Current State of Invasive Fungal Infections: Available Therapies & Unmet Needs

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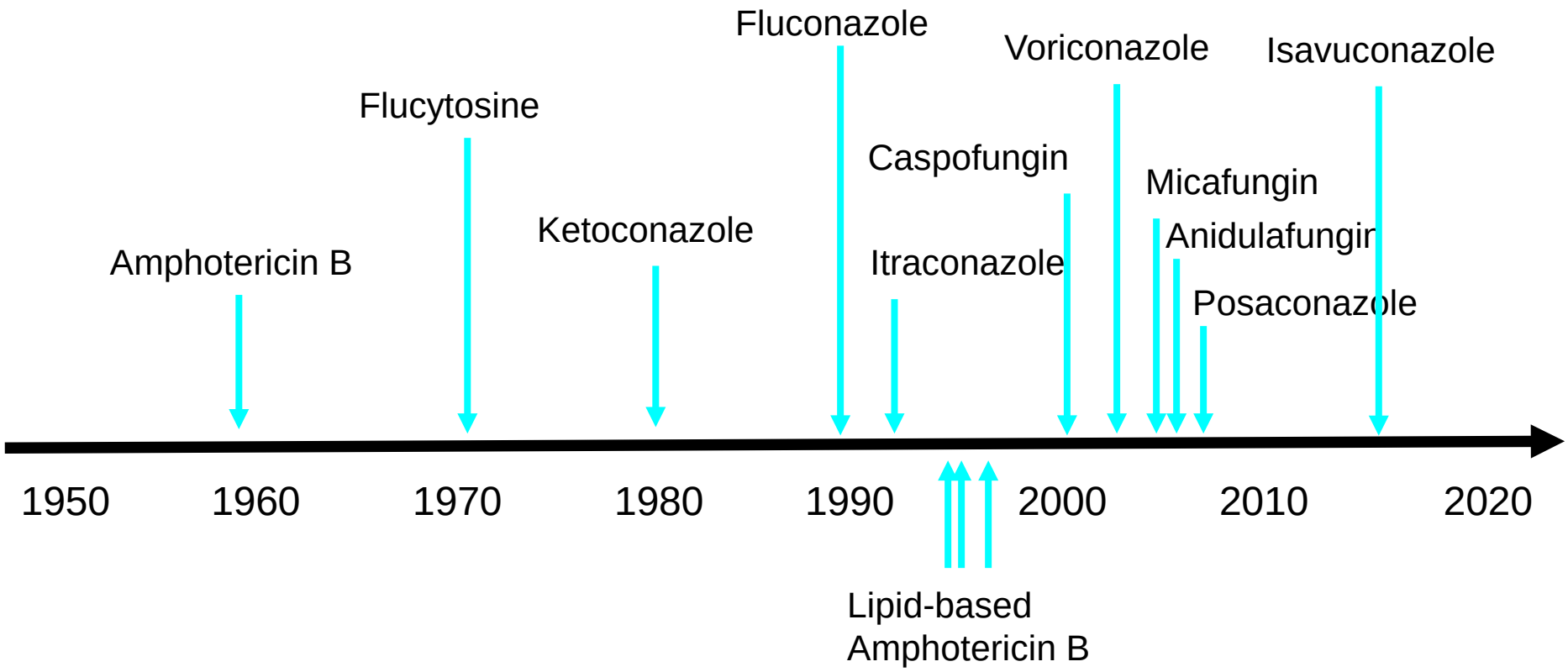
Antifungal Agents: Timeline

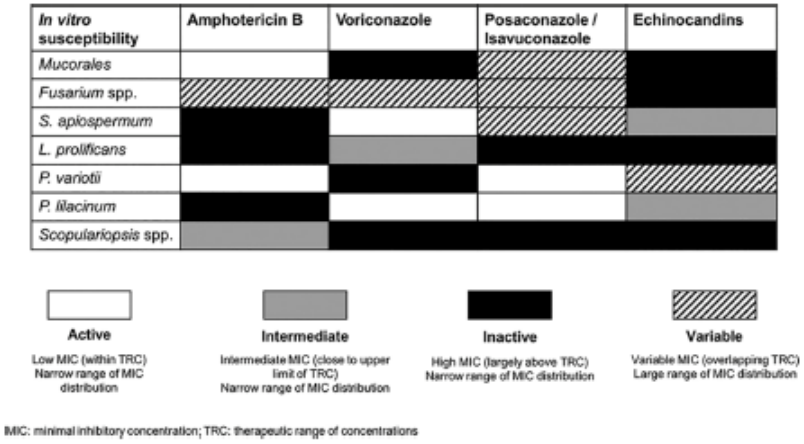


Why do we fail?
Not just a drug vs. bug issue

- Inadequate antifungal spectrum
  - To provide targeted coverage for a very resistant mold
  - To minimize failure from acquired drug resistance
  - To support preventative applications (prophylactic or empirical coverage when 1st line therapy is needed)
- Drug PK / PD limitations
  - Formulation (parenteral, enteral), infeasible dosing frequency, unpredictable metabolism and poor target exposure
- Unacceptable, intolerable safety
  - Toxicities
  - Drug interactions
- Context-specific needs

