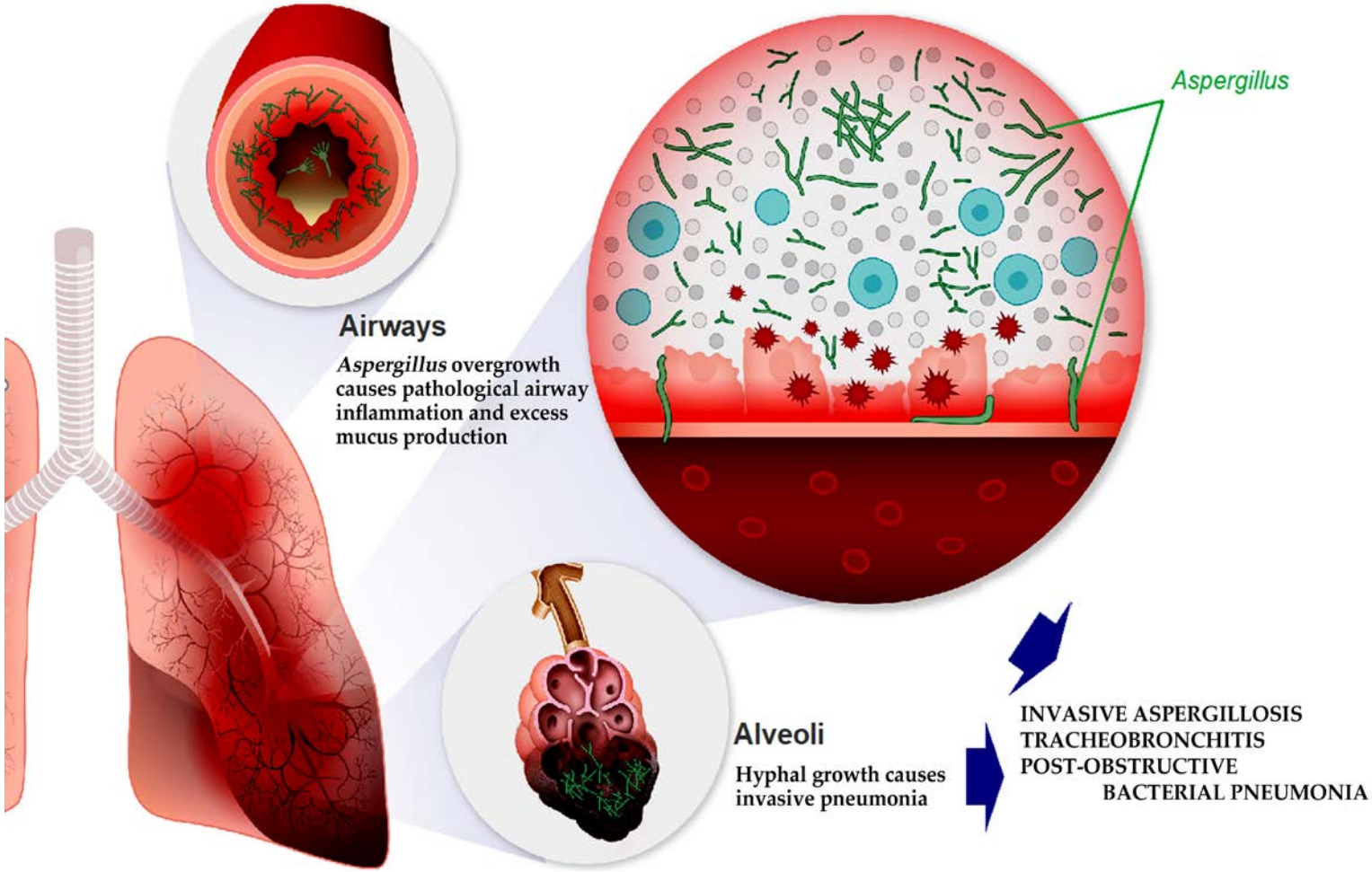
Overview

- Disease is dependent on immunity with common early pathogenesis – poor clearance of inhaled conidia
- Goal of airway drug delivery dependent on host and stage: prevention and therapy
- Caveats
  - Use of different formulations, devices and treatment algorithms impairs conclusions from data presented to date
  - Overview of disease and clinical use: not drug specific



