INVASIVE FUNGAL INFECTIONS IN ICU

Dr Kaniz Fatema

FCPS (Medicine), MD (Critical Care Medicine)

Associate Professor

Dept of Critical Care Medicine

BIRDEM General Hospital

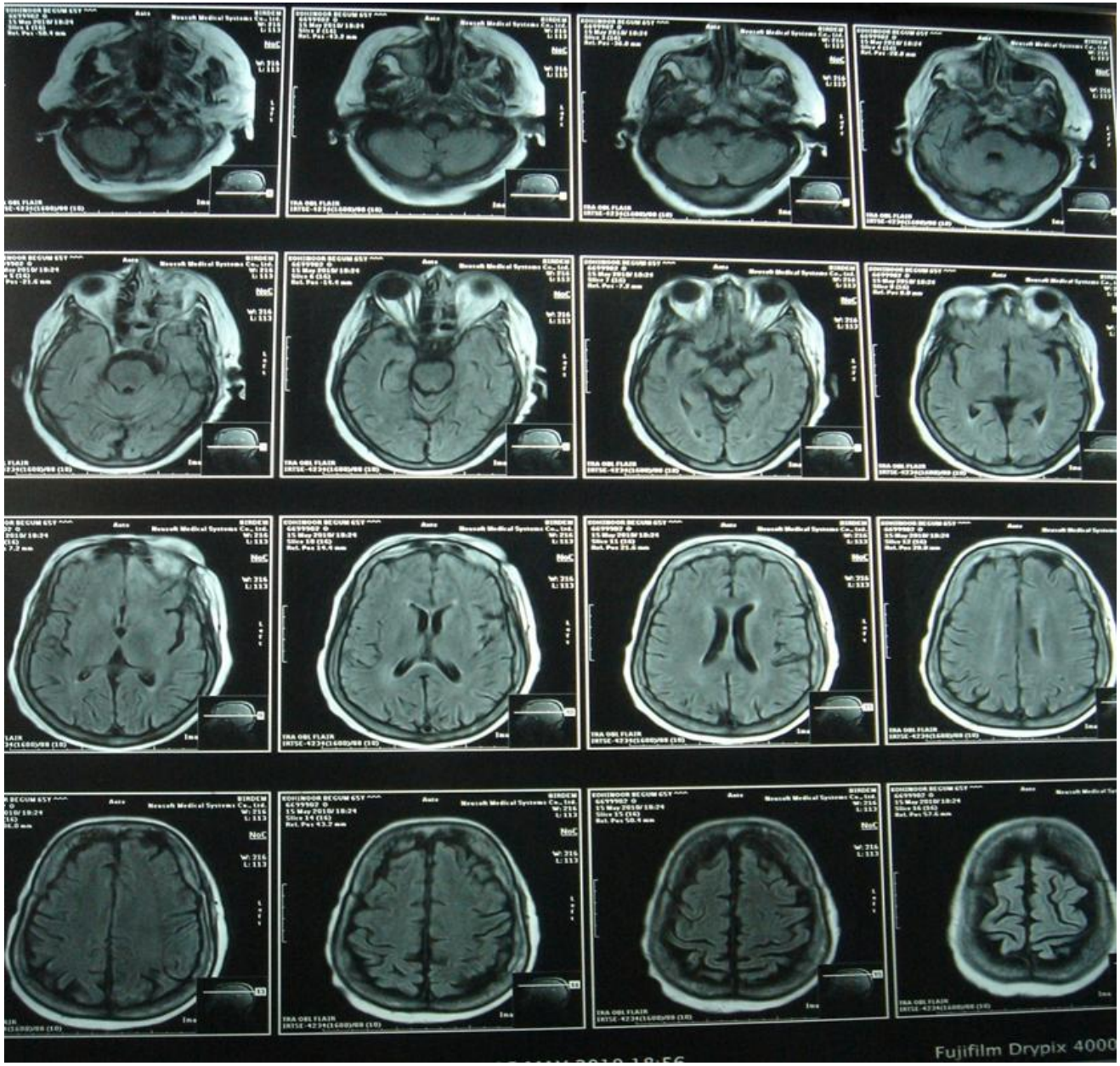
Poisonous Mushroom


11
BIRD

Case 1

- 65-years old lady
- HTN (15 yrs)
- Adult Still's Disease (2 mon)
- Prednisolone (40mg/day)
- Fever & swelling of left eye for 7 days
- Altered level of consciousness for 1 day

- RBS → 32 mmol/L
- DKA
- Grade III unconscious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Rhinocerebral Mucormycosis

