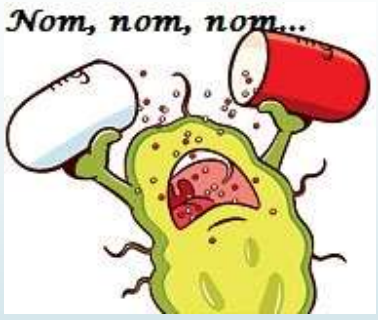
Newly Emerging Antimicrobials in Endocarditis

Marwa Sayed Meshaal, MD
Kasr Al Ainy

- Corner stone in treating IE patient is complete eradication of the infective organism
- Surgery contributes to the cure by removing the main/all bulk of the infected tissues
- Yet remains the main role for the antimicrobial to achieve complete cure
- Bactericidal/fungicidal drugs should be used
- Combination therapy are usually preferred to monotherapy to ensure eradication of tolerant organisms

- *Tolerant microbes* are not resistant, they escape the drug killing effect, keep dormant and resume activity after drug discontinuation
- This explains the need for combination therapy and long term treatment
- Use of large doses for long time
- Bactericidal/ Fungicidal agents
- Parenteral route is usually required

- So Are We Done with These Monsters ?



Unfortunately , NOT YET

- With development f more drug resistance, we are in a continuous need for new potent bactericidal and fungicidal drugs
- Linezolid and Daptomycin are the main valuable antibiotic addition in ESC and AHA 2015 guidelines
- Ecinocandins represent the new hope in fungal endocarditis with high efficacy, limited toxicity and minimal drug to drug interaction

Linezolid

- The molecule was originally invented by Pfizer as serotonin reuptake inhibitor anti-depressant
- As anti -staphylococcal effect against VRSA was noticed, the drug was released and marketed as antibiotic therapy
- Available as IV infusion drip, oral tablets and oral suspension
- Rapidly and extensively absorbed with oral bioavailability of 100%

- It is a reversible, nonselective inhibitor of monoamine oxidase.
- Therefore, linezolid has the potential for interaction with adrenergic and serotonergic drugs
- Its antimicrobial mechanism of action is not well understood, but it mainly works through inhibition of protein synthesis through inhibiting mRNA translation

- ***?? Magic Wand***

Unfortunately No

- Main Draw- back is ***Big list of drug-drug interaction***
  - MAOI , serotonin reuptake inhibitors, SSRI, antidepressants, tramadol for fear of serotonin reuptake syndrome
  - Sympathomimetics and vasopressors causing severe hypertension and remarakable variability of ABP
  - Insulin or other diabetes medicines (eg, glyburide) because the risk of low blood sugar may be increased
  - Barbiturates (eg, phenobarbital), carbamazepine, hydantoins (eg, phenytoin), or rifamycins (eg, rifampin) because they may decrease linezolid's effectiveness
- It is mainly indicated for VRSA, Vancomycin resistant enterococci

- Drug main side effects are ***Serotonin Syndrome*** and ***Bone marrow suppression***
- Bone marrow suppression increase significantly after 2 wk
- Drug should not be used more than 4 wk

Serotonin Reuptake Syndrome

- Serotonin syndrome is an increasingly common adverse drug reaction, which can be life-threatening
- Many physicians are not aware of the presentation and management of it
- Symptoms usually present within *6 to 8 hours* of initiating or increasing serotonergic medications or it *can happen late after relative long* time of drug use
- Approximately 15% of SSRI overdoses result in moderate symptoms
- Severe cases appear to be more likely after drug interactions

Mild Form

- Afebrile or low-grade fever
- Tachycardia
- Mydriasis
- Diaphoresis or shivering
- Intermittent tremor
- Myoclonus , Mild hyperreflexia
- Restlessness & Anxiety

Moderate

- Increased tachycardia, variability of blood pressure
- Fever (up to 41°C)
- Diarrhea with hyperactive bowel sounds
- Diaphoresis with normal skin colour
- Inducible clonus, Ocular clonus (slow continuous lateral eye movements)
- Increased confusion, Agitation
- Rhabdomyolysis
- Metabolic acidosis & Renal failure
- Disseminated intravascular coagulopathy (secondary to hyperthermia)

Severe

- Temperature often more than 41°C (malignant hyperthermia)
- Increased muscle tone (lower limb > upper)
- Spontaneous clonus , hyperreflexia
- Delirium
- Coma; agitated coma with marked variability of conscious level

Treatment

- Prompt recognition of toxicity and ***discontinuation*** of offending medications is most important
- Many cases of the syndrome are self-limiting if medications are stopped early
- Supportive care, including intravenous fluids
- Hyperthermia should be aggressively managed (dantrolin)
- Benzodiazepines

