



**Dimitrios P. Kontoyiannis, MD,
ScD**

**Frances King Black Endowed
Professor**

THE UNIVERSITY OF TEXAS

**MDAnderson
Cancer Center**

Making Cancer History®

Disclosures

- **Research support from Merck, Pfizer and Astellas and has served as speaker for Gilead/Merck, Mylan, Inc and as consultant for Merck, Astellas and T2 Biosystems.**

Hyalohyphomycetes

- *Aspergillus*
- *Scedosporium*
- *Fusarium*
- *Penicillium marneffe*
- *Paecilomyces*
- *Acremonium*
- *Scopulariopsis*

Factors Affecting Severity of These Infections

Host deficiency/Net State of Immunosuppression

Correctability of host deficiency

Organism virulence

Inoculum size

Site of infection

Tissue damage

Antifungal susceptibility

POPULATIONS AT RISK

POPULATION

FACTOR

Chronic sinusitis

Local factors, ? Antibiotics

Trauma victims

Damaged tissue

Acute leukemia

Neutropenia

Prosthetic devices

Foreign body

Transplant recipients

Immunosuppression, neutropenia

AIDS patients

Lymphopenia

Cushing's syndrome

Excessive adrenal function

Diabetes mellitus

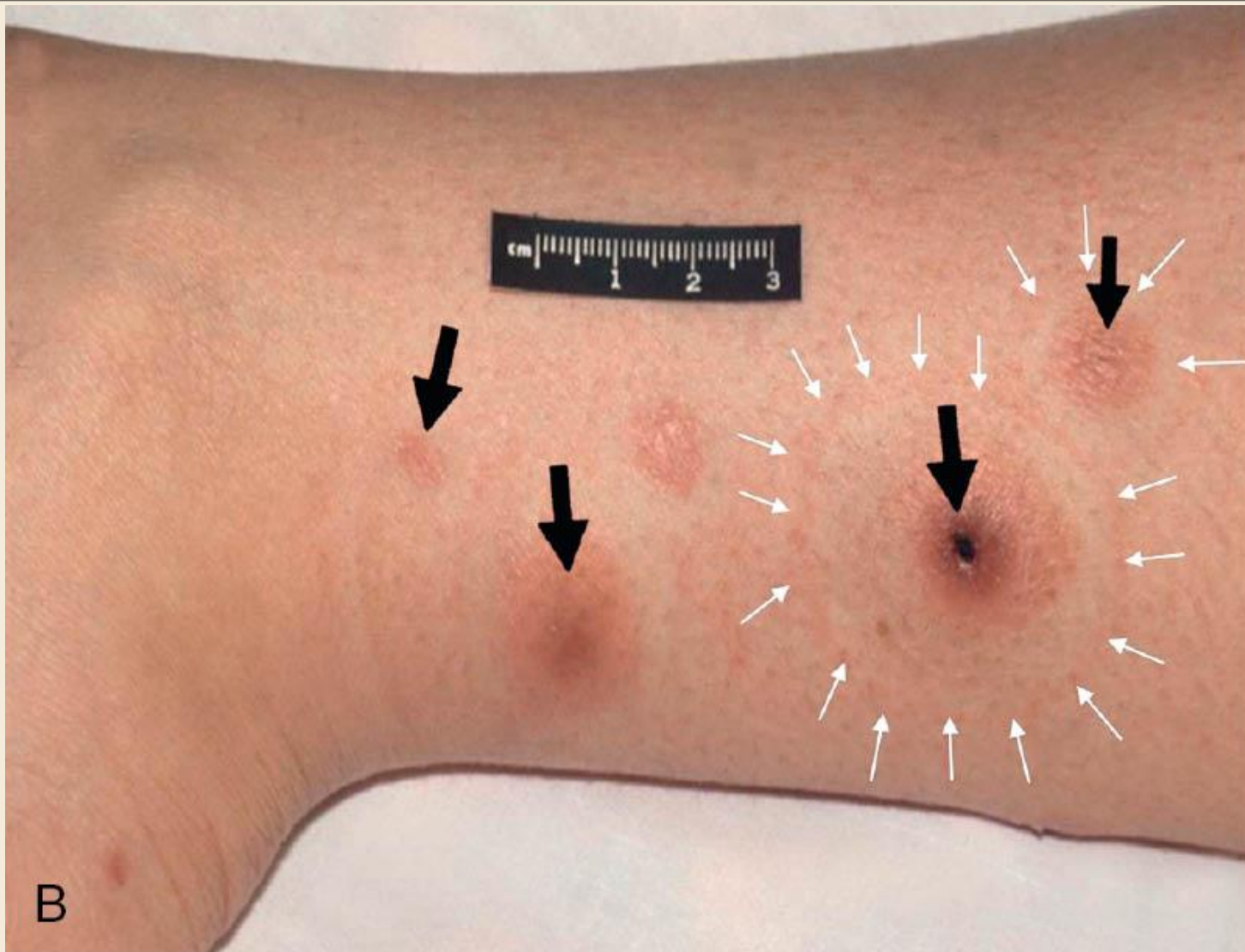
Hyperglycemia, ketoacidosis,
impaired circulation