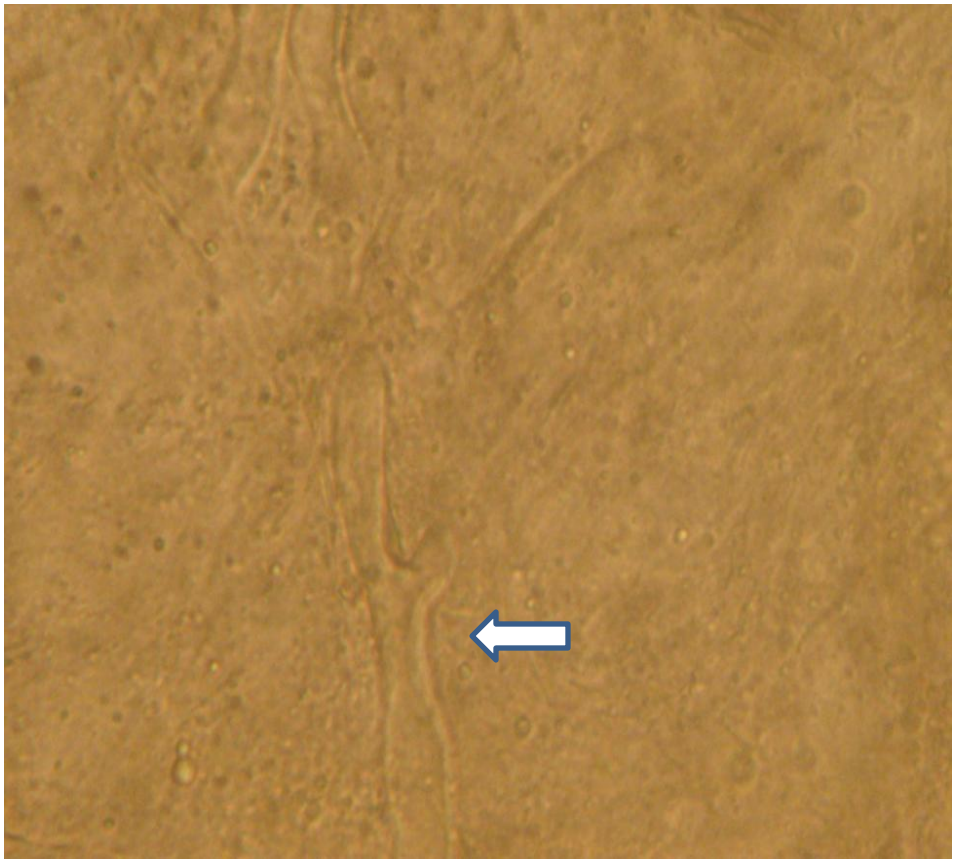


Fig: Broad aseptate fungal hyphae in direct sample under Microscopy

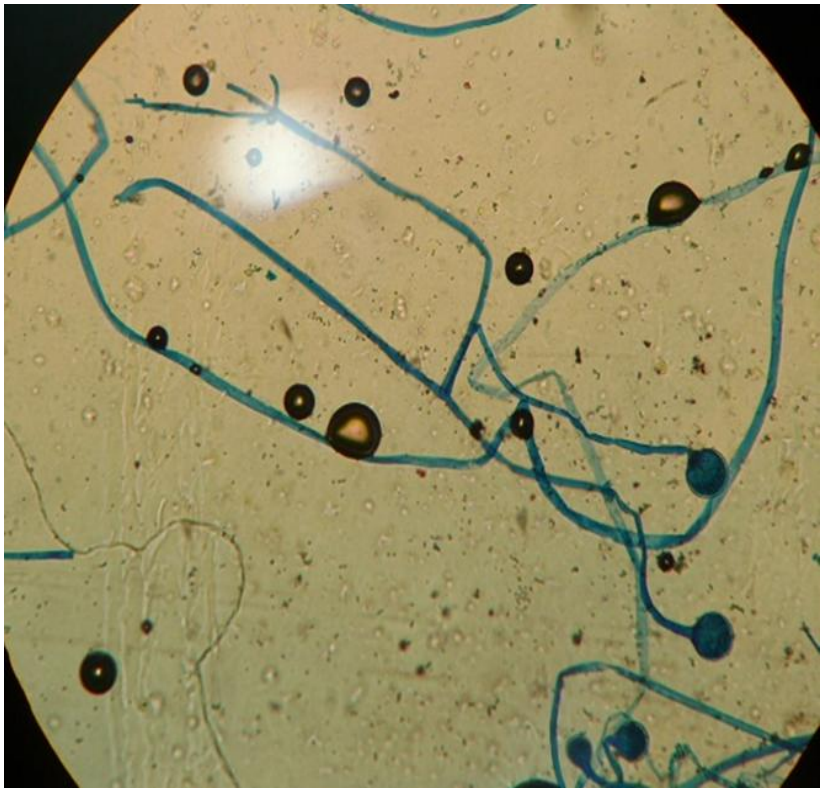
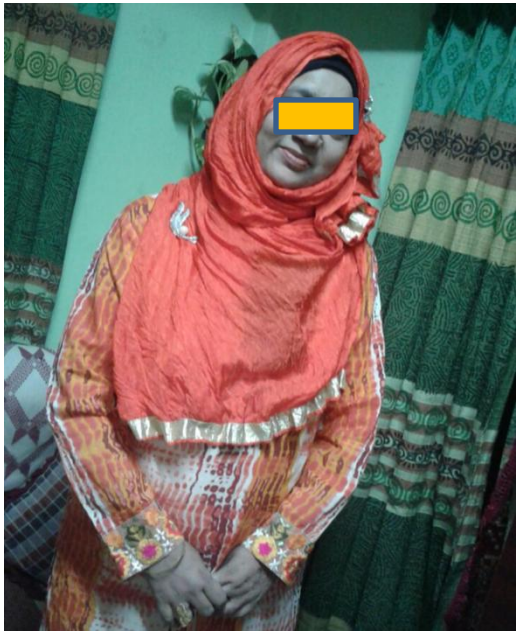


Fig: Fungal hyphae with sporangia from culture growth with fungal stain under Microscopy

Case 2

- 45-year-old diabetic lady, Home maker
- Sub-acute intestinal obstruction, DKA
- Type II resp failure
- Blood C/S → *Esch. Coli*
- After 7 days of ICU admission,

  Septic shock, AKI
- Blood C/S → *Candida albicans*
- Anidulafungin



With permission

Why is it important?

- Increasing problem
- Mortality higher than bacterial infection
- Early diagnosis is challenging
- Delay in diagnosis & treatment increases mortality
- New strategies for recognition & treatment

Topics to be addressed

- Fungal biology
- Classification of fungal infection
- Risk factors
- Common fungal infections in ICU
- Laboratory diagnosis
- Therapeutic approaches

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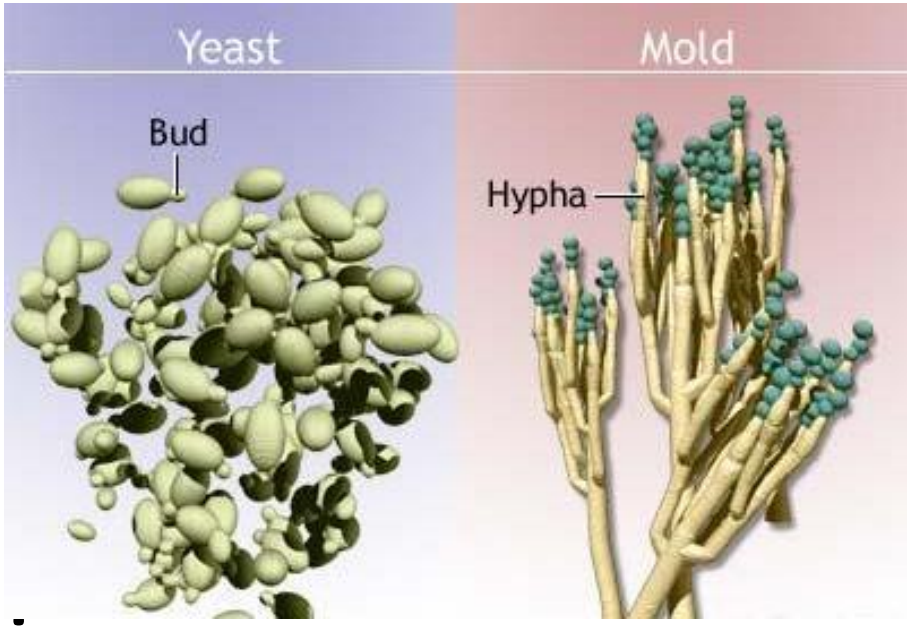
Topics to be addressed

- **Fungal biology**
- Classification of fungal infection
- Risk factors
- Common fungal infections in ICU
- Laboratory diagnosis
- Therapeutic approaches

Fungal Biology

- Eukaryotes
- Non-motile
- Aerobic
- Saprophytic or parasitic
- Glucan, Mannan & Chitin in cell wall
- Ergosterol in cell membrane



Topics to be addressed

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- **Classification of fungal infection**
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Classification of Fungal infection

Anatomical Location:

- **Muco-cutaneous**

  Morbidity high

  Mortality low/nil

- **Invasive infection**

  Morbidity high

  Mortality very high

Epidemiology:

