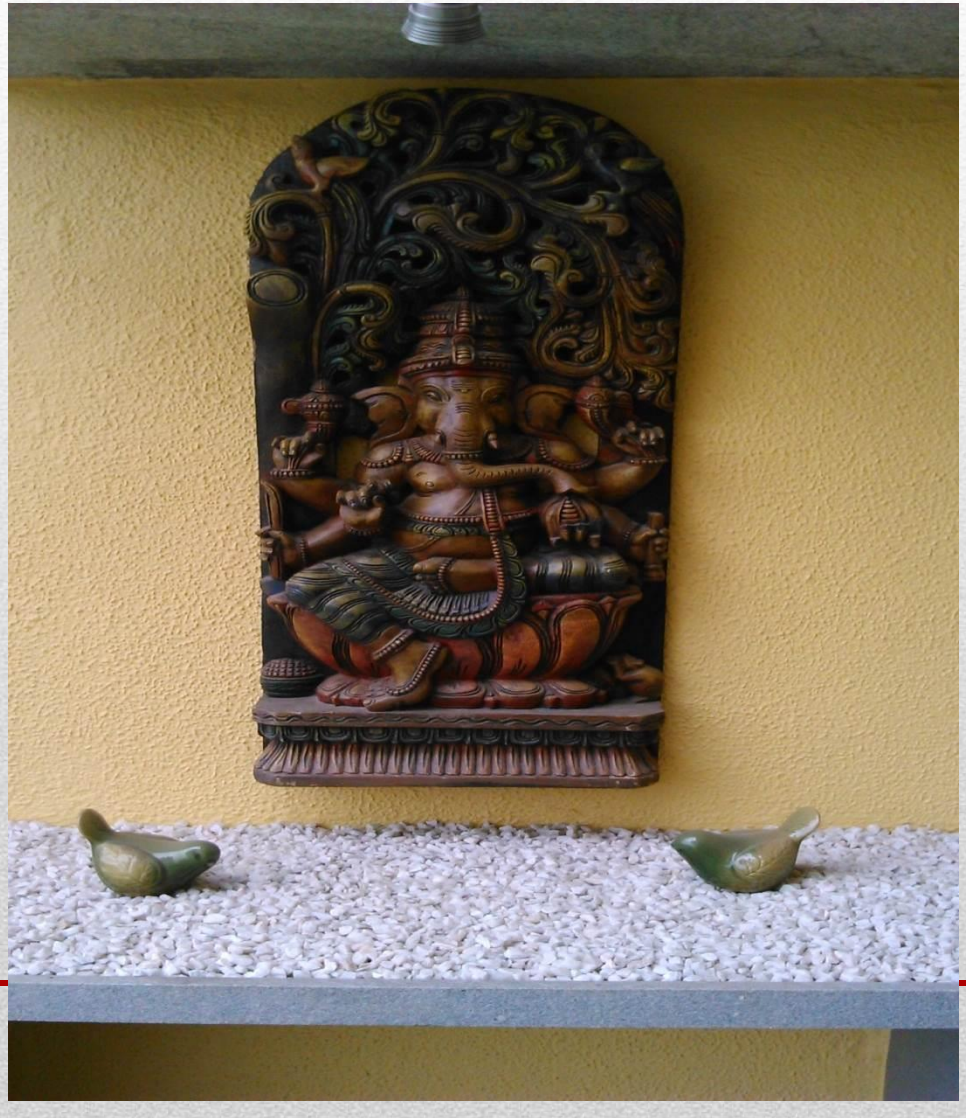
CATHETER RELATED FUNGAL SEPSIS

DR. SHIRISH PRAYAG
M.D. F.C.C.M.,
PUNE

Greetings from Pune,



INTRODUCTION

- Catheter related blood stream infections (CRBSI) are an important cause of mortality and morbidity worldwide
- Central venous catheters remain the predominant source of these infections
- Approximately 90% of the estimated 50,000 to 100,000 CRBSI's annually in the U.S. occur with CVC's.

EPIDEMIOLOGY

- Incidence of CRBSI associated with central lines has reduced from 3.64 infections per 1000 central line days to 1.65 from 2001 to 2009

- In contrast, pooled data from 422 ICU's across Europe, Asia and South America in 2009 showed an incidence of 6.8 events per 1000 central line days.