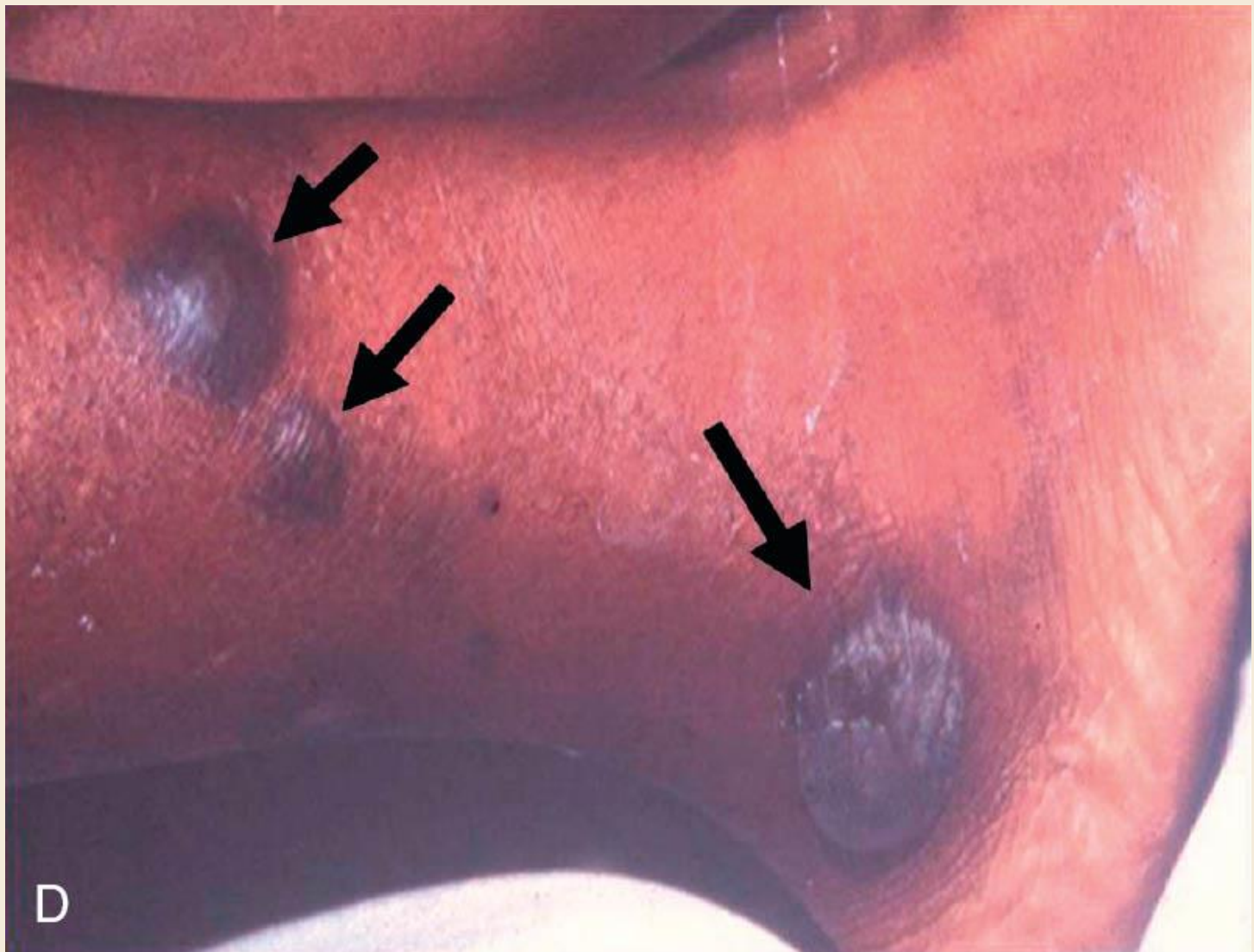
Adrenal corticosteroids

Impaired macrophage function

Fusarium Species

- **Fusariosis- disseminated infection**
 - 50-85% of cases reported from US, others from Mediterranean, also Brazil
 - Most common cause of fungemia in one study, 2nd most commonly isolated filamentous fungal pathogen in cancer patients (after *Aspergillus*)
- **Portal of entry: resp, GI, skin, burn, CVC**
- **Produces mycotoxins, angioinvasive**







