

Θεσσαλονίκη

Scedosporiosis in children

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Transparency disclosures

- Independent Contractor (research grants) of significant value from Pfizer, Gilead, Enzon, Schering
- Scientific Advisor (Review Panel or Advisory Committee) of Schering, Gilead, Astellas, Pfizer
- Speaker's Bureau of Gilead, Cephalon, Pfizer, Wyeth, Schering, Merck, Aventis, Astellas

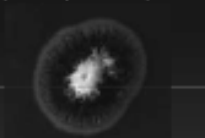

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Scedosporium species

Scedosporium apiospermum
(teleomorph *Pseudallescheria boydii*)

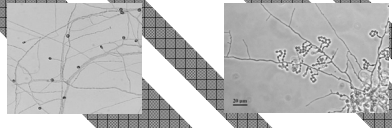



Scedosporium prolificans
(teleomorph unknown)

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Scedosporium apiospermum *Scedosporium prolificans*



- n cause refractory life-threatening infections
- n are resistant to most antifungal agents

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Taxonomy of *Pseudallescheria boydii* and *Scedosporium prolificans*

1 March 2012 Cortex K, et al. *Clin Micro Rev* 2008; 21: 157-97 5

Susceptibility of *S. prolificans*

1 March 2012 Cortex K, et al. *Clin Micro Rev* 2008; 21: 157-97 6

Susceptibility of *S. apiospermum*

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Cortez K, et al. *Clin Micro Rev* 2008; 21: 157-97

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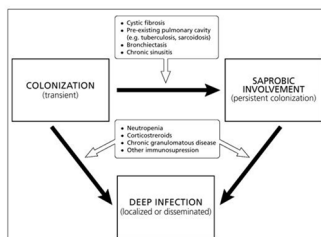
Scedosporium epidemiology

- Ubiquitous saprophytic fungi in the environment
- Especially in polluted waters
- Under specific conditions may cause life-threatening infections
- Hospital outbreaks

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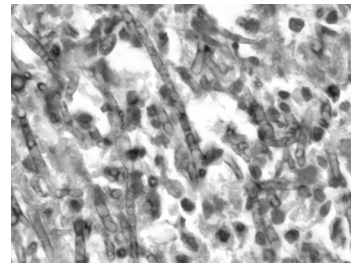
Host-Pathogen interaction in pulmonary scedosporiosis



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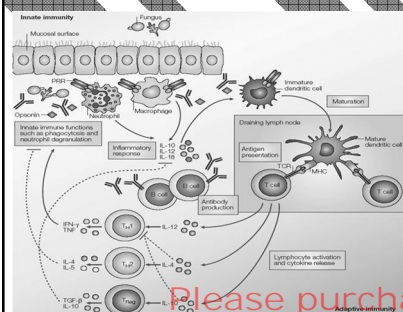
Scedosporium apiospermum infection in human tissue



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Antifungal innate immunity



Innate and adaptive immune responses to *Scedosporium* spp. have been studied much less than those to *A. fumigatus*.

The increasing importance of these emerging fungal pathogens has made the thorough study of the host defense against them necessary

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Antifungal innate immunity

- Recognition by phagocytes & signal transduction
- Gene expression and cytokine release
- Modulation of antifungal function of phagocytes and lymphocyte activation
- Intra- or extra-cellular damage of fungi by phagocytes

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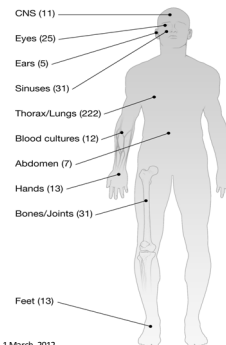
Host susceptibility to *Scedosporium*

- Immunocompromised hosts
 - Hematological malignancies
 - Corticosteroids
 - Chronic granulomatous disease
- Immunocompetent hosts
 - Victims of near drowning
 - Trauma

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Infections caused by *Scedosporium*spp.



- Fungal pneumonia
- Sinusitis
- Osteomyelitis/arthritis
- Fungemia/disseminated disease
- Meningitis/Brain abscess
- Endocarditis

Cortez K, et al. *Clin Micro Rev* 2008; 21: 157-97

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Classification of *Scedosporium* spp. infections Selected examples of other mycoses

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Cortez K, et al. *Clin Micro Rev* 2008; 21: 157-97

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Pediatric cases

- Cases of scedosporiosis published in the English literature (Pubmed) up to 2005
- Among 434 cases of scedosporiosis there were 50 pediatric patients
- Underlying diseases
 - hematological malignancies
 - chronic granulomatous disease
 - no underlying condition except for near drowning
- A greater percentage of children had no underlying chronic condition (52% vs 35% for adults, $p=0.028$), with the greatest frequency occurring in victims of trauma
- Mortality was 28%

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Cortez K, et al. *Clin Micro Rev* 2008; 21: 157-97

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Multifistulous right lower limb *S. apiospermum* mycetoma -
Calcaneus osteomyelitis