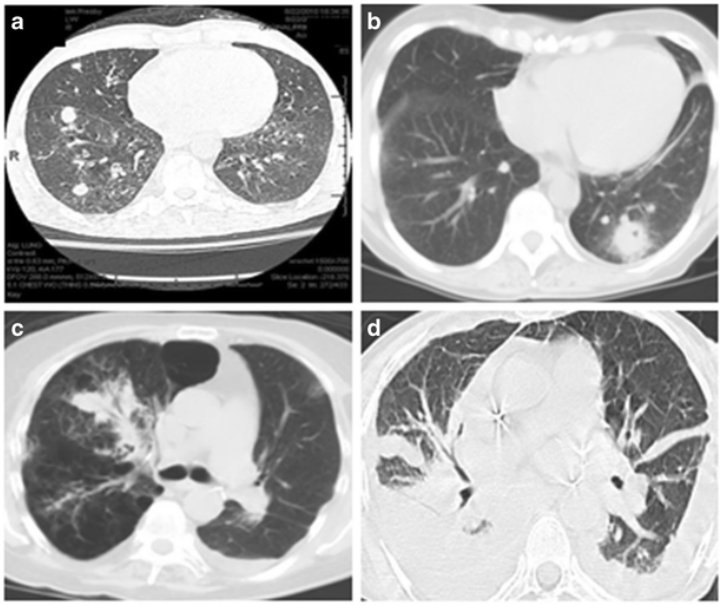
Chotirmall and Martin-Gomez Mycopathologia 2018

Mixed, multiple manifestations



Hematology / Oncology

- High risks for IMI with unique needs
  - Inhaled conidia 'escape' 1st and 2nd line defenses to invade into lung, +/- angioinvasion
  - Poor outcomes in treating advanced disease and difficult to diagnose
  - Azole-based prevention is a mainstay during periods of prolonged risks
    - Fluconazole, posaconazole
    - New therapies have presented unique unmet needs



Samanta and Nguyen. Fungal Gen & Patho 2017

Prevention POC shown for AmB in immunosuppressed animals

Trends in favor of prevention using inhaled AmB and L-AmB in different animal models

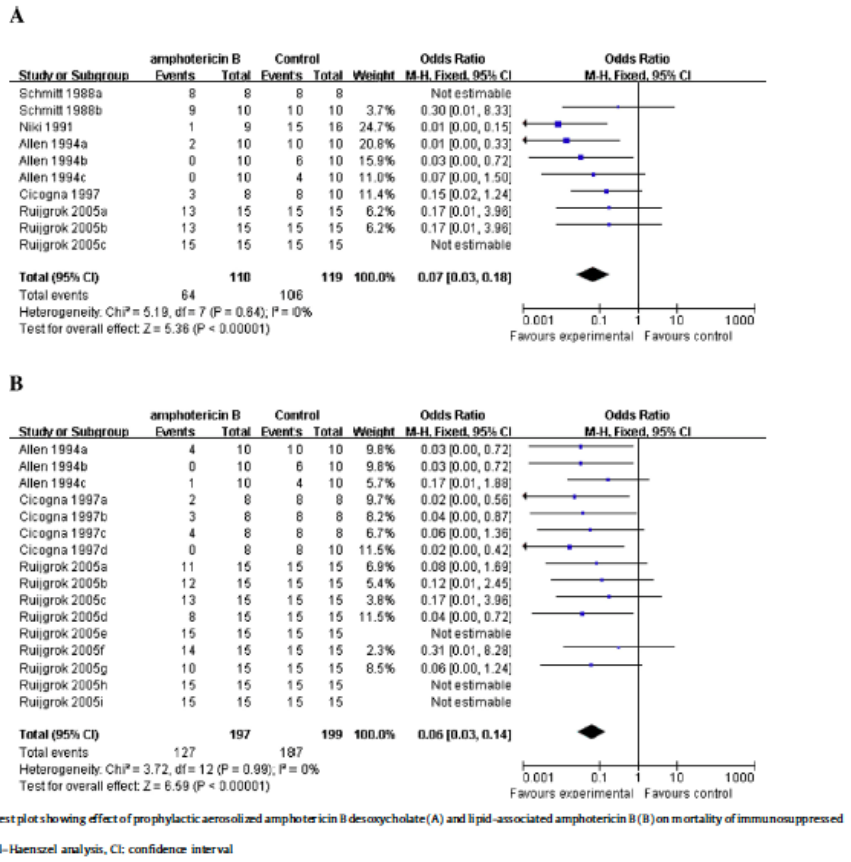


Figure 3. Forest plot showing effect of prophylactic aerosolized amphotericin B desoxycholate (A) and lipid-associated amphotericin B (B) on mortality of immunosuppressed animals.
M-H: Mantel–Haenszel analysis, CI: confidence interval