Clinical Manifestations

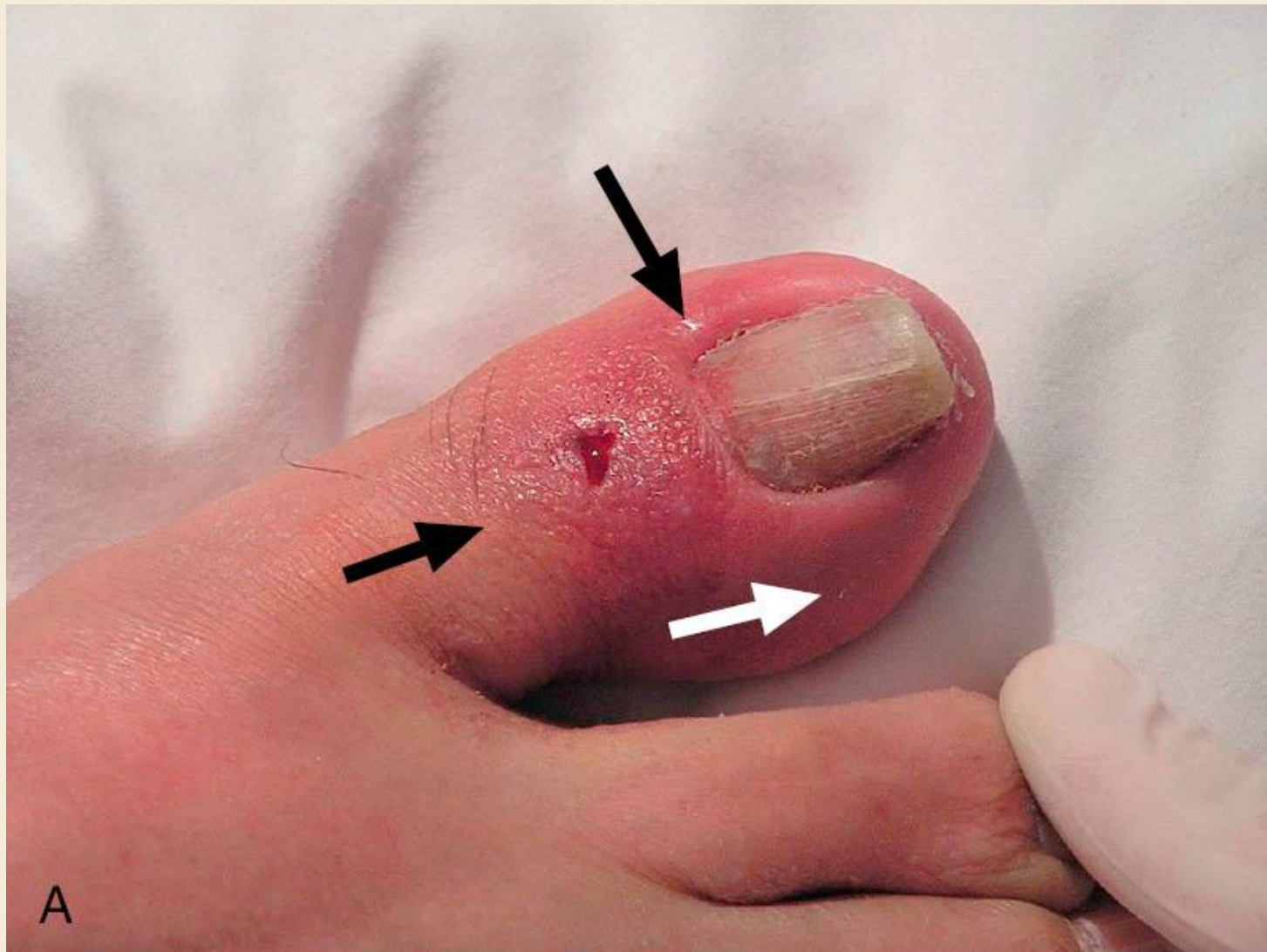
Table 3 Clinical manifestations of Fusariosis according to underlying condition

Underlying condition	Clinical manifestations
Acute leukemia or other hematologic malignancy	FUO, sinopulmonary infection, catheter-associated fungemia, disseminated infection, osteoarticular infections
Hematopoietic stem cell transplant	Disseminated infection, pneumonia, sinusitis, meningoencephalitis
Solid organ transplant	Cutaneous infection, lung abscess, liver abscess, peritonitis, disseminated infection
Solid tumors	Onychomycosis, localized soft-tissue infection, disseminated infection (rare)
Severe burns	Burn-wound colonization or wound infection, necrotizing local infection, disseminated infection
Miscellaneous conditions ^a	Onychomycosis, invasive intranasal infection, endophthalmitis, disseminated infection
Immunocompetent host ^b	Osteomyelitis, keratitis, endophthalmitis, chronic invasive rhinosinusitis