Inadequate Spectrum of Activity

- Need to provide targeted coverage for a very resistant molds, or refractory infection
  - *In vitro* susceptibilities and clinical outcomes poor with azoles, polyenes, and echinocandins
  - *Fusarium* spp. or *Scedosporium* / *Lomentospora* spp.
  - Host risks overlapping with *Aspergillus* spp. and diagnostically difficult to distinguish – yet, we don't have a good, safe drug that works across the whole spectrum when diagnosis is uncertain



Lamoth and Kontoyiannis AAC 2019

Inadequate Spectrum of Activity

- Mucormycosis
  - Resistance to voriconazole
  - Insufficient outcomes with ‘best’ therapy (polyenes)
- Innately resistant *Aspergillus* species
  - *A. terreus*
    - Polyenes
  - *Aspergillus ustus* group
    - Variable, high MICs with poor outcomes (historical >50% 6 mo. mortality)
  - Unusual ‘sibling’ species: Ex. *Aspergillus lentulus*
    - High MICs to azoles (cyp51a) & polyenes with poor clinical responses
    - Identified as ‘breakthrough’ isolates with azole prophylaxis
- Difficult to diagnose, and study with low frequency of disease but very poor outcomes

Glampedakis et al, Clin Infect Dis 2020
Mellado et al, AAC 20122

Inadequate Spectrum of Activity

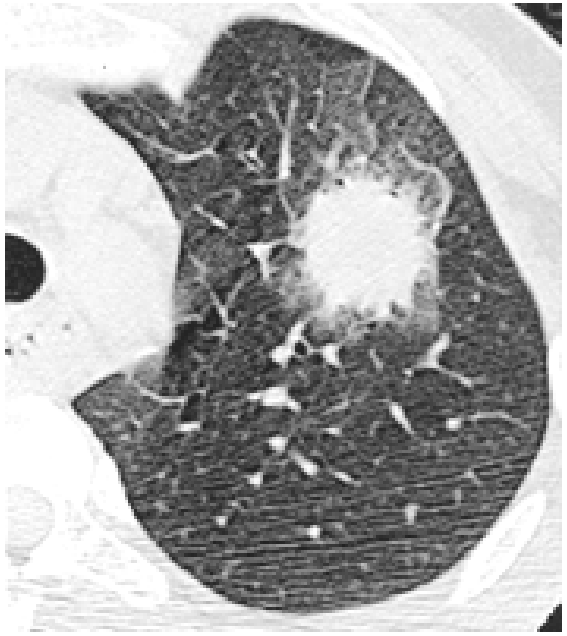
- Need to minimize failure from *acquired* drug resistance
- Azole – resistant *Aspergillus fumigatus*
  - Acquired resistance associated with multiple mutations in *cyp51A* gene
  - Episodic frequency in different environments
  - First reported in Netherlands. Now identified elsewhere in EU, S. America, Japan, India, Taiwan, Africa, Australia, U.S…

Inadequate Spectrum of Activity

- Large populations of people in which overall goal is to prevent infections, or to treat them early during the course of disease
  - So, we give broad prophylactic drug and treat early, with signs of infection (empirical therapy)
    - Fever during neutropenia
    - Syndromic (radiographic)
    - Biomarker - guided

Inadequate Spectrum of Activity

- Optimally, we would have a drug that would have activity against all molds without causing undo harm as a prophylactic agent, or with signs of mold infection
- Still have unmet needs in preventative indications
  - Prophylaxis and early empirical therapy (not defined by fever)



Early pulmonary lesions, +/- biomarker positivity

Drug PK / PD limitations

- Abundant holes in all mold-active agents
- Polyenes, echinocandins – lack of enteral formulation
- Azoles – unpredictable oral absorption and metabolism
- Poor target exposure – especially with airway needs
- Getting good drug into epithelial / lung lining fluid (ELF/LLF) has been problematic, yet critical for airway disease and treatment in certain contexts (lung transplant, chronic lung disease)
  - Inhalational exposure to address balance between airway delivery and avoidance of systemic toxicities