SCOPE trial

[Clin Inf Dis : 2004, 39, 309 -17]

- Evaluated characteristics of 24,179 nosocomial blood stream infections from 49 hospitals across the United States
- Incidence of nosocomial BSI was 60 per 10,000 admissions
- Approximately 51 % cases occurred in the ICU
- Central venous catheters were the culprit in 72 % of the cases
- Crude mortality rate was 27 %

RISK FACTORS – HOST RELATED

- Chronic illness
- Bone marrow transplantation
- Immune deficiency – especially neutropenia
- Malnutrition
- TPN administration
- Previous BSI
- Extremes of age
- Loss of skin integrity – e.g. burns

CATHETER RELATED RISK FACTORS (WITH CENTRAL LINES)

- Femoral or Internal jugular more than subclavian
- Repeated catheterization
- Septic focus elsewhere
- Non-tunneled more than tunneled
- Tunneled more than totally implantable device
- Lower risk with antibiotic impregnated short term catheters

CATHTER RELATED RISK FACTORS (WITH PA CATHETERS)

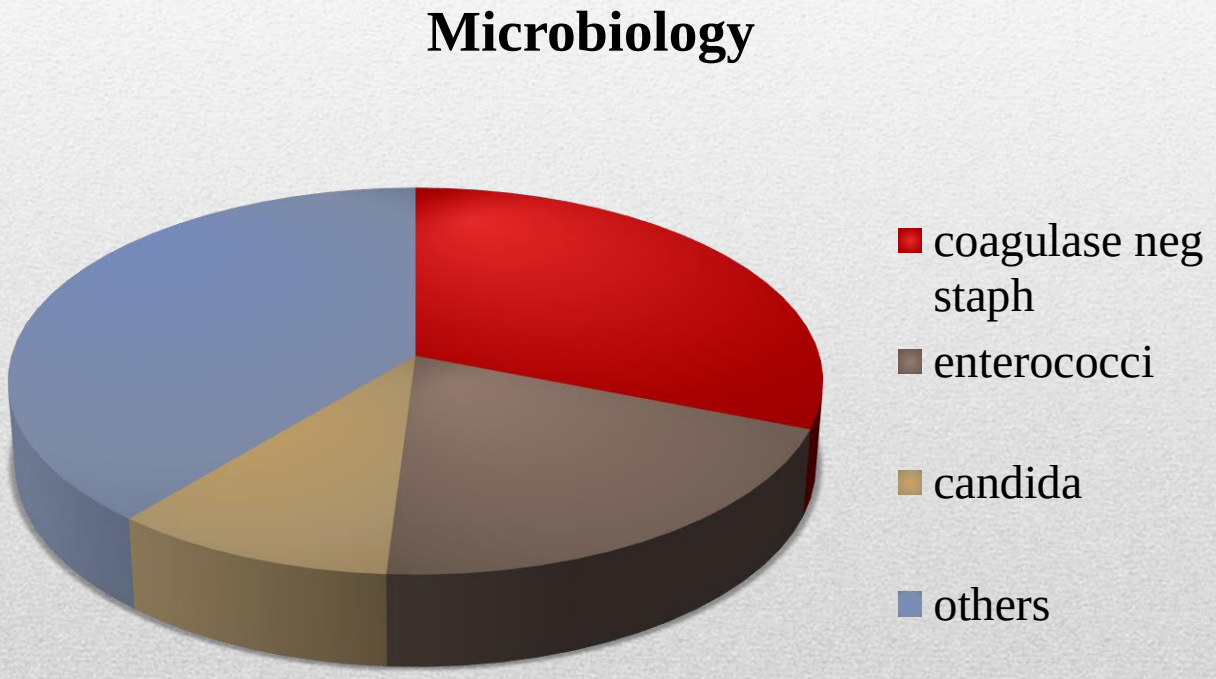
- Catheterization more than 3-5 days
- IJ more than subclavian
- Colonization of skin at insertion site
- Catheter insertion using submaximal barrier precautions

MICROBIOLOGY

SCOPE database analyzing 24179 nosocomial bloodstream infections in the U.S showed:

- Coagulase negative staph – 31 %
- Staph aureus – 20 %
- Enterococci – 9 %
- Candida species – 9 %
- E. coli – 6 %
- Pseudomonas – 4 %

Other studies in the U.S. and Europe have shown similar results with coagulase negative Staph, enterococci and candida accounting for majority of the infections