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S. apiospermum infection after near-drowning

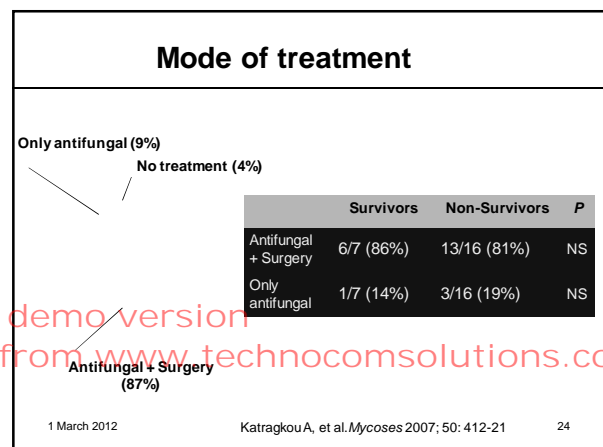
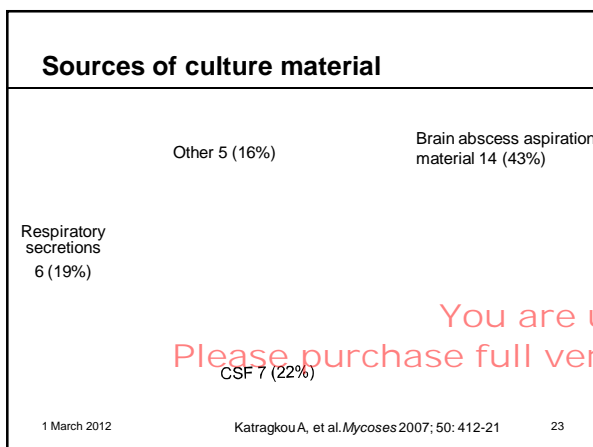
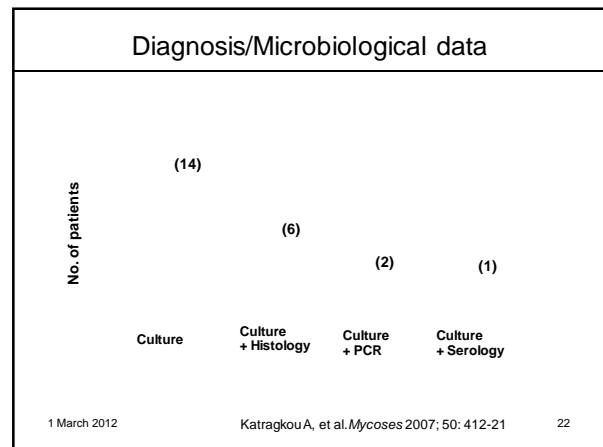
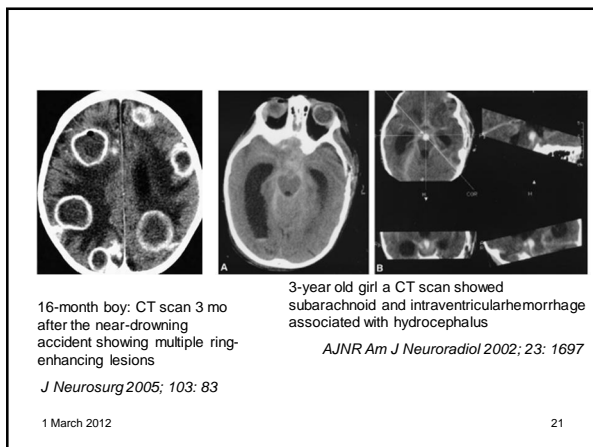
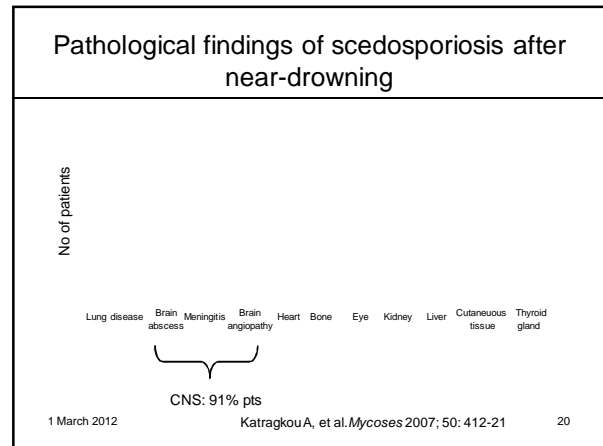
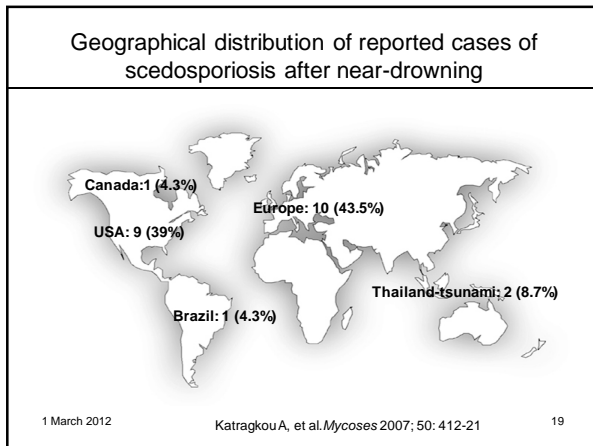
Total 23 cases (9 children + 14 adults)