- **Endemic**

  Acquired from environment

  True pathogenic fungi

- **Opportunistic**

  Acquired ubiquitously

  Fungi that are part of normal flora

Incidence & Trends

- **EPIC II study revealed that 19% of pathogens isolated in ICU patients were fungi.**
- ***Candida spp* are predominantly isolated followed by *Aspergillus spp*.**
- **Candidaemia is the 4th most common nosocomial ICU BSI in U.S.A., and between 6th & 10th cause in European studies.**

অন্য বাংলাদেশ

বারডেম হাসপাতালের একটি সাধারণ ওয়ার্ডে চিকিৎসা নিচ্ছেন রোগীরা ● প্রথম আলো

বিশ্বের সবচেয়ে বড় হাসপাতাল

শিশির মোড়ল ●

শহিদুল্লাহর বয়স ৫৮ বছর। রাজধানীর লালবাগ এলাকার মুদি দোকানি। বেশ কিছুদিন শরীরটা তাঁর ভালো যাচ্ছে না। পাড়ার চিকিৎসকের সন্দেহ, ডায়াবেটিস হয়েছে। নিশ্চিত হওয়ার জন্য রক্ত পরীক্ষা করাতে বলেছেন। পরীক্ষায় রক্তে শর্করার পরিমাণ জানা যাবে।

শাহবাগ মোড়ে বারডেম হাসপাতালের বহির্বিভাগে সকালে পা রাখার জায়গা থাকে না। মানুষ আর মানুষ। ছুটি আর হরতালের দিন ছাড়া প্রতিদিন রোগীর ভিড়ের একই দৃশ্য। রোগীর চাপ সামলাতে বারডেম কর্তৃপক্ষ ভবনের বাইরে রোগী বসার ব্যবস্থা করেছে। সেখানে অপেক্ষমাণ শহিদুল্লাহ প্রথম আলোকে বলেন, 'রক্ত দিছি। দুই ঘণ্টা বইতে কইছে। এক ঘণ্টা হইছে, এক ঘণ্টা বাকি।'

ডায়াবেটিস চিকিৎসায় বারডেম

- প্রতিদিন ৩ হাজার রোগী এখানে বহির্বিভাগে চিকিৎসা নেয়
- হাসপাতাল থেকে যে আয় হয়, তা দরিদ্র রোগীদের চিকিৎসায় ব্যয় করা হয়

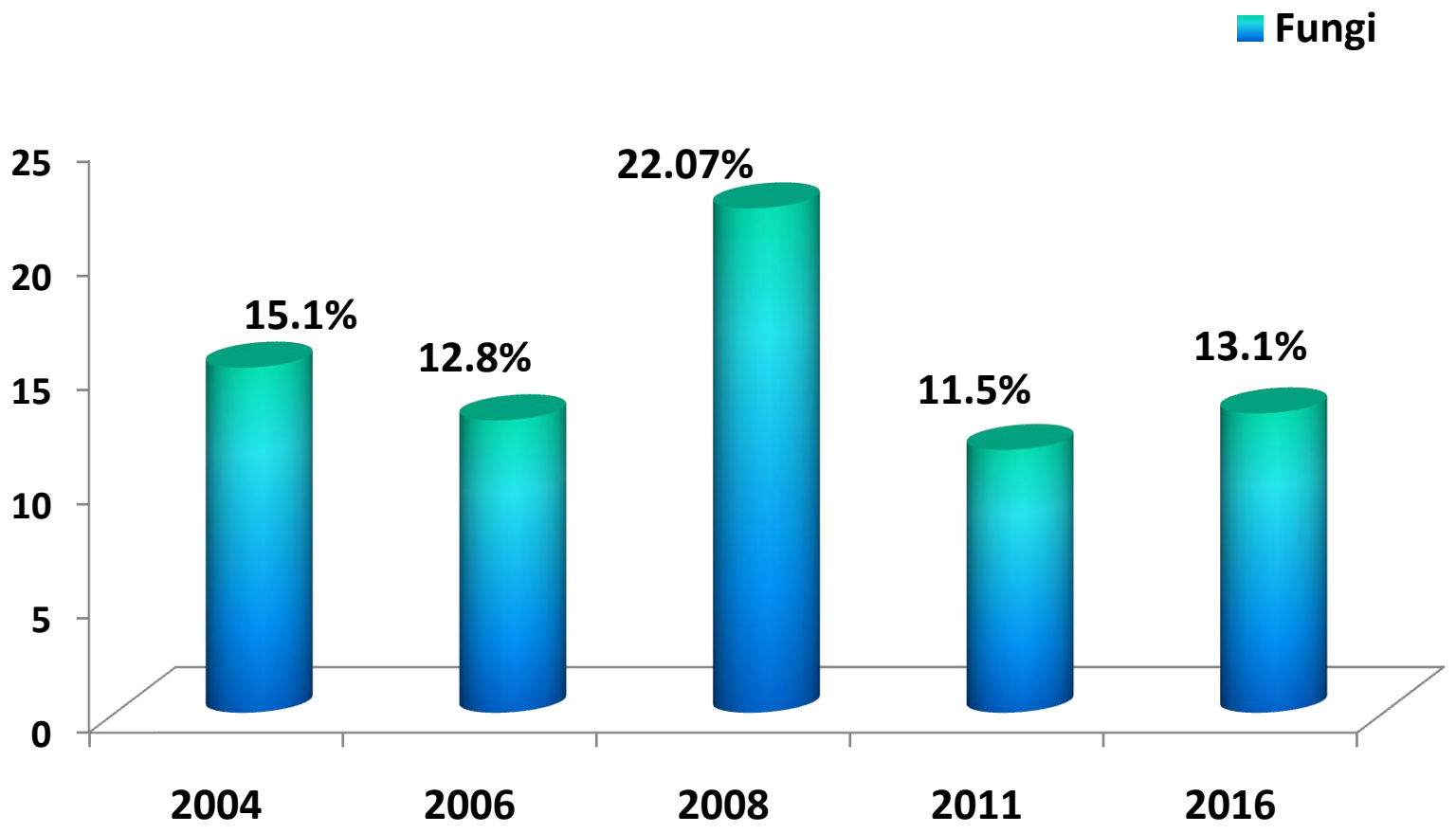
অপারেশন হইছে, এক টাকাও লাগে নাই। ওষুধও পাইছি ফ্রি।'

প্রথম সপ্তাহে এই হাসপাতাল পরিদর্শন করতে এসে বলেন, বেসরকারি খাতে ডায়াবেটিস চিকিৎসায় বিশ্বের সবচেয়ে বড় হাসপাতাল বারডেম।

জনস্বাস্থ্য বিশেষজ্ঞরা বলছেন, দেশে ডায়াবেটিস রোগীর সংখ্যা প্রায় ৭০ লাখ। ২০৪০ সালে এই সংখ্যা বেড়ে দ্বিগুণ হবে। এই রোগের চিকিৎসা ও প্রতিরোধে বারডেম বড় ভূমিকা রেখে চলেছে।