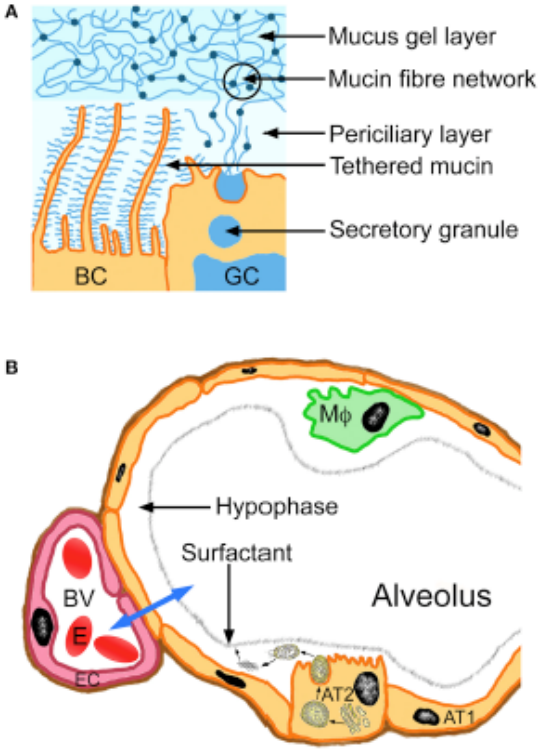


FIGURE 1 | Composition of the lung lining fluid of large airways (bronchi, A) and alveolus (B). The blue arrow indicates exchange between alveolus and blood vessel (BV). Alveolar type I cells (AT1) represent the predominating cell type of the epithelial lining of the alveolus. Surfactant production (small arrows) occurs in endoplasmic reticulum and Golgi apparatus of the alveolar type II cells (AT2) and the surfactant layer self assembles upon secretion from the cells. BC, bronchial epithelial cell; EC, endothelial cell; MΦ, alveolar macrophage, erythrocyte (E).

Frohlich et al. Front Pharmacol 2016

Unacceptable, intolerable safety

- Toxicities are abundant
  - Learned helplessness has taught us to accept toxicities in almost every organ system, especially
    - Liver toxicities (azoles)
    - Renal toxicities (polyenes)
  - Cumulative exposure contributes to poor outcomes in vulnerable people
    - Oncology, ICU, transplant

Unacceptable, intolerable safety

- Increased drug interactions that limit our preventative and therapeutic options
  - Azoles are mainstay for prevention and therapy, but p450 interactions limit use in the largest growing populations in need
    - Historical: anti-rejection drugs mandating dose alterations
    - Old and new drugs (and biologics)

The expanding list of agents that complicate azole – prevention & therapy

- Interactions limit preventative and therapeutic use in growing numbers
- 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

Context-specific needs
Lung Transplant

- Common – candida anastomotic and pleural space infections & airway mold infections
  - Poor clearance: risks for tracheobronchial and invasive disease
  - Prevalence of infection 19/100 surgeries
  - High risks for late complications: graft rejection
- Antifungal prophylaxis has become standard
- Many centers use combined inhaled drug +/- systemic drug to assure airway coverage early
  - Early inhaled dAmB, ABLC, liposomal
  - Early echinocandins
  - Prolonged azoles (toxicities with early discontinuation >60%)