Xia et al. Ing J Infect Dis 2015

Inhaled AmB: 1990's

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Table 1. Inhaled Amphotericin B for Prophylaxis of Invasive Aspergillosis in Hematology Patients

Reference	Design	Organism/Population	Prophylaxis	Antifungal	Outcomes
Schwartz (1999)[7]	P, R, MC	*Aspergillus* neutropenic leukemia, BMT, solid tumor MDS treatment (n = 227), control (n = 155)	IH AmBd started before onset of neutropenia and continued until 1 of 4 endpoints achieved	IH AmBd 10 mg bid	4% of treatment group vs 7% of control group developed IA (p = 0.37); 5% overall incidence
Conneally (1990)[8]	cohort	*Aspergillus* neutropenic oncology, BMT, hematology treatment (n = 34), control (n =123)	IH AmBd until ANC >1/nL	IH AmBd 5 mg bid	0 of treatment group vs 14 of control group developed IA
Beyer (1993)[9]	P, case based	*Aspergillus* germ cell tumors, BMT treatment (n = 40)	oral AmBd plus IH AmBd, mean length of inhaled therapy 17 days	oral AmBd 2400 mg qd plus IH AmBd 10 mg bid	incidence of IPA decreased with IH AmBd; 1 pt. had positive *Aspergillus* antigen on day 47, 1 pt. with documented IPA died from CNS toxicity and multi-organ failure, 1 pt. with pneumonia died 10 days post-BMT
Hertenstein (1994)[10]	observational	*Aspergillus* neutropenia, BMT treatment (n = 303)	oral AmBd or fluconazole plus IH AmBd initiated 1–6 days before graft and continued until ANC >1/nL	oral AmBd 500 mg qid (n = 293) or fluconazole 100 mg qd (n = 10) plus IH AmBd 10 mg bid	overall incidence of fungal infections 3.6% (n = 11), 6 infections due to *Aspergillus*, 8 pts. died despite IH AmBd and iv therapy, 4 infections occurred during neutropenia and IH AmBd

Mohammad and Klein. Ann Pharmcother 2006

Inhaled AmB prophylaxis

Table 1. Clinical Trials for Prophylactic Nebulized Amphotericin B.