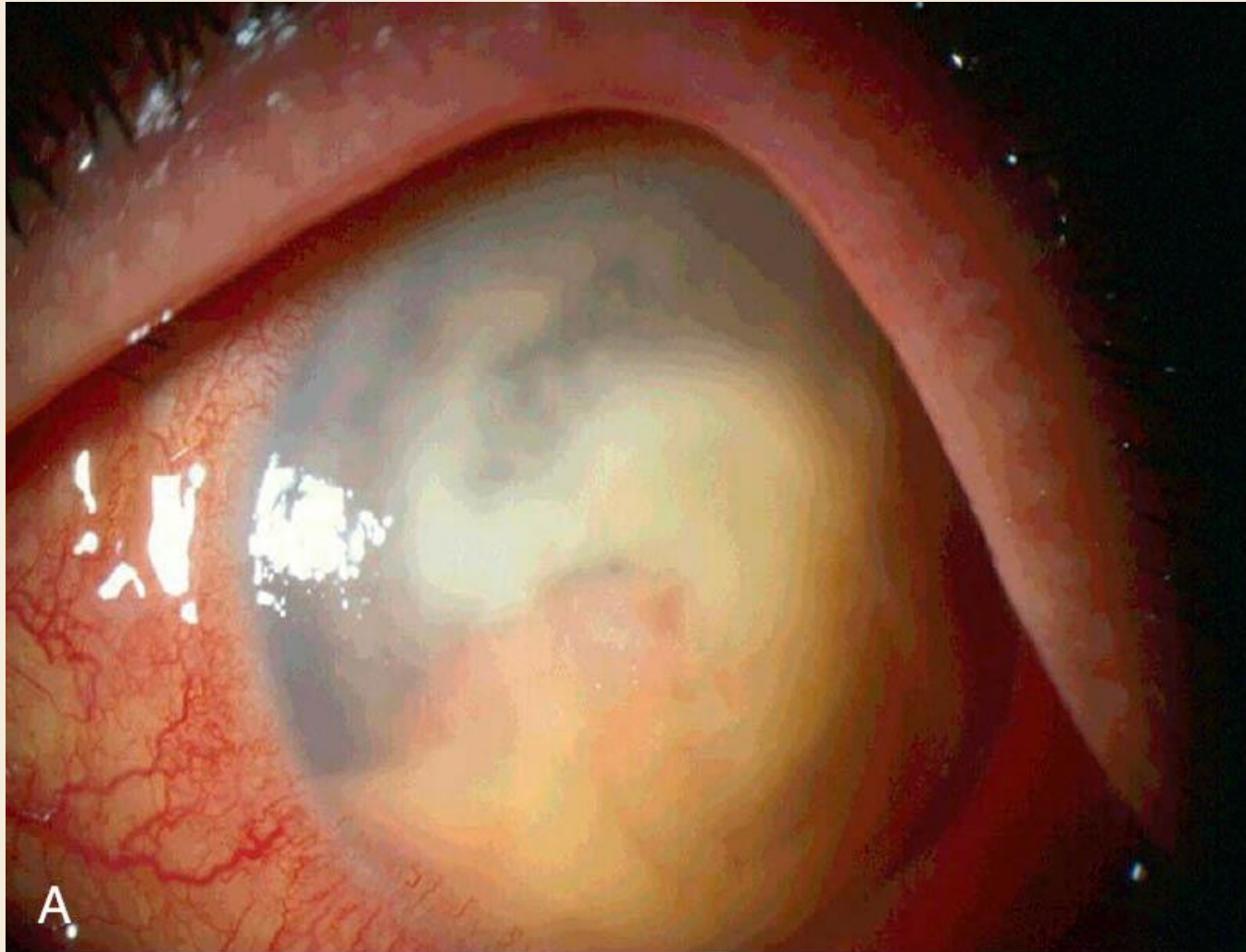
FUO fever of unknown origin

^aDiabetes mellitus, chronic renal failure, myasthenia

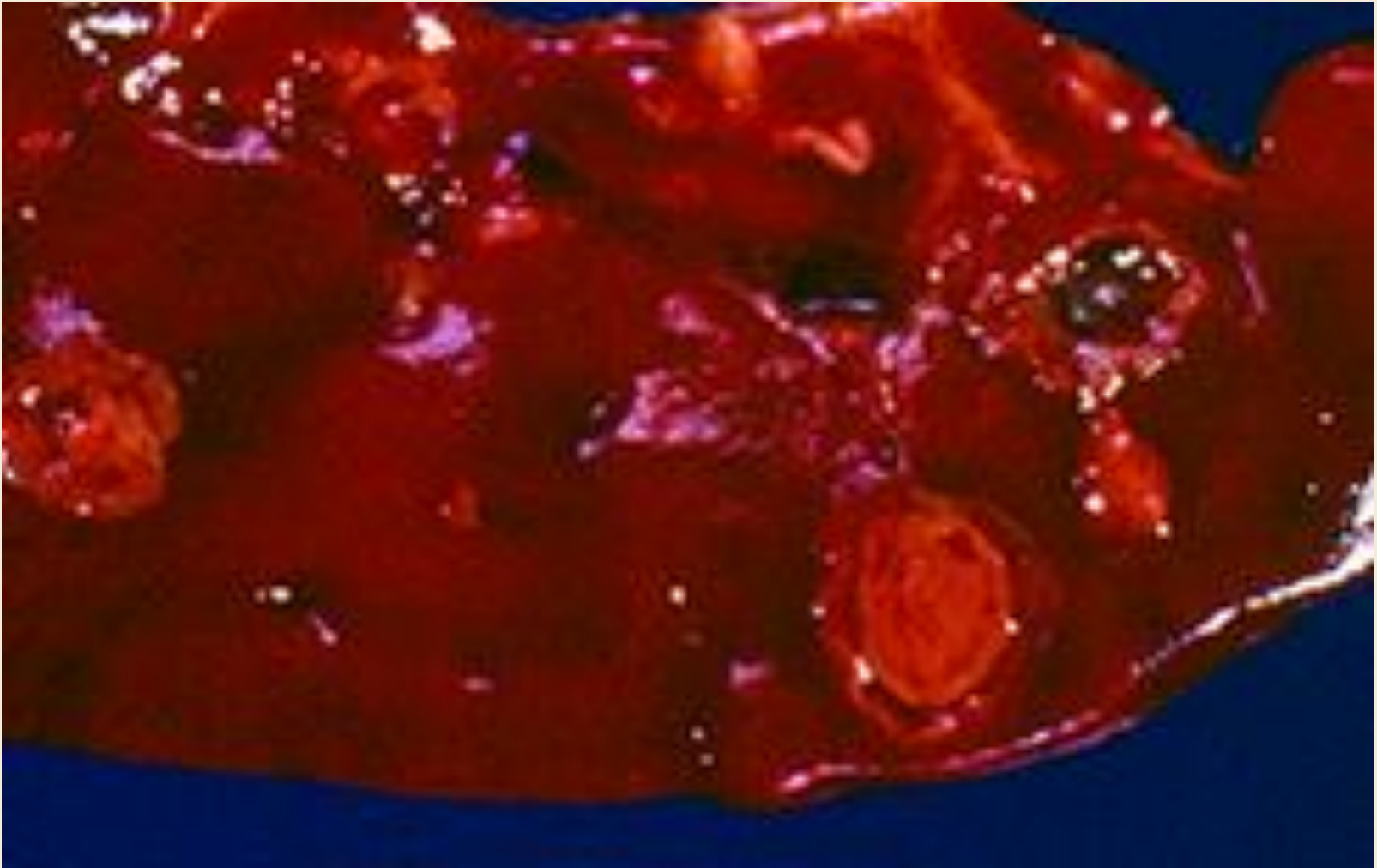
^bFollowing trauma or surgery



A



Kidney involvement by Fusariosis



Fusarium Endophthalmitis Associated with Compounded Products. Christina A. Mikosz et al , for the Fungal Endophthalmitis Outbreak Response Team. Emerg Infect Dis Feb 2014, www.cdc.gov

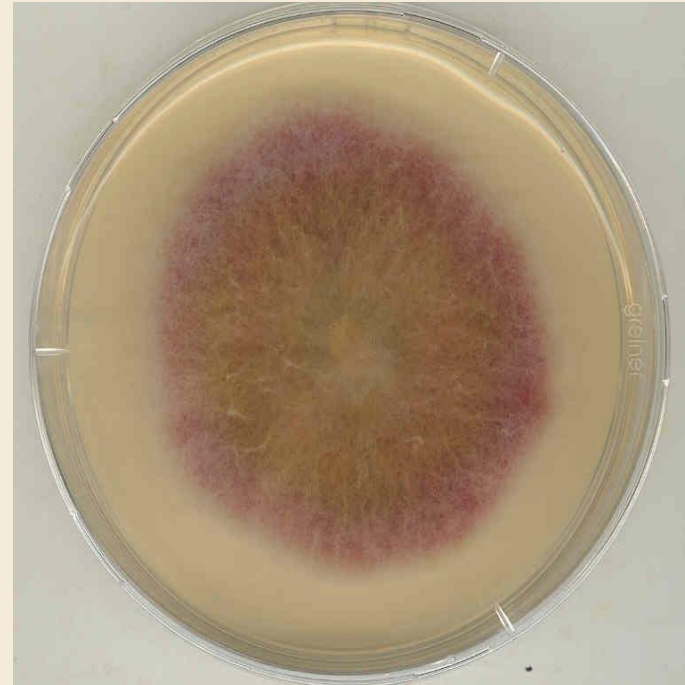
- **Multistate (9) outbreak**
- **Intense investigation, vigorous testing of both intraocular specimens, vials by Cx, DNA sequence analysis and typing, case-control analysis**
- **21 cases (10/2011-12/2011) followed vitrectomy where Brilliant Blue G dye (BBG) was injected, mold: a rare *Fusarium* spp (*F. incarnatum*)**
- **Dye were produced by the same compounding lab, exposure to either product was the only factor associated with the case cluster, identical fungi (ML DNA sequencing from the vials and pts -> product recall**