স্বাস্থ্য অধিদপ্তরের মহাপরিচালক অধ্যাপক আবুল কালাম আজাদ প্রথম আলোকে বলেন, বারডেম হাসপাতাল বাংলাদেশের গর্ব। বারডেম বাংলাদেশে ডায়াবেটিসের আধুনিক চিকিৎসা ও ডায়াবেটিস সম্পর্কে জানচর্চার সূচনা করেছে। বহু মানুষকে তারা বছরের পর বছর সেবা দিয়ে যাচ্ছে। স্বাস্থ্য খাতে বেসরকারি অবদানের এটি এক উজ্জ্বল দৃষ্টান্ত।

Fungal Infection in BIRDEM ICU



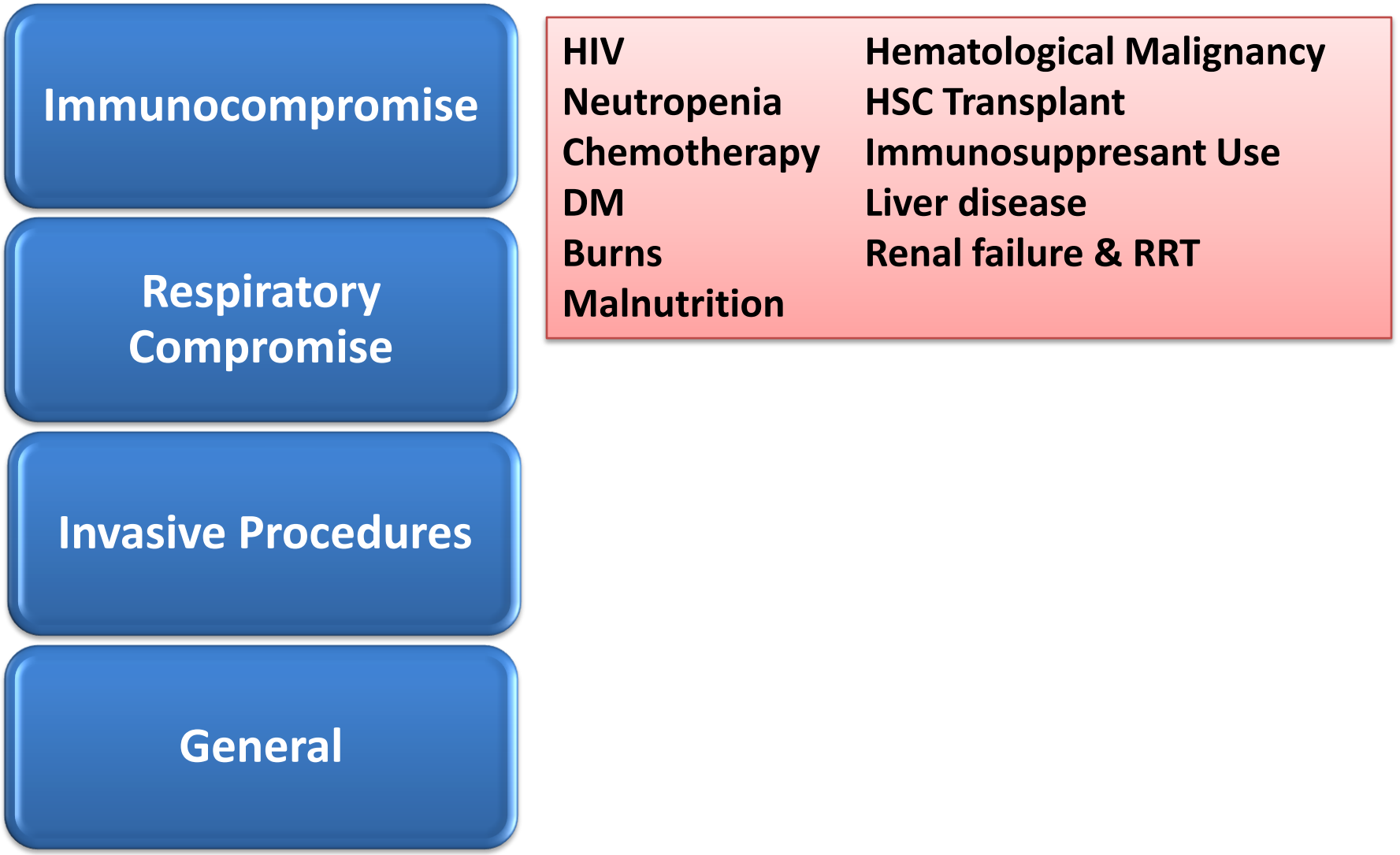
Samples include sputum/tracheal aspirates, blood, pus/wound swab, pleural/peritoneal fluid & urine