Ecinocandins

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- Three echinocandins are currently available and FDA approved caspofungin, micafungin, and anidulafungin
- Principal mechanism of action of the echinocandins is the noncompetitive inhibition of β-(1,3)-D glucan synthase
- Glucan is an important component of fungal cell wall that is not present in human cell wall
- Echinocandins are fungicidal against *Candida* species, including triazole-resistant isolates
- They are fungistatic against aspergillus, but when used in combination with amphotericin B or broad-spectrum triazoles, such as voriconazole they can be highly effective

Main Side Effects:

- Echinocandins have a rather limited adverse-effect profile compared with other antifungals

1. *Infusion-related reactions,* such as facial swelling, rash, and vasodilatation, which is most probably a histamine-mediated reaction

   easily treated with an antihistamine, reduce the rate of infusion

   should not prevent continuation of necessary echinocandin therapy

2. *Elevating liver enzymes,*

   can happen with the three of them

   regular follow up of liver enzymes and liver functions

   benefit/risk balance to continue or stop treatment

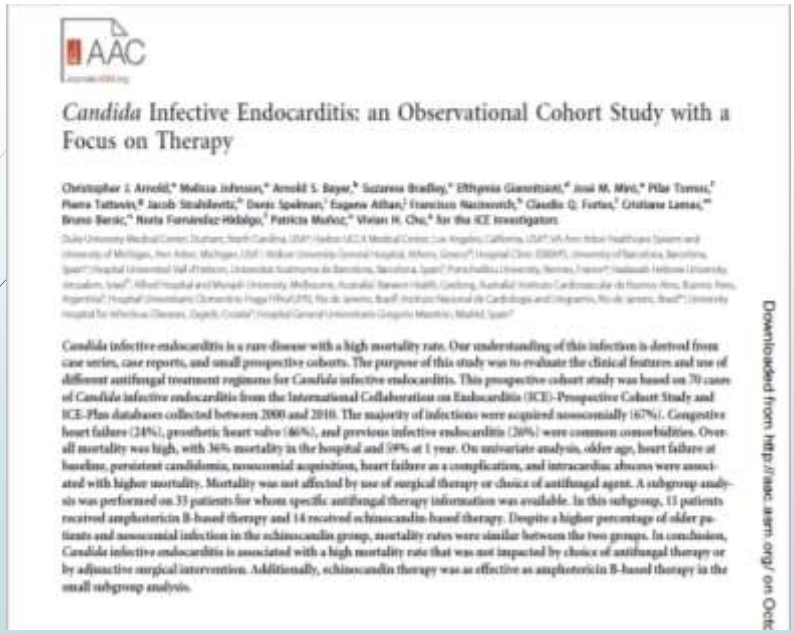
3. *Bone marrow suppression and neutropenia*
4. *Renal affection and electrolyte disturbance,* much less common than all other antifungals

Cuspofungin

- Available as IV vials
- Diluted in 0.9% saline or sterile water for injection
- Diluted solution should be used within 24 hr
- Over 1 hr
- Loading dose of 70 mg on 1st day then 50 mg daily
- No dose adjustment with renal impairment or dialysis patients
- No dose adjustment for mild hepatic affection, while moderate hepatic insufficiency (Child-Pugh score, 7-9), 35 mg daily is recommended with no change in loading dose

Micafungin

- Available as vials containing 50 mg
- Diluted in 0.9% saline or 5% dextrose
- Diluted solution should be used within 24 hr
- Over 1 hr
- Dose of 100-200 mg /day (IDSA guidelines recommend 150 mg/day)
- No dose adjustment with renal impairment or dialysis patients
- No dose adjustment for mild hepatic affection, or moderate hepatic insufficiency (Child-Pugh score, 7-9), no available data for severe hepatic affection