Implications

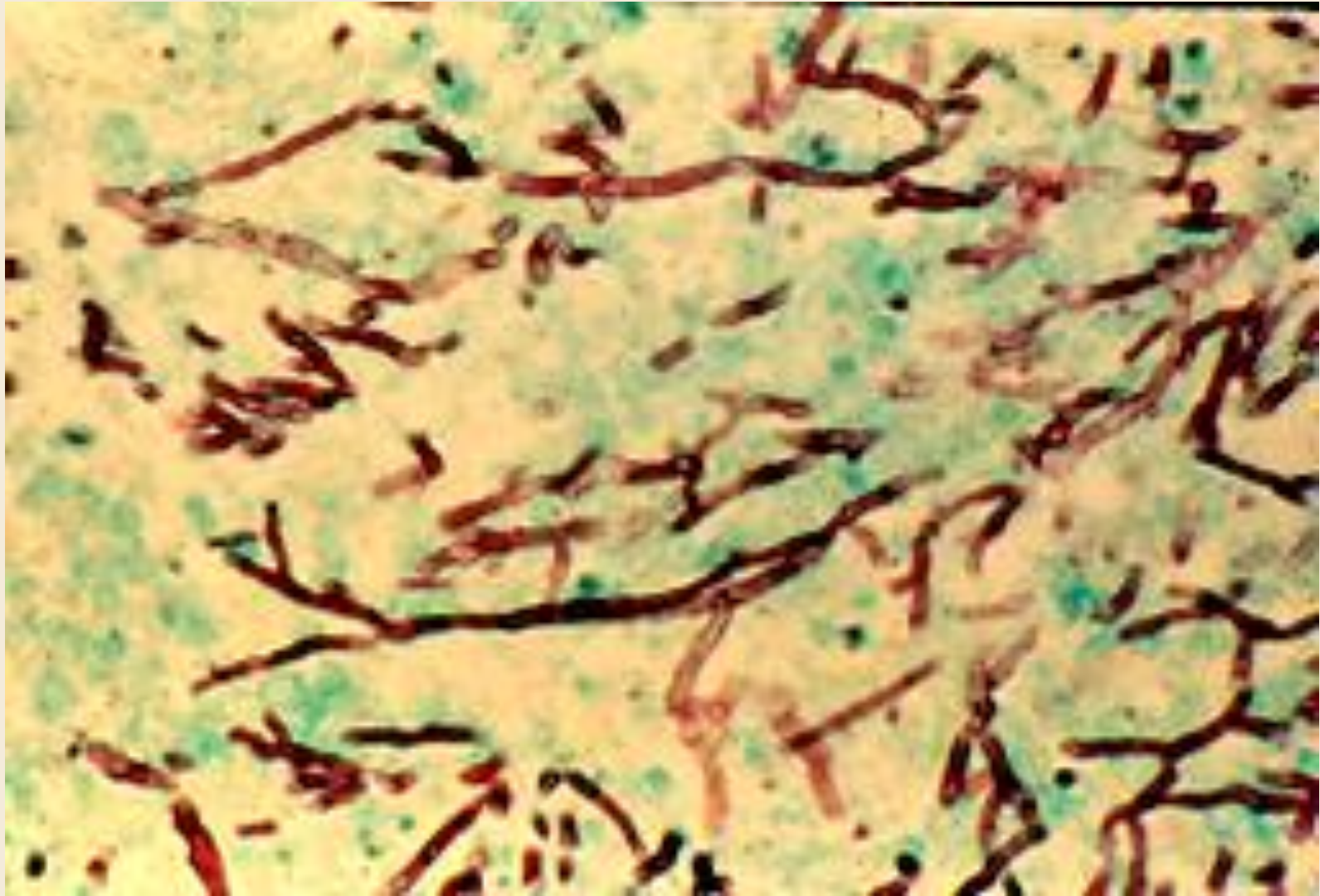
- BBG was not FDA approved, no guarantees of quality
- Epidemic quite reminiscent of the *Exserohilum* tragedy, rare opportunistic fungi when injected, cause unusual infection in anatomically restricted, sterile spaces
- Clear need for federal oversight of compounding pharmacies
- That compounding pharmacy was a previous offender (2005): need for transparency of prior disciplinary action and disclosure of an FDA approval status

Diagnosis

- Growth in blood culture
- Resembles *Aspergillus* in tissue biopsy
- Culture of sinus or respiratory secretions or blood in immunocompromised is true disease
- Confirmatory Dx: Histopathology
- 1,3- β -D-Glucan usually +positive
- Galactomannan –usually positive
- PCR in blood and tissue
- Recovered from urine