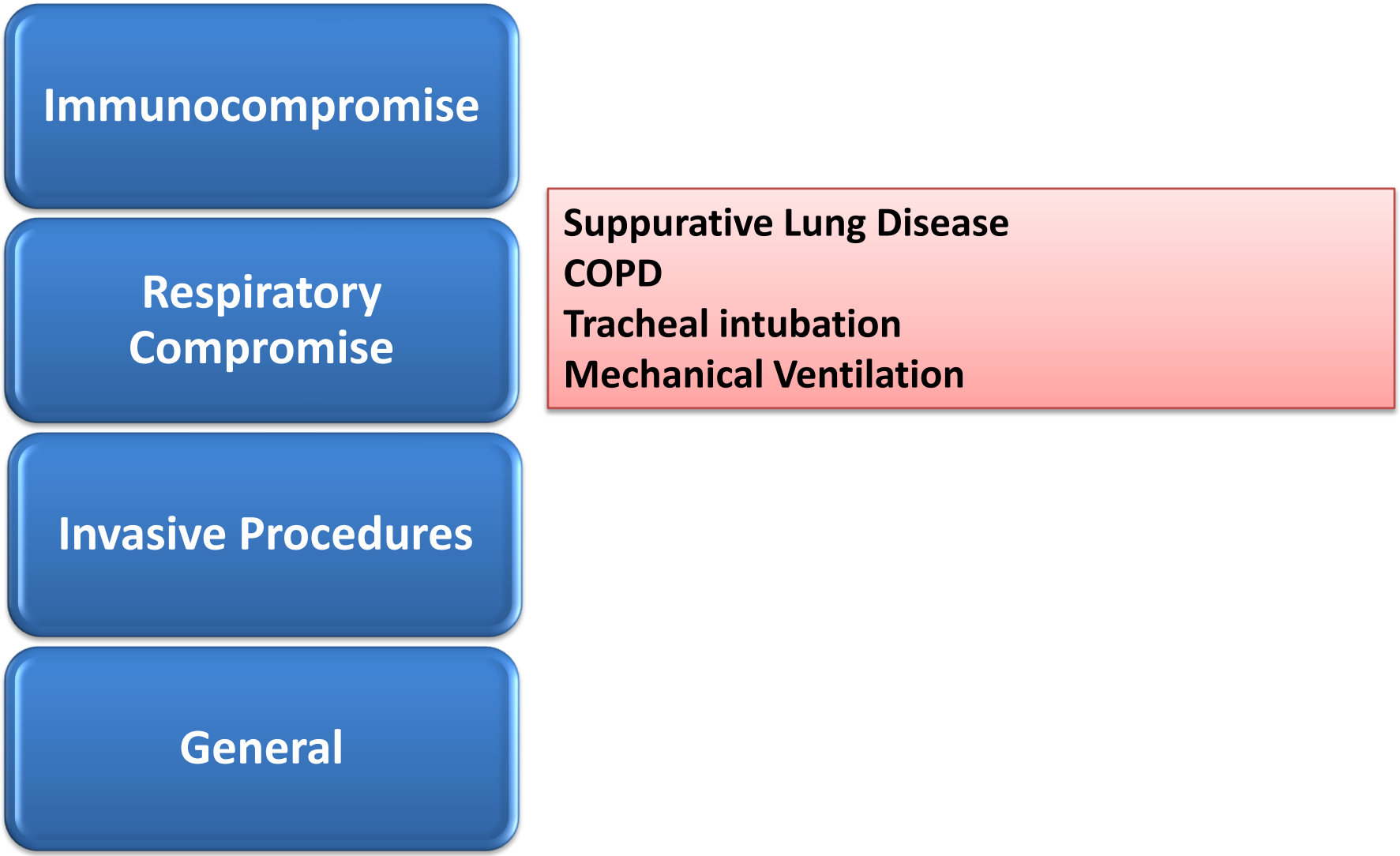
Topics to be addressed

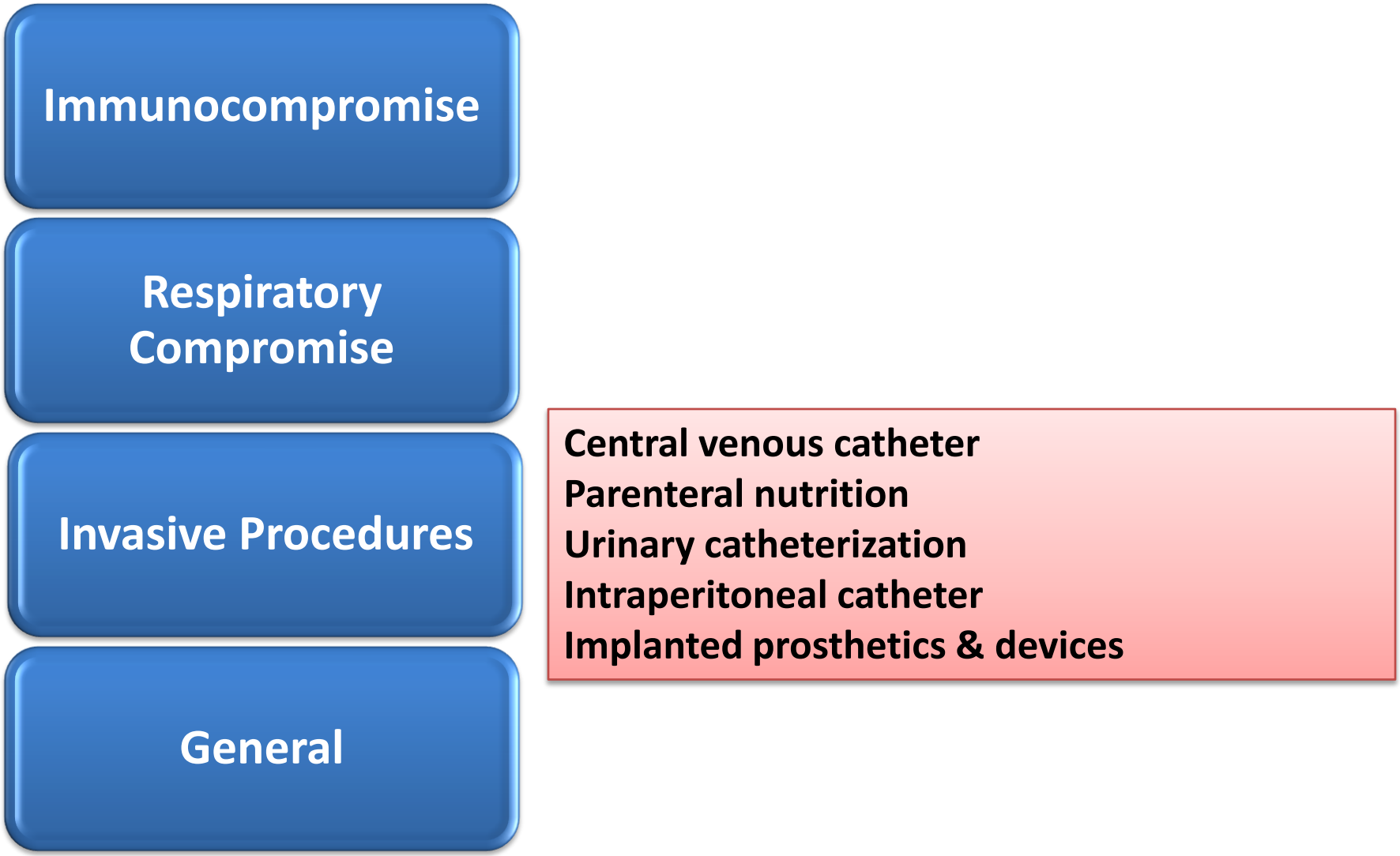
- Fungal biology
- Classification of fungal infection
- **Risk factors**
- Common fungal infections in ICU
- Laboratory diagnosis
- Therapeutic approaches

Risk Factors for Invasive Fungal Infection in the ICU

- Immunocompromise
- Respiratory Compromise
- Invasive Procedures
- General


Immunocompromise
Respiratory Compromise
Invasive Procedures
General
HIV
Neutropenia
Chemotherapy
DM
Burns
Malnutrition
Hematological Malignancy
HSC Transplant
Immunosuppresant Use
Liver disease
Renal failure & RRT


Immunocompromise
Respiratory Compromise
Invasive Procedures
General
Suppurative Lung Disease
COPD
Tracheal intubation
Mechanical Ventilation


Immunocompromise
Respiratory Compromise
Invasive Procedures
General
Central venous catheter
Parenteral nutrition
Urinary catheterization
Intraperitoneal catheter
Implanted prosthetics & devices

Immunocompromise

Respiratory Compromise

Invasive Procedures

General

Increased use of broad spectrum antibiotics
IV drug misuse
Length of stay in ICU
Gut lumen contamination of body compartments