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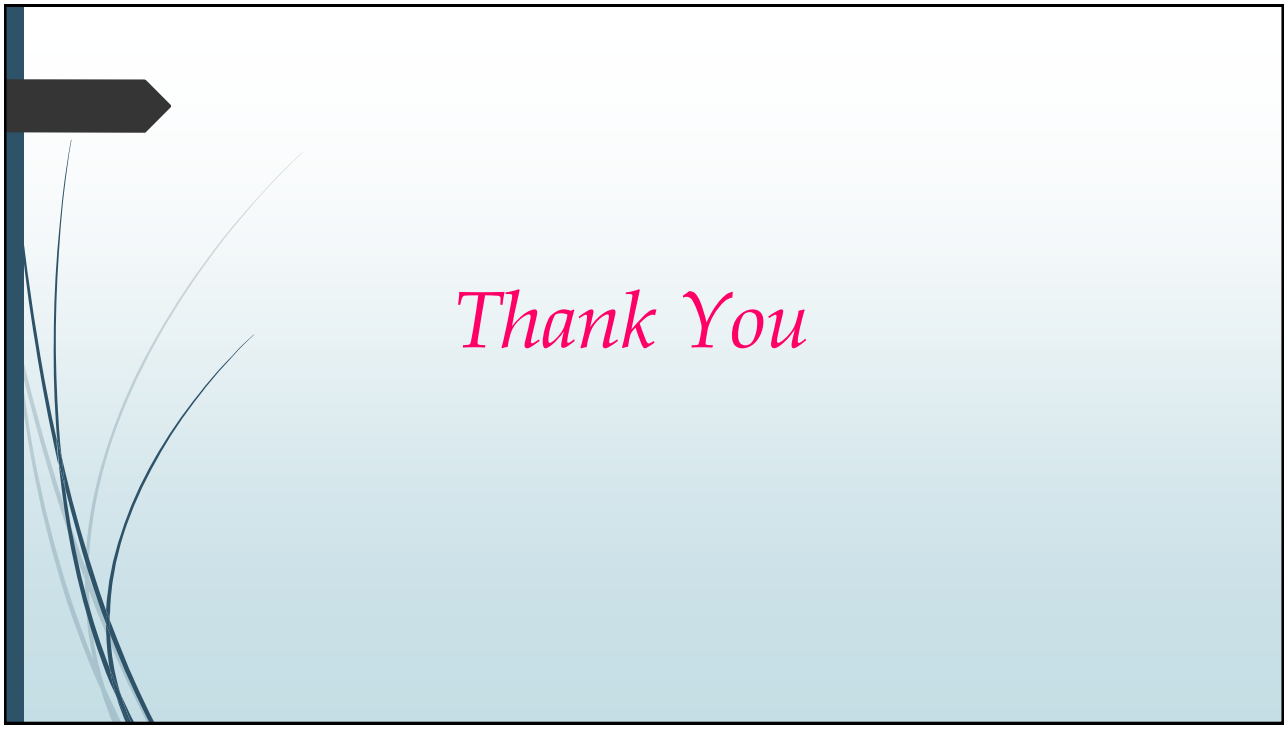
Candida Infective Endocarditis: an Observational Cohort Study with a Focus on Therapy

Christopher J. Arnold,[a] Melissa Johnson,[a] Arnold S. Bayer,[b] Suzanna Bradley,[a] Efthymia Giannitsioti,[d] José M. Miró,[e] Pilar Torres,[f] Pierre Tattevin,[g] Jacob Strahilevitz,[h] Doris Spelman,[i] Eugenia Athan,[j] Francisco Nacinovich,[k] Claudio G. Fortes,[l] Cristiane Lamas,[m] Bruno Barsic,[n] Nuria Fernandez-Hidalgo,[o] Patricia Muñoz,[p] Vivian H. Chu,[a] for the ICE Investigators

Candida infective endocarditis is a rare disease with a high mortality rate. Our understanding of this infection is derived from case series, case reports, and small prospective cohorts. The purpose of this study was to evaluate the clinical features and use of different antifungal treatment regimens for *Candida* infective endocarditis. This prospective cohort study was based on 70 cases of *Candida* infective endocarditis from the International Collaboration on Endocarditis (ICE)-Prospective Cohort Study and ICE-Plus databases collected between 2000 and 2010. The majority of infections were acquired nosocomially (67%). Congestive heart failure (24%), prosthetic heart valve (46%), and previous infective endocarditis (26%) were common comorbidities. Overall mortality was high, with 36% mortality in the hospital and 59% at 1 year. On univariate analysis, older age, heart failure at baseline, persistent candidemia, nosocomial acquisition, heart failure as a complication, and intracardiac abscess were associated with higher mortality. Mortality was not affected by use of surgical therapy or choice of antifungal agent. A subgroup analysis was performed on 33 patients for whom specific antifungal therapy information was available. In this subgroup, 13 patients received amphotericin B-based therapy and 14 received echinocandin-based therapy. Despite a higher percentage of older patients and nosocomial infection in the echinocandin group, mortality rates were similar between the two groups. In conclusion, *Candida* infective endocarditis is associated with a high mortality rate that was not impacted by choice of antifungal therapy or by adjunctive surgical intervention. Additionally, echinocandin therapy was as effective as amphotericin B-based therapy in the small subgroup analysis.


Thank You