Pennington et al. Transplant ID 2019
Baker et al. Clin Infect Dis 2020

Context-specific needs
Other lung disease

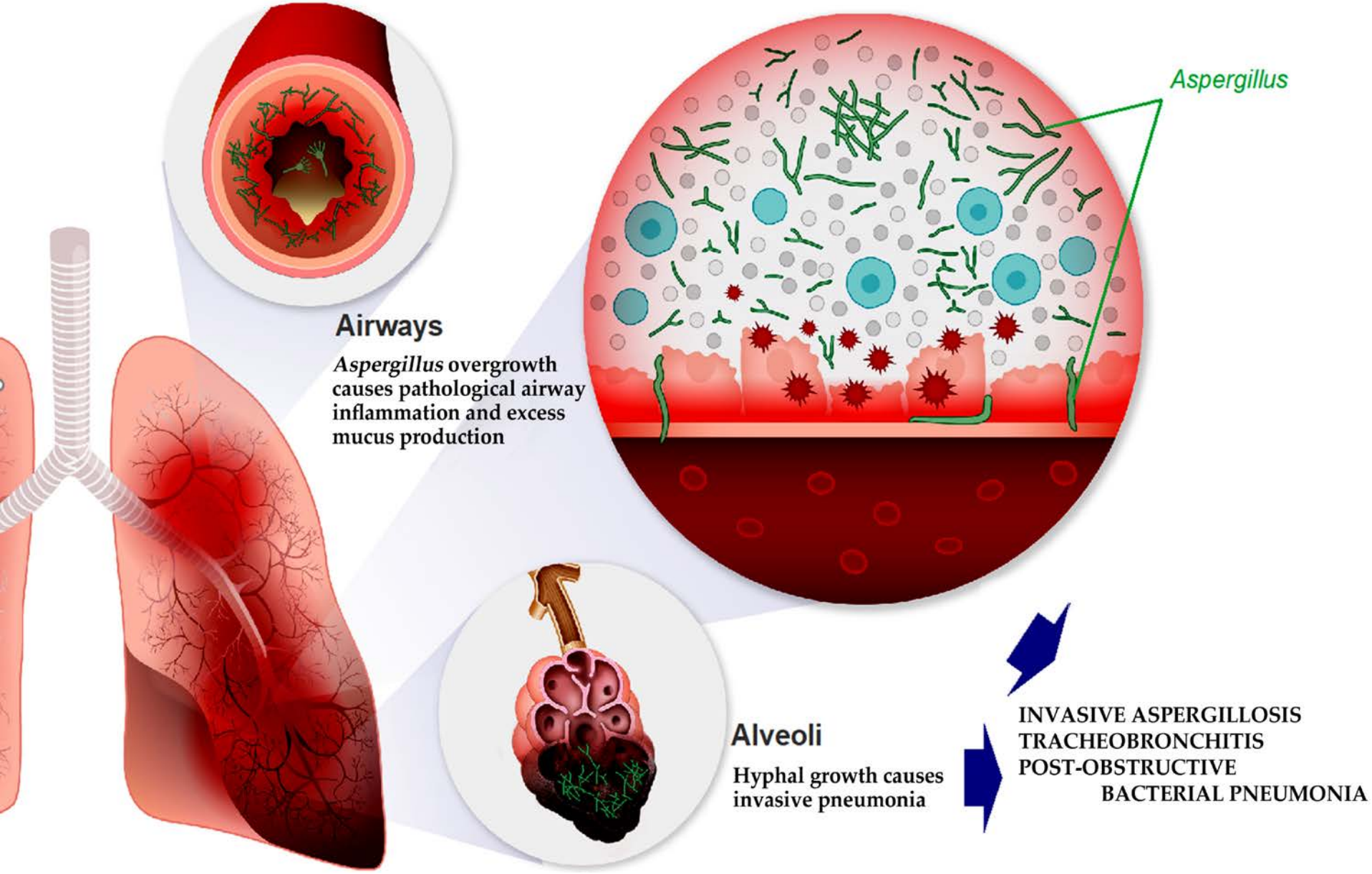
- Cystic fibrosis
  - Inhaled tobramycin used to prevent Pseudomonas – evoked progressive lung disease
  - New studies suggest that there's a role for preventing Aspergillus colonization / infection, with systemic or inhaled delivery
    - Airway aspergillosis associated with hospitalization
- Chronic necrotizing aspergillosis

Breuer et al. AJRCCM 2019

Context specific needs
Post-viral aspergillosis

- Influenza associated aspergillosis in studies published since 2015: 7 – 31%
  - Poorly recognized in U.S.; diagnostic bias
- Covid-associated pulmonary aspergillosis (CAPA) an increased recognized entity
  - Many case reports: EU
  - Prospective study (Italy) using biomarkers and culture on BAL: 30/108 (27.7%)patients on ventilation. Predictor of death in multivariable model
- Preventative, treatments needed in this context

Bartoletti et al. Clin Infect Dis 2020


Aspergillus
Airways
Aspergillus overgrowth causes pathological airway inflammation and excess mucus production
Alveoli
Hyphal growth causes invasive pneumonia
INVASIVE ASPERGILLOSIS
TRACHEOBRONCHITIS
POST-OBSTRUCTIVE BACTERIAL PNEUMONIA

Summary

- Good drugs but limited in spectrum, toxicities, drug interactions
- Many unmet needs
  - Treatment of unusual but resistant pathogens, and
    - Broadly active prophylactic and 1st line empiric therapy without AmB-associated toxicities
    - Needs exacerbated by azole failure (resistance) and contraindication (a growing list in oncology)
  - Better options for treatment and prevention in settings of poor delivery: lung transplant, chronic lung disease, including post-viral syndromes

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Thank you

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