Topics to be addressed

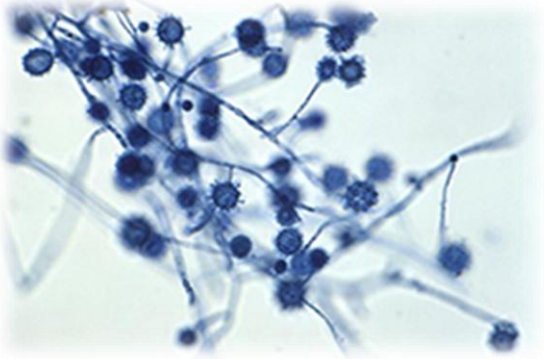
- Fungal biology
- Classification of fungal infection
- Risk factors
- **Common fungal infections in ICU**
- Laboratory diagnosis
- Therapeutic approaches

Common Fungal Infections in ICU

ENDEMIC MYCOSES	OPPORTUNISTIC INFECTIONS
➢ Histoplasmosis	➢ Candida
➢ Blastomycosis	➢ Aspergillus
➢ Coccidioidomycosis	➢ Mucor
	➢ Cryptococcus

TRUE PATHOGENIC FUNGI

Histoplasmosis

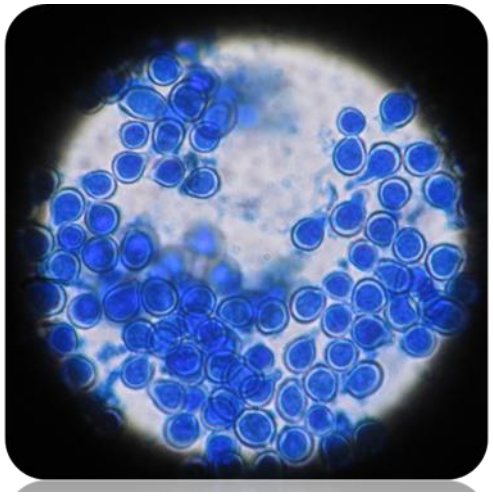


- *Histoplasma capsulatum*
- Portal of entry: Respiratory tract
- Mild, severe & Chronic pulmonary disease, Disseminated histoplasmosis
- Ag in urine, blood or BAL. Bone marrow biopsy
- Self limited
- Amphotericin B, followed by Itraconazole

Blastomycosis

- CAP not responding to antibiotics
- Meninges, Skin, Bones, Genitourinary tract
- Fungus in resp secretions
- Open lung biopsy
- Amphotericin B,

  followed by Itraconazole



OPPORTUNISTIC FUNGI

Candida

- *C. albicans*
- *C. parapsilosis*
- *C. tropicalis*
- *C. glabrata*
- *C. krusei*
- *C. dublinsiensis*

Non-albicans

Candidaemia

Disseminated hematogenous infections

Chronic disseminated candidiasis

Laboratory Diagnosis

- **Microscopy: Wet preparation, KOH preparation**
- **Culture**
- **Histopathologic identification**
- **Newer:** - **Mannan kits**
  - **1,3 β D glucan**
  - **PCR**
  - **MALDI-TOF**
  - **PNA-FISH**

Prediction of Invasive Candidiasis

Year	ICU	Design	Number	Independent Determinants	Score
1994	Surgical	Prospective 1-center	29	Colonization, APACHE II score	Colonization index >0.5
2003	Surgical	Retrospective	221	Female, upper GIT, cardiac failure, previous antibiotics	Any 3 factors
2003	CTS	Prospective 1-center	150	Ventilation, nosocomial bacterial infection, DM, cardiopulm bypass time > 2 hours	-
2004	Surgical	Prospective cohort	478	Colonization	Colonization index >0.4
2005	Medical	Prospective 1-center	92	Colonization	Colonization index >0.5
2005	Surgical	Prospective cohort	327	DM, hemodialysis, TPN, antibitoics	Positive score
2006	All	Prospective multicenter	1,699	Colonization, surgery, severe sepsis	Candida score >2.5
2007	All	Retrospective multicenter	2,890	ICU stay, CVC, antibiotics, TPN, dialysis, surgery, steroids	Positive score
2009	All	Prospective multicenter	1.107	Colonization, surgery ,TPN, severe sepsis	Candida score >=3
2009	All	Retrospective multicenter	64,019	Age, prior hospitalization, ventilation, altered mental status	Simple equal weight score

Kratzer C, et al. Mycoses. 2011;54:467-74.

Candida Score

Variable	Points
Multifocal Candida spp colonization	1
Surgery on ICU admission	2
Severe sepsis	1
Total parenteral nutrition	1

- ✓Cut-off of 2.5: sensitivity 81%, specificity 74% in the initial study
- ✓Cut-off of <3.0 can be used as a negative predictive value in non-neutropenic ICU patients

Leon C, et al. Crit Care Med. 2006;34:730-7.
Leon C, et al. Crit Care Med. 2009;37:1624-33.