- Sex: M>F (2.5/1)
- Age: 24 ± 3.6 yrs (mean \pm SE)
 - adults (>18 yrs) 35 ± 3.4 yrs
 - children (<18 yrs) 3 (2-14.5) yrs (median, IQR)
- Underlying conditions: 78% adults } immunocompetent
all children }

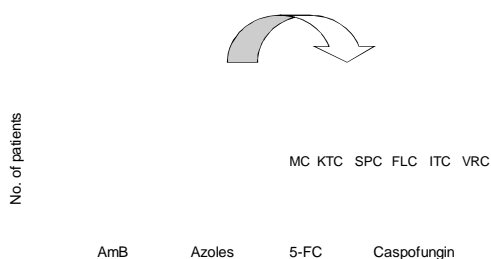
Katragkou A, et al. *Mycoses* 2007; 50: 412-21

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Commonly used antifungals



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Katragkou A, et al. *Mycoses* 2007; 50: 412-21

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Diagnostic difficulties

Median time to diagnosis was 28 days
3 cases diagnosed postmortem



Low sensitivity of routine culture methods
Histological similarity with other filamentous fungi
Cross-reactivity to *Cryptococcus* capsular antigens
High genetic variability of *Pseudallescheria* spp.
=>False negative immune reactions

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Katragkou A, et al. *Mycoses* 2007; 50: 412-21

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Conclusions

Scedosporiosis after near-drowning = 'delayed', highly lethal infection (70% mortality)

Diagnosis = delayed and difficult based on routine culture methods

PCR-based techniques not widely accepted

S. apiospermum isolates are usually resistant to amphotericin B and sensitive to newer azoles (i.e. voriconazole)

Voriconazole used empirically very early in cases of suspected scedosporiosis after near-drowning may improve outcome

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Katragkou A, et al. *Mycoses* 2007; 50: 412-21

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Bronchopulmonary scedosporiosis & cystic fibrosis

- Scedosporium* spp. is the second most frequent isolate of filamentous fungi from CF patients after only *Aspergillus* spp.
- Environmental abundance CF lung colonization (ie Australia)
- While cases are still few, *Scedosporium* spp. has also been implicated to allergic bronchopulmonary mycosis causing similar symptoms to allergic bronchopulmonary aspergillosis

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Harun A, et al. *Med Mycol* 2010; 48 Suppl 1: S70-6

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Bronchopulmonary scedosporiosis & cystic fibrosis (2)

- Bacterial colonization & antimicrobial exposure likely influence *Scedosporium* colonization. Studies are required to confirm independent risk factors for *Scedosporium* colonization and to determine its impact on lung function

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Blyth CC, et al. *Med Mycol* 2010; 48: S37-S44

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Filamentous fungi isolated in specimens from CF patients

Blyth CC et al. *JCM* 2010 48: 314-316

Organism(s)	No. (%) of specimens ^a
<i>Aspergillus</i> spp.	110 (50.5)
<i>A. fumigatus</i>	99
<i>A. flavus</i>	19
Other <i>Aspergillus</i> spp.	9
<i>Scedosporium</i> spp.	32 (14.7)
<i>S. aurantiacum</i>	17
<i>S. prolificans</i>	11
<i>S. apiospermum</i>	4
<i>Penicillium</i> spp.	18 (8.3)
<i>Paecilomyces</i> spp.	7 (3.2)
Other hyaline hyphomycetes	9 (4.1)
<i>Cladosporium</i> spp.	4 (1.8)
<i>Curvularia</i> spp.	3 (1.4)
<i>Alternaria</i> spp.	3 (1.4)
Other dematiaceous fungi ^b	4 (1.8)
<i>Rhizopus</i> spp.	2 (0.9)
Other fungi	3 (1.4)

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Treatment challenges

- Distinctively difficult to treat given their inherent resistance to available antifungal agents including polyenes, triazoles and echinocandins
- Empiric treatment: voriconazole and combination with LAMB
- Isolation, proper identification and susceptibility testing are essential steps for their optimal treatment
- Surgical debridement
- Augmentation of host defenses

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Ped. scedosporiosis - Summary

- Emerging opportunistic pathogens
- Infections in both immunocompetent & immunocompromised hosts
- Fungal pneumonia, fungemia, brain abscess, osteomyelitis, etc.
- After near drowning, bronchopulmonary scedosporiosis in CF patients
- Resistance to antifungal agents
- Voriconazole, AmB, surgery

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