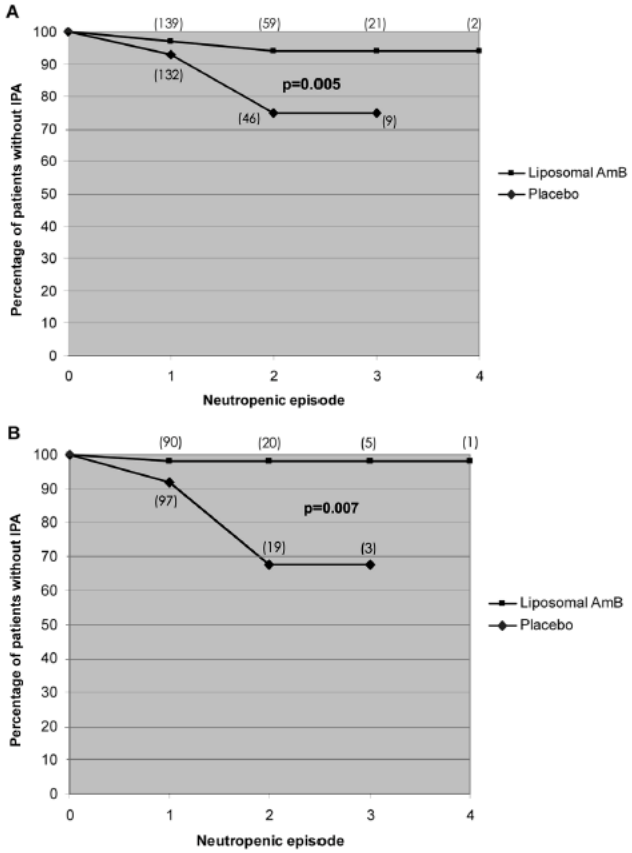
REFERENCE	PATIENTS	DEMOGRAPHICS	STUDY POPULATION	DOSAGE	DISCONTINUATION CRITERIA/DURATION	OUTCOME	SIDE EFFECTS	COMMENTS
Inhaled amphotericin B deoxycholate (InAmB D)								
Conneally et al[11] Retrospective cohort	InAmB D n = 34 historical control n = 123	NR	BMT recipients and acute leukemia	20 mg/4 mL over 10 min bid vs no inhalation	Granulocytes > 1.0 × 10^3/μL	IPA in 0/34 InAmB D vs 14/123 control statistics NC ARR = 11.4%; RRR = 100%	Mild nausea 0 discontinued	No systemic antifungal prophylaxis
Schwartz et al[12] RCT unblinded	InAmB D n = 227 control n = 155	mean age (y): 46 InAmB D 48 control Sex NR	AML, MDS, CML, ALL, NHL, and solid tumors undergoing BMT	10 mg/5 mL over 15-20 min bid vs no inhalation	Neutrophils > 1.0 × 10^3/μL or stable neutrophils > 0.5 × 10^3/μL or >day 50 Median 27 days	IA in 10/277 InAmB D vs 11/155 control NS P = .37 ARR = 3.5%; RRR = 49.2%	Cough, bad taste, and nausea 39 discontinued for ADRs	Oral AmB or fluconazole prophylaxis allowed
Nihtinen et al[13] Comparative	InAmB D n = 354 historical control n = 257	median age (y): 47 InAmB D 44 control 53.8% men	Allogeneic SCT with GvHD receiving high-dose MP	25 mg/5 mL over 10-15 min daily vs no inhalation	2-3 months Mean 84 days	IPA in 9/354 InAmB D vs 17/257 control (P = .007) ARR = 4.1%; RRR = 62.1%	Specific ADRs experienced NR but well tolerated 0 discontinued	No systemic antifungal prophylaxis Only 111 patients received InAmB D prophylaxis Albuterol pretreatment
Inhaled liposomal amphotericin B (InLipAmB)								
Rijnders et al[14] RCT double-blinded	InLipAmB n = 139 control n = 132	mean age (y): 49 InLipAmB 50 control 58.3% men	Hematologic cancers undergoing chemo, allogeneic or autologous SCT	12.5 mg/2.5 mL vs placebo 2.5 mL over 30 min twice per wk	Neutrophils > 0.3 × 10^3/μL	IPA in 11/139 InLipAmB vs 23/132 placebo (P = .005) ARR = 9.5%; RRR = 54.6%	Cough Discontinued for ≥ 1 wk 45% InLipAmB Vs 30% placebo	Oral fluconazole prophylaxis given 56 patients discontinued for delivery system limits (technical issues or being too weak)
Hullard-Pulstinger et al[15] Prospective with historical controls	InLipAmB n = 93 historical control n = 105	mean age (y): 49 InLipAmB 49 control 65.2% men	AML and other acute leukemias and/or allogeneic SCT	12.5 mg over 10-20 min daily × 4 days then twice per wk vs no inhalation	Neutrophils > 1.0 × 10^3/μL	IA in 2/98 InLipAmB vs 4/118 control NS P-value NR ARR = 1.4%; RRR = 41.2%	Bad taste, cough, and nausea 41 discontinued	Majority received fluconazole prophylaxis 69% of patients received additional systemic antifungals
Chong et al[16] Cohort	InLipAmB n = 126 historical control n = 107	mean age (y): 55.6 InLipAmB 52.2 control 54.9% men	AML, MDS, and CML	12.5 mg/3 mL twice per wk vs no inhalation	Neutrophils > 0.2 × 10^3/μL × 2 or >0.5 × 10^3/μL once	IPA in 12/126 InLipAmB vs 25/107 control (P = .0064) ARR = 13.9%; RRR = 59.4%	ADRs and discontinuation rates NR Reported as well tolerated	Oral fluconazole prophylaxis given All analysis done on day 28

Abbreviations: ADR, adverse drug reaction; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ARR, absolute risk reduction; BMT, bone marrow transplant; CML, chronic myeloid leukemia; IA, invasive aspergillosis; IPA, invasive pulmonary aspergillosis (proven or probable); MDS, myelodysplastic syndrome; MP, methylprednisolone; NC, not conducted; NHL, non-Hodgkin lymphoma; NR, not reported; NS, not significant; RCT, randomized controlled trial; RRR, relative risk reduction; SCT, stem cell transplant; wk, week; y, years.