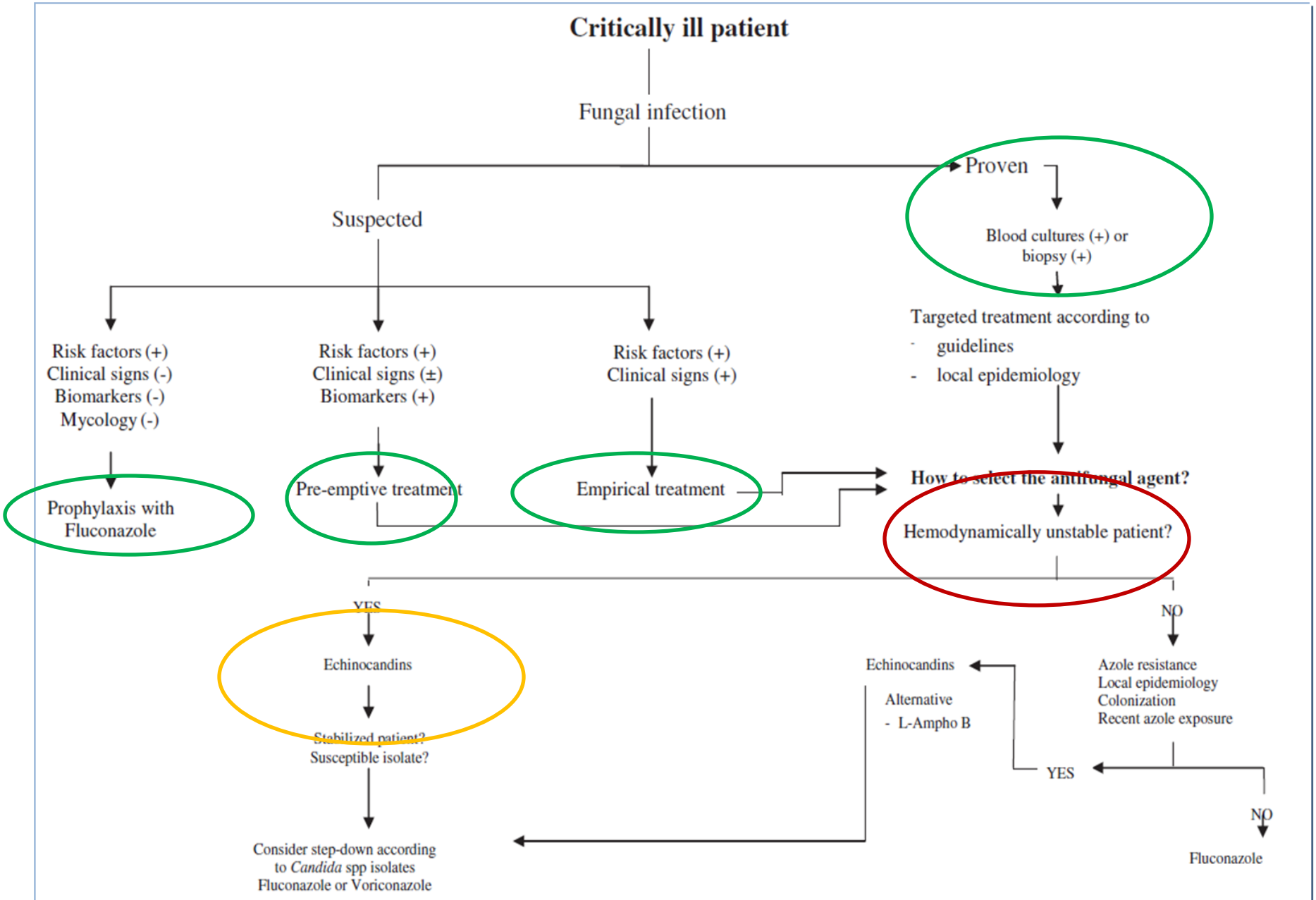


Fig. 1 Suggested algorithm for the management of candidiasis in the ICU patient.

Treatment of Documented Candidiasis

Antifungal	Diseases
Echinocandins	Candidaemia, Empirical in ICU patients, Intra-abdominal
Azoles	Prophylactic in ICU patients, Osteoarticular infection, Endophthalmitis, Oro-pharyngeal, Oesophageal, Symptomatic cystitis & pyelonephritis,
Amphotericin B	CNS infection, Chronic disseminated candidiasis, Intravascular Candidiasis, Suppurative thrombophlebitis, Neonatal candidiasis

Clinical practice guideline for the management of Candidiasis:2016 update by IDSA

- **Consecutive blood cultures should be obtained.**
- **Treatment should be continued for 14 days after the 1st negative blood cultures.**
- **Central venous catheters & /or implanted devices should be removed.**
- **Fundoscopic examination must be done.**

- **Growth of *Candida spp* from respiratory specimen alone should not prompt the use of anti-fungals in most patients.**
- **Candiduria can represent colonization of lower urinary tracts or urinary catheters in the absence of symptoms.**

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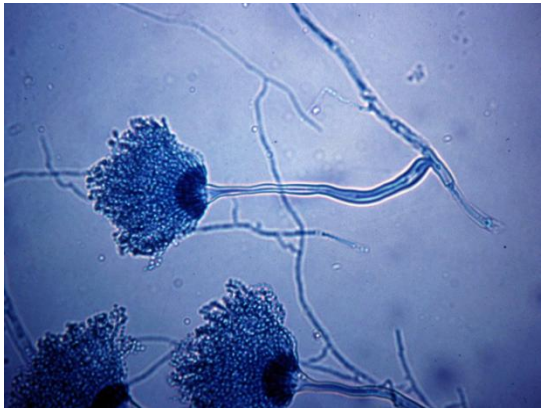
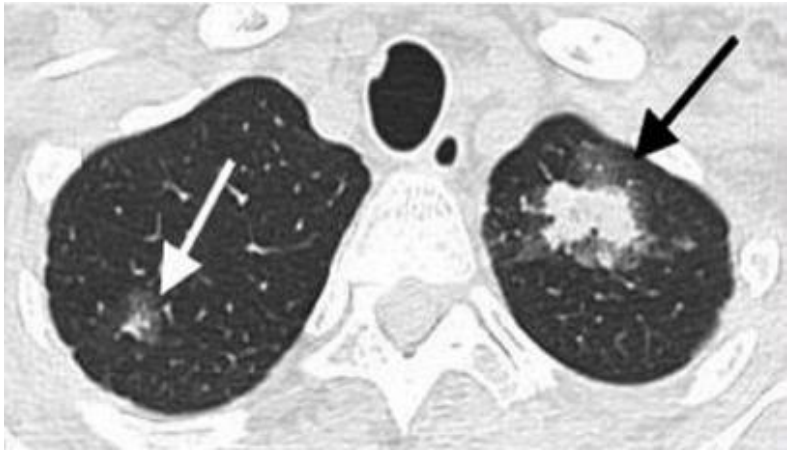
Aspergillosis

- ***A. fumigatus, A. flavus, A. niger, A. nidulans*** **etc**
- **Wide environmental distribution**
- **Incidence: 0.1% to 10%**
- **Mortality: 17%**
- **Sino-pulmonary involvement, Angioinvasive aspergillosis, Endocarditis, Osteomyelitis**



Laboratory Diagnosis

- ✓ Cultures
- ✓ Biopsies
- ✓ Radiological findings
- ✓ Galactomannan
- ✓ β D glucan
- ✓ PCR



Treatment

- ✓ Voriconazole: IV followed by oral
- ✓ Amphotericin B followed by oral voriconazole
- ✓ Salvage therapy: Capsofungin, or Posaconazole
- ✓ Galactomannan test: marker of effectiveness of therapy
- ✓ Adjunctive therapies: G-CSF, γ IFN
- ✓ Surgical resection

Mucormycosis

- *Rhizopus, Rhizomucor, Mucor*
- **May affect any organ: Sinuses, Brain, Skin, Lungs, & GIT**
- **Typically affects immunocompromised hosts, esp DKA**
- **Prompt surgical debridement with Amphotericin B**

Cryptococcosis

- *C. neoformans, C. gattii*
- **CNS, Lungs**
- **Immunocompetent patients:**

  Fluconazole/Itraconazole for mild disease

  Amphotericin B ± Flucytosine
- **Immunocompromised patients:**

  Fluconazole/Itraconazole for pulmonary dis.