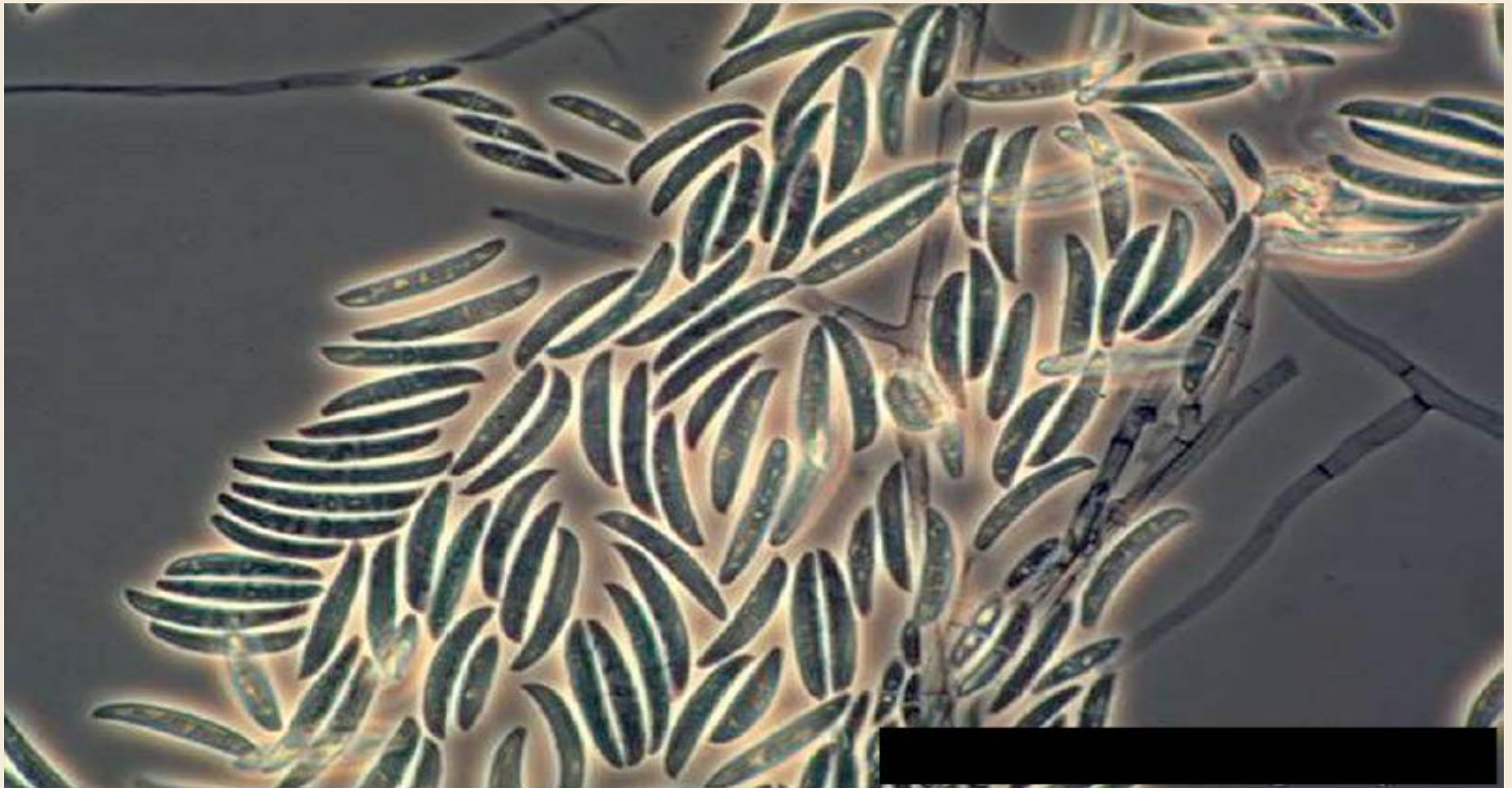


Lung involvement by Fusariosis



Laboratory Diagnosis

- Most common species: *F. solani* (50%), *F. oxysporum* (14%), *F. verticillioides* (10-11%)
- Macroconidia are classic (banana-shaped)
- PCR, rRNA in situ hybridization available being developed
- Positive blood culture in 30-50% of cases
- Can be recovered from urine in disseminated infection



Principles of therapy in fusariosis

- **Early aggressive treatment with high doses of lipid amphotericin B**
- **with a triazole with activity against *Fusarium* species (e.g., voriconazole)**
- **Rapid tapering of steroids, if possible**
- **Consideration for G-CSF-primed granulocyte transfusions**
- **Long duration of antifungal therapy, which should be individualized**
- **Remove catheter for CVC-related fungemia**
- **Debridement of devitalized tissue of localized disease (e.g., onychomycosis, sinusitis, abscess)**

Posaconazole as Salvage Treatment for Invasive Fusariosis in Patients with Underlying Hematologic Malignancy

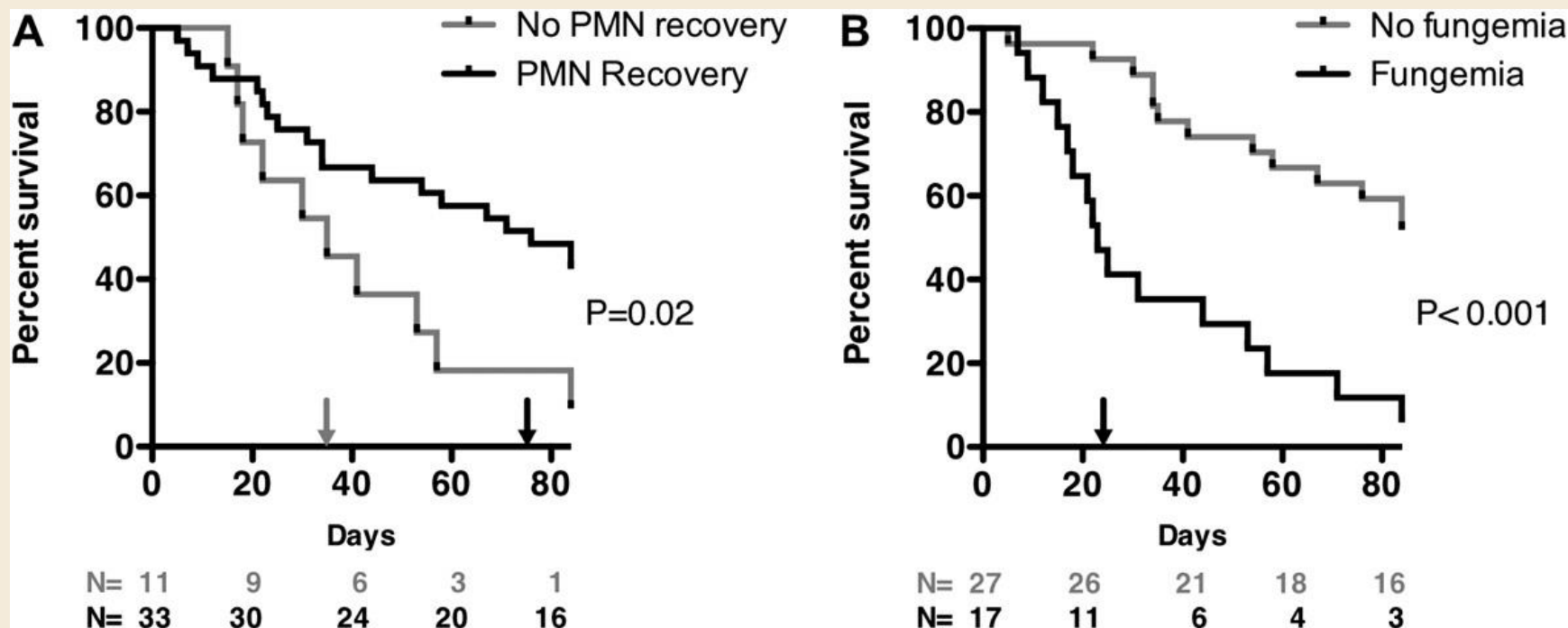
- **Response rate to posaconazole in patients with fusariosis refractory or intolerant to standard therapy approached to 50%, still very poor in patients with active leukemia**