Duckwall et al. Microbiol Insights 2019

Inhaled AmB

- 40 allo BMT, non-comparative ABLC 1x/day x 5 days then 1x/week x 13 week (458), + fluconazole
  - 25 withdrawal (empirical therapy), 1 IFI
  - AE's common -cough and 16/40 (40%) pts developed >20% decrease FEV1 at least once after administration of drug
- 271 neutropenic heme malignancy patients (407 episodes) randomized
  - 2x/week L-AmB vs. placebo
  - Decreased incidence of IFI
  - Cough more common L-AmB



Rjinders et al. Clin Infect Dis 2008
Alexander et al. Transpl Infect Dis 2006

“Real life” outcomes

- 127 AML patients L-AmB during 1st, 2nd cycle (2008) vs. 108 historic controls (2005-’08)
  - L-AmB prophylaxis associated with decreased IPA, systemic antifungal therapies (53 vs 30%), cost savings
  - Timing of administration important (trial design)

Incidence of proven/probable invasive pulmonary aspergillosis (IPA) according to treatment[a].

Treatment	Control group (n = 108)	L-AmB inhalation group (n = 127)	P-value
Overall	28/108	15/127	0.0066
First chemotherapy[b]	16/108	10/127	0.0994
Second chemotherapy[b]	11/92	3/99	0.0246
Third chemotherapy	0/34	0/38	N/A
Allogeneic HSCT	1/28	2/46	1.0000

L-AmB, liposomal amphotericin B; HSCT, haematopoietic stem cell transplantation; N/A, not applicable.

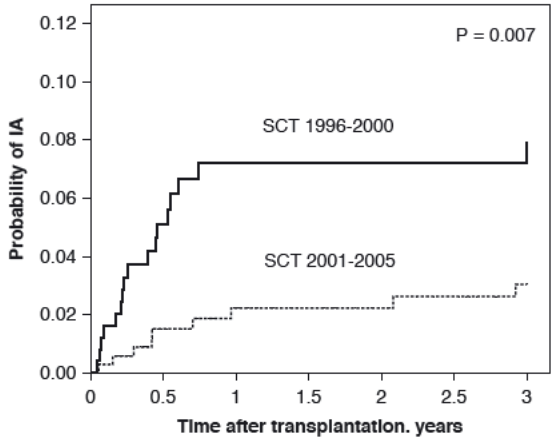
[a] All 235 patients were used for this analysis, including patients who underwent HSCT.

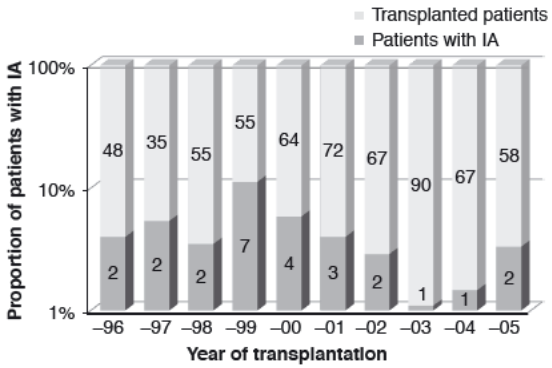
[b] Patients who had their first or second chemotherapy cycle combined with another chemotherapy cycle or HSCT and developed proven/probable IPA were counted in the initial chemotherapy group.

Chong et al. Int J Antimicrob Agents 46 (2015)

Retrospective: alloBMT + GVHD

- Retrospective 611 alloBMT (‘96-’05) – inh AmB + fluconazole
  - Drugs started with steroids
  - Lower incidence IFI
  - Many clinical changes during this period
    - Conditioning, diagnosis (GM EIA)





Nihtinen et al. Transpl Infect Dis (2011)