  Amphotericin B + Flucytosine in CNS involvement

Topics to be addressed

- Fungal biology
- Classification of fungal infection
- Risk factors
- Common fungal infections in ICU
- **Laboratory diagnosis**
- Therapeutic approaches

Traditional Methods

- **Microscopy**
- **Culture**

  Gold standard

  Not positive always
- **Radiography**

  Classic signs may be absent in patients with immunosuppression
- **Histopathology**

  Challenging to obtain

Rapid Diagnostic Tests

Test	Application	Sensitivity	Specificity	Limitations
β-D glucan	*Candida* *Aspergillus*	57%-97%	56%-93%	False +ve
Mannan Ag Anti-Mannan Ab	*Candida spp*	Ag: 58% Ab: 59% Comb: 83%	Ag: 93% Ab: 83% Comb: 86%	+ve results later in disease course
Galactomannan	*Aspergillus* & some other molds	Serum: 71% BAL:76-88%	Serum: 89% BAL: 87-100%	False +ve
Nucleic acid PCR	All species But available currently for *Candida* only	96%	97%	Unavailable for many organisms

Topics to be addressed

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- **Therapeutic approaches**

Anti Fungal Drugs

- Azole: Itraconazole, Fluconazole, Voriconazole, Posaconazole
- Polyenes: Amphotericin B deoxycholate, Liposomal AmB
- Echinocandins: Capsofungin, Micafungin, Anidulafungin
- Antimetabolites: Flucytosine
- Allyamines: Terbinafine
- Miscellaneous: Griseofulvin
- Future options:

  Isavuconazole, Ravuconazole, Albaconazole, Mycograb (human recombinant monoclonal Ab)

Spectrum of Anti-fungal drugs

Drugs	*C.albicans*	*C.para*	*C.glab*	*Aspergillus*	*Mucorales*	*Crypto*
AZOLE						
Fluconazole	S	S	SDd-R	R	R	S
Itraconazole	S	S	SDd-R	S	R	Ms
Posaconazole	S	S	SDd-R	S	S	S
Voriconazole	S	S	SDd-R	S	R	S
POLYENE						
AmB	S	S	S	S*	S	S
ECHINO						
Capsofungin	S	Rc	S	S	R	R
Micafungin	S	Rc	S	S	R	R
Anidulafungin	S	Rc	S	S	R	R
PYRIMIDINE						
Flucytosine	S	S	S	R	R	S

S=susceptible, SDd-R= Susceptible depending on dose, S*= not all spp are susceptible,
R=Resistant, Ms=modest activity, Rc=Resistant depending on concentration

Mortality

- **Invasive Candidiasis → 40% to 60% in ICU patients**

  & 80% to 90% for patients with septic shock

- **Invasive Aspergillosis → 60% to 90% in ICU patients**

Current Practices & Challenges in Bangladesh

Local epidemiology of IFI in ICU	Candida
Diagnosis	Microscopy, Culture
Commonly prescribed antifungals	Fluconazole, Itraconazole
Local published data: Epidemiology , Treatment & Outcome	Sporadic case reports
Gaps in current practice	Awareness- both in Intensivists/ Clinicians & Microbiologists Rapid diagnostic tests, AST Expensive treatment

Take Home Message

- Candidiasis is the leading Invasive Fungal Infection in ICU patients followed by Aspergillosis & Mucormycosis
- Increased clinical vigilance, a multifaceted diagnostic approach & timely use of anti-fungals are necessary to reduce the mortality & morbidity.
- Bangladesh may be experiencing increased load of opportunistic fungal infections in ICUs.

Acknowledgement

Dept of Microbiology, BIRDEM

Thank You All

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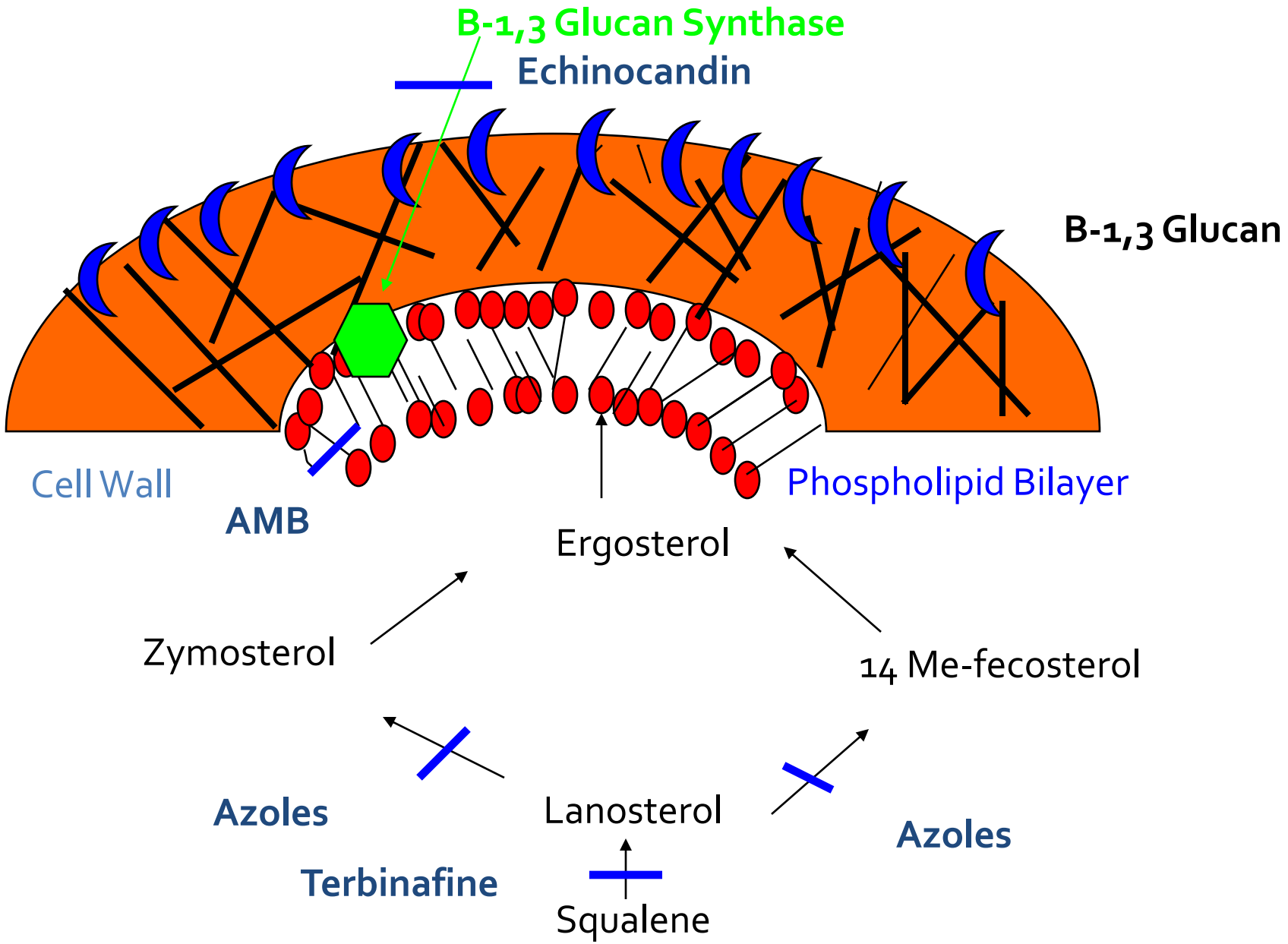
B-1,3 Glucan Synthase
Echinocandin
B-1,3 Glucan
Cell Wall
AMB
Phospholipid Bilayer
Ergosterol
Zymosterol
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Azoles
Lanosterol
Azoles
Terbinafine
Squalene