Outcome Determinants of Fusariosis in a Tertiary Care Center: The Impact of Neutrophil Recovery

- 42/42 patients had underlying hematologic malignancy, 12(29%) received SCT (allogenic in 10/12)
- 36(86) had profound *neutropenia*
- 20(49%) received adrenal corticosteroids within 1 month
- Recovered neutropenia was the most important predictor of outcome, no patient with refractory myelosuppression survived

Invasive fusariosis in patients with hematologic malignancies at a cancer center: 1998-2009

Campo M, Lewis RE, Kontoyiannis DP. J Infect 2010



Crude mortality 66% in week 12

Fungemia the only independent factor for 12 w mortality by MV

New azoles, combination therapy (used in 84% of pts) did not appear to be protective

PSEUDALLESCHERIASIS

Pseudallescheria boydii is the teleomorph (sexual) state,
Scedosporium apiospermum is the anamorph (asexual) state

Found in soil and water (especially stagnant or polluted) throughout the world. Huge concentrations in manure

Scedosporium apiospermum most common fungus found in potted plants in the hospital

Sites of entry: By inhalation to sinus or lung-primarily in immunocompromised hosts. By penetration due to trauma of skin, eye, bone or joint – primarily in health hosts

→ Most common cause of eumycetoma in N. America

Wide variation in pathogenicity of various strains

Scedosporium Infections at MDACC: 25 Cases, 1989–2006. Lamaris G et al. CID 2006

- *Scedosporium apiospermum* in 21, *Scedosporium prolificans* in 4 patients), all with active hematologic cancer
- Incidence of *Scedosporium* infection increased from 0.82 cases per 100,000 patient–inpatient days (1993–1998) to 1.33 cases per 100,000 patient–inpatient days (1999–2005)
- Dissemination occurred in 16 patients (64%)
- 2-week mortality rates were 70% and 100% for *S. apiospermum* and *S. prolificans* infection, respectively
- 5 of 6 survivors received a triazole with in vitro activity against *S. apiospermum* (posaconazole in 3 patients and voriconazole in 2 patients); only 1 of 12 patients who died of *Scedosporium* infection received an active triazole (p.003)
 - *S. apiospermum* caused 4/23 of endogenous fungal endophthalmitis (1991-2007)-Lamaris G ... Kontoyiannis DP. Eur J Microbiol and Infect Dis 2008

Disseminated *Scedosporium prolificans* in 26 Immunocompromised Patients

Severely neutropenic acute leukemia 20, BMT on steroids 3

Blood cultures positive in 80% with dissemination to multiple organs

Numerous erythematous or purplish skin nodules of different sizes, many with necrotic centers, in 30% of patients

Neurological signs and symptoms (focal, confusion, come in 25%, myalgias in 15%

Visual complaints due to **endophthalmitis** in 25%

Fatality rate 90% - no effective therapy

Skin Lesions Due To *S. Apiospermum* Infection

Infections mainly in immunocompromised host. Often occurs after trauma, even small bruises. Can be nosocomial.

Lesions described as folliculitis – like eruptions, indurated erythema, bullous, necrotic purpura, erythema with necrotic center, eschar, macules, papules, subcutaneous abscess.

May develop spreading cellulitis extending deeply, lymphagitis, or disseminated cutaneous lesions.

In a report of 20 cases, 16 on steroids +/- immunosuppressive agents. Sites: arm/hand 10, leg/foot 5, disseminated 5. 10 patients cured. 4/5 disseminated died.

Large survey found 46 patients with *P.boydii* on skin but only 10 had significant infection.

Uenotsuchi:Acta Derm Venereol 85:156, 2005

Therapy of *S. apiospermum*

- Amphotericin B, echinocandins and fluconazole ineffective
- Voriconazole active in-vitro against *S. apiospermum*
- Voriconazole- 64% successful response in 70 patients
- Sometimes combined with surgical drainage
- Posaconazole and isavuconazole may be effective
- Reverse cause of immunosuppression
- Consider immune adjunct therapy: WBC txs, IFN- γ +
 - GM-CSF

Scedosporium prolificans

- ❖ Natural habitat unknown – probably soil, polluted water animals (horses, cats). Isolated from plants in hospital.
- ❖ Related to *Scedosporium apiospermum*, the anamorph (asexual form) of *Pseudallescheria boydii*.
- ❖ Most human infections reported from Spain, Australia and United States (California).
- ❖ In animal models, tropism to kidneys and brain.
- ❖ Visual complaints due to endophthalmitis in 25%.
- ❖ Causes vascular thrombosis
- ❖ Resistant to AMB, 5FC and azoles, but occasional clinical responses,
- ❖ ? Synergism between azoles and terbinafine.

Management

- Reduce immunosuppression
- Surgical debridement
- Voriconazole and posa breakthrough reported
- Voriconazole and caspo; voriconazole and terbinafine have been successful
- Mortality higher than with *S. apiospermum* (HSCT 78% vs. 62%)

Common Themes

- **Immunocompetent: trauma-or device-associated**
- **Immunocompromised: severe pneumonia, more commonly disseminated**
- **Surgical debridement**
- **Immune restoration**
- **Therapy individualized**
- **The host is the most**