Unmet Needs: Expanding list of agents that azoles complicate

- People with acute lymphocytic leukemia (ALL) receiving:
  - Vincristine-based remission-induction chemotherapy
- People with acute myelogenous leukemia (AML) receiving:
  - FLT-3 inhibitors (midostaurin)
  - BCL-2 inhibitors (venetoclax)
  - IDH1 or IDH2 inhibitors (ivosidenib or enasidenib)
- People with chronic lymphocytic leukemia (CLL), receiving targeted B cell therapies: ibrutinib, idelalisib, venetoclax
- People receiving any of these drugs for multiple types of disorders:
  - Ibrutinib (with other drugs) for CLL, Waldenstroms macroglobulinemia, lymphoma, or severe chronic graft vs. host disease, or relapsed/refractory lymphoma

Adjunctive Therapy

- Reports of successful therapy in concurrent tracheobronchial disease, structural lung disease.
- Multiple therapies (nAmB, voriconazole)
- Example case of fistula, empyema after tumor resection
- Complicated courses of concurrent therapies with severe influenza

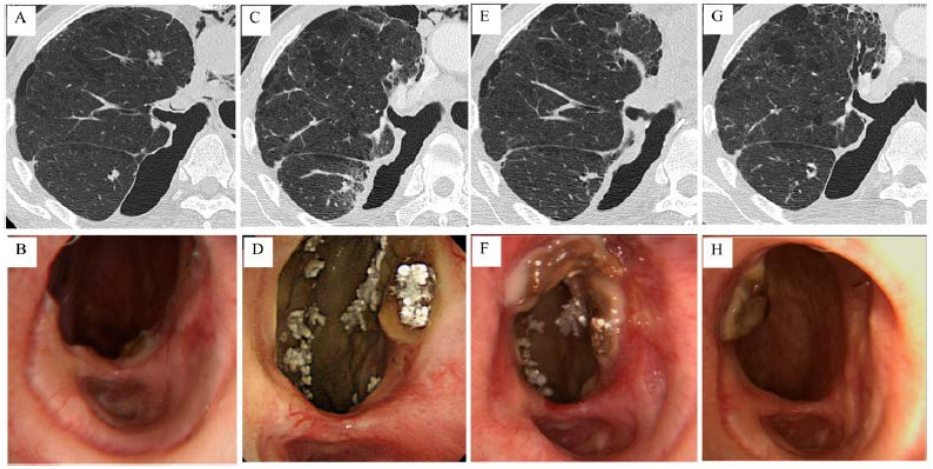
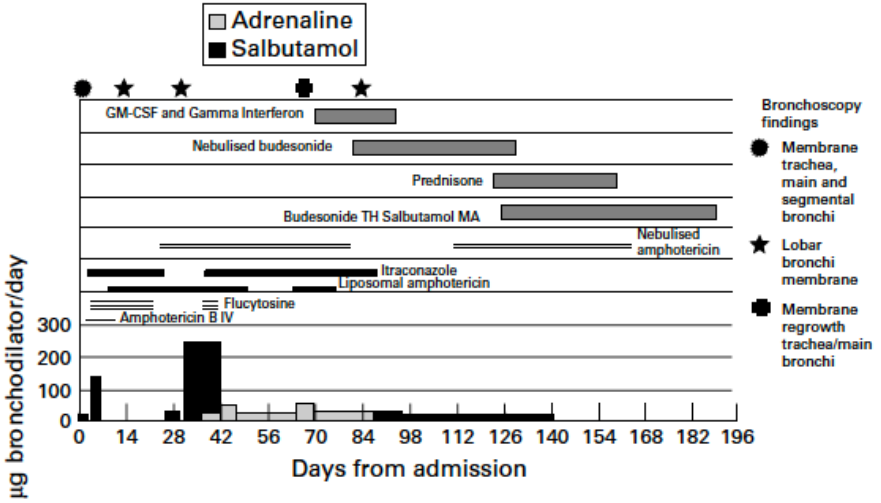


Figure 1. (*A*, *B*) Chest computed tomographic (CT) scan (*A*) and fiber-optic bronchoscopy (*B*) showed a large opening of the right inferior lobar bronchus indicating a bronchopleural fistula. (*C*, *D*) Two months later, the patient developed *Aspergillus* empyema. (*E*, *F*) After treatment with intravenous voriconazole for 6 weeks, a chest CT scan showed improvement of the ground-glass opacities around the cavity (*E*), but the bronchoscopic view was unchanged (*F*). (*G*, *H*) Both CT and bronchoscopic findings markedly improved after substituting nebulized liposomal amphotericin B and oral voriconazole for only 2 weeks (*G*, *H*).



