

Fungal Infections: Insights from the bench side

Dr Mamie HUI

Dept of Microbiology

The Chinese University of Hong Kong

Invasive Fungal infections

- Difficulties from the diagnostic point of view:
 - Non-specific symptoms & signs
 - Especially during early stage of disease
 - Attenuated by other treatment modalities
 - Cultures are of low sensitivity
 - When cultures are positive ...
 - Is it predictive?
 - Is it too late?

Invasive Fungal Infections

- Microscopy & Culture:
 - Non-sterile body sites vs Sterile body sites (blood, respiratory secretions, tissue biopsies)
 - Non-sterile body sites :
 - Diagnostic confusion?
 - Sterile body sites :
 - Timely specimen collection
 - Patient in critical condition

Alternative Methods

- A “perfect” diagnostic test :
 - Sensitive
 - Specific
 - Predictive (presence / absence of disease)
 - Speedy & readily available
 - Preferably non-invasive
 - Relative inexpensive
- No single test can fulfill all these criteria

Case

- M/14
- Persistent fever, chills, rigors ~ 1 week.
- Consulted family doctor, but symptoms did not resolve. Worsening shortness of breath.
- Admitted to hospital
- Hb 8.6g/dL, WBC $1.4 \times 10^9/L$, plt $33 \times 10^9/L$
- Blasts seen on peripheral blood smear
- Dx: Acute Myeloid Leukaemia M1

Case

- Induction chemotherapy started
- Went into neutropenic fever
- Given Ceftazidime & amikacin
 - Meropenam / vancomycin + Amphotericin
- Skin rash (July 10) – biopsied
- Urine (July 26) – *Candida tropicalis*
- CT (July 26) – lung nodules (voriconazole)
- Urine (Aug 1) – *Candida parapsilosis*
- Bronchoscopy (Aug 9) – NAD
- Open lung biopsy (Aug 20) - ? Degenerating spores
- CT (Sep 3) – liver/spleen multiple lesion ? Subtle hyperattenuation (casposfungin)

Course of events

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■ Date	BDG	CRP
■ 3/7/2007	30	57
■ 21/7/2007		83
■ 27/7/2007	59	192
■ 30/7/2007	279	227
■ 7/8/2007	541	205
■ 20/8/2007		93
■ 3/9/2007		90
■ 6/11/2007	107	36

Beta-d-glucan

- Cell wall component of many fungi
- EXCEPT : Zygomycetes, Cryptococcus
- Using horseshoe crab clotting cascade as substrate
- Initially developed for industrial use
 - Monitoring for contamination of health-care products
 - Detection limit (pg/mL)
- In human use : < 60 (negative); >80 (positive)

Beta-D-glucan

- Sort of “Pan-fungal marker”
- Kinetics of the beta-d-glucan release:
 - Encased from infected sites?
 - Circulation in blood / body fluids?
 - Clearance in normal / critically ill subjects?
- False negative?
- False positive?
 - Environmental source / contamination?
 - Haemodialysis cellulose membrane?
 - Pharmaceutical products?

What about the other alternatives

- Galatomannan
 - Blood, body fluids, tissues
 - Detection limit (ng/mL)
 - Mostly aspergillus mould
- False positive
 - Reduced clearance, cross-react with other antigen (cotton), Bifidomacterium
- False negative
 - Variable release / encased / angio-invasion
 - Anti-GM produced by patients

Fungal DNA

- Variable availability
- Variable performance
- Pan-fungal markers vs genus / species –specific markers

The place with beta-d-glucan

■ Monitoring

- Pre-emptive treatment?
- Success of treatment?
- Frequency? Once ? Twice per week?
- Leading to a battery of diagnostic work up?
- Part of a series of tests?
- Streamline other investigations? E.g. CT.