Hanada etal. AJRCCM (2014)
Boots et al. Thorax 1999

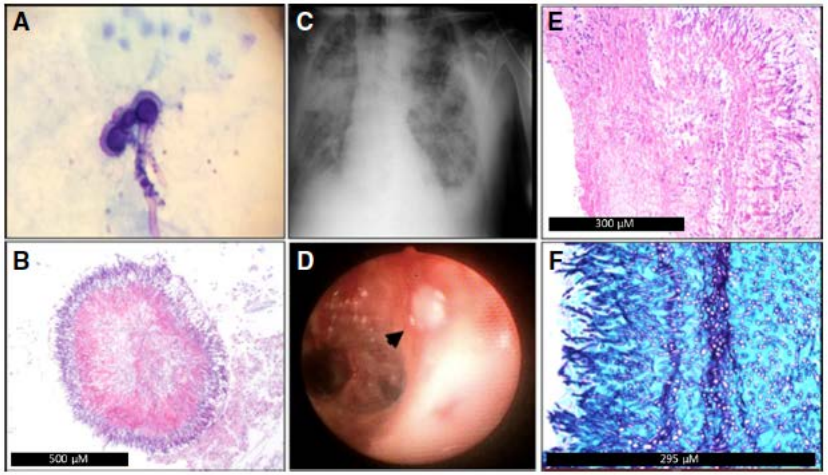
Influenza – Associated Aspergillosis

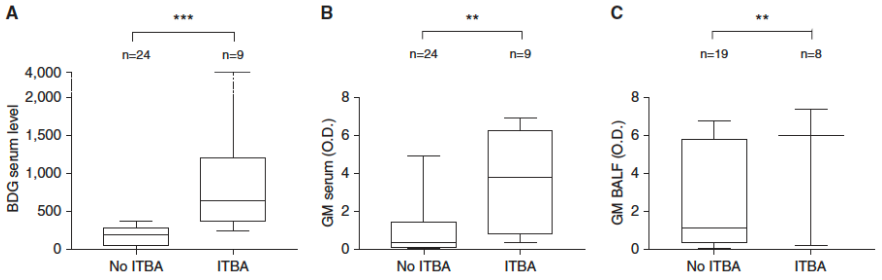
- Increased recognition
- IAPA case definition distinct from tracheobronchitis
- Geographic and seasonal variation (strain)

Reference	Venue	Patients (n)	Aspergillosis
Martin-Loeches et al	148 Spanish ICU 2009 - 2015	2901	IAA in 35 (1.2% of cohort and 7.2% of co-infections)
Rodriguez-Goncer et al	Single UK tertiary center 2012 - 2016	134	IPA in 10 (7%), IAA in 5 (3.5%)
Cavayas et al	ECMO international registry (>300 centers), 2006 - 2016	19,697	Aspergillus colonization and/or infection in 272 (1.4%)
Contou et al			
Yu et al	Single center Chinese ICU with H1N1 influenza, 2017 - 2018	19	IFI in 11(57.9%); IPA in 5 (26.3%)
Van de Veerdonk et al	Influenza patients in ICUs in 8 centers in Netherlands, 2015-2016	144	IAA in 23 (16%)
Beumer et al	Influenza patients admitted to 2 hospitals in Netherlands, 2015-2016	200	IFI in 15/199 (7.5%)[1]
Ku et al	Influenza patients admitted to one hospital in Taiwan, 2015 – 2016	124	IAA in 38/124 (31%)
Schauwvlieghe et al	Influenza patients admitted to ICUs from 7 centers in Belguim and Netherlands, 2009 - 2016	432	IAA in 83 (19%)
Huang et al	Influenza patients admitted to ICU in one center in China, 2017 - 2018	64	IAA in 18 (28%)
Schwartz et al	Influenza patients in one Canadian center, 2014 – 2019	650	IAA in 8 / 111 (7.2%) ICU patients
Zou et al	Influenza (H7N9) patients admitted to 17 hospitals in China, 2013 – 2018	335	IAA in 18 (5.4%)

Influenza – Associated Aspergillosis

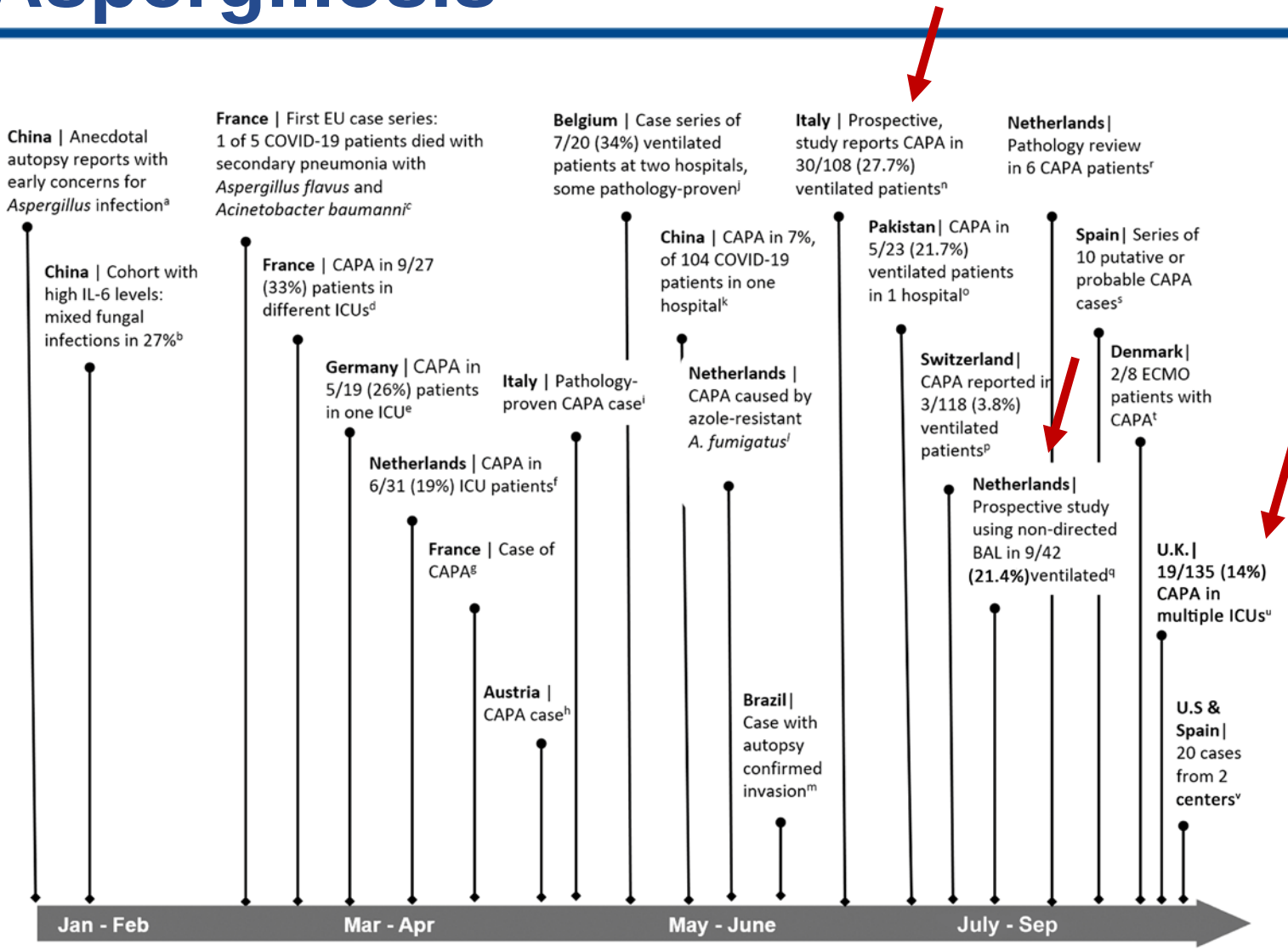
- French retrospective study 2010-19
  - 45/213 (21%) with IPA
  - 10 (29%) with tracheobronchitis (ITBA)
  - Sporulating in airway, invasive disease
  - Higher fungal markers
  - Worse survival





Nyga et al. AJRCCM 2020

COVID-Associated Pulmonary Aspergillosis



Conclusions

- Inhaled antifungals compelling for prevention of IFI
  - Proof shown in heme – neutropenia
  - Potential utility in severe viral infections
- Therapeutic efficacy suggested, particularly with airway complications

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Thank you

kmarr4@jhmi.edu