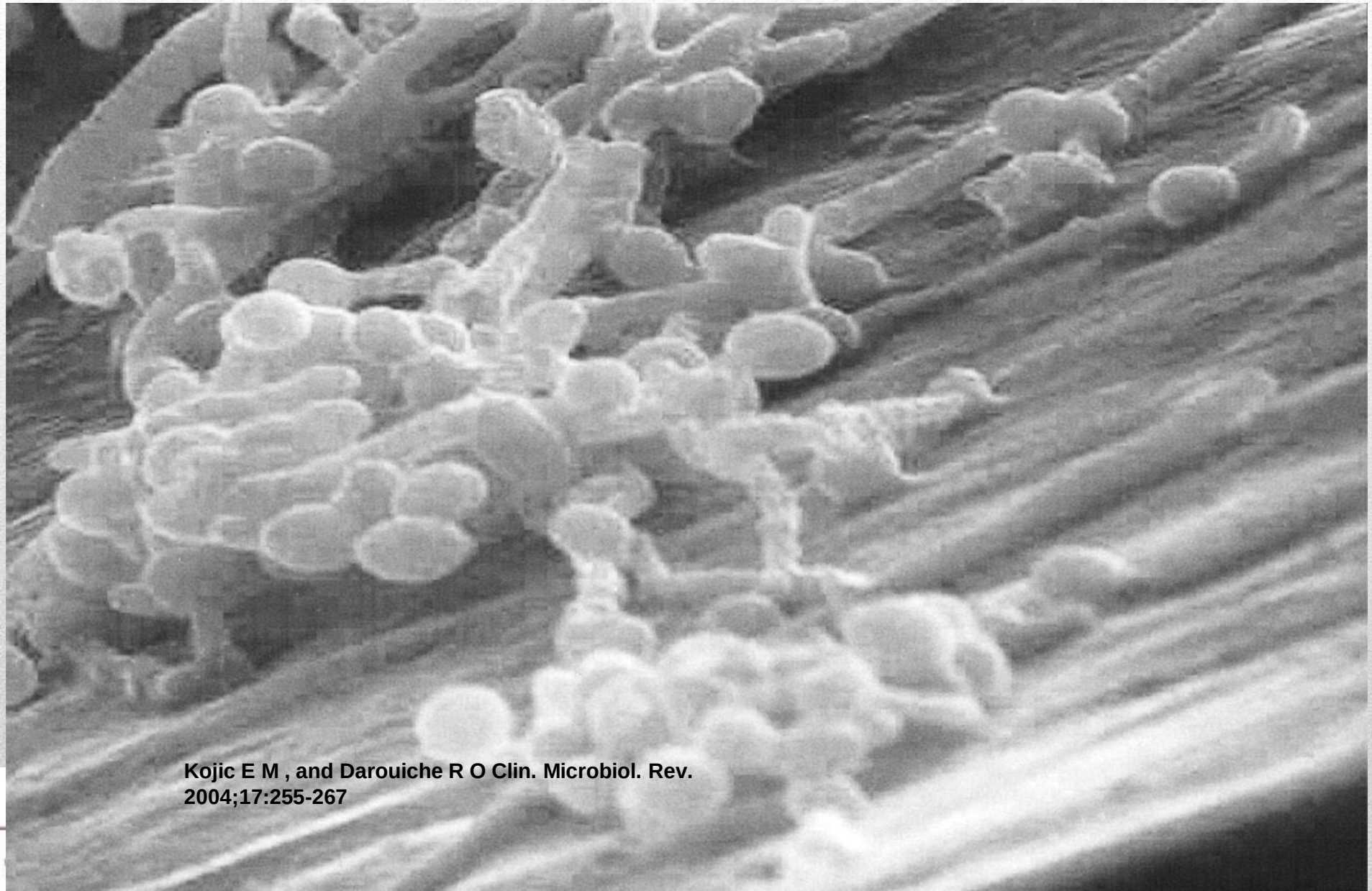


Some peculiar risks with fungi

- Fungal infections are of particular concern in patients receiving TPN
- Data suggests that Candida species can grow rapidly in almost all TPN solutions regardless of the acidity, lipid, and NaHCO3 content
- Particular concern with a high glucose load in i.v. hyperalimentation
- There is some evidence to suggest that patients with intestinal failure, gastrostomy tube, and those receiving frequent blood transfusions are also at increased risk of CRBSI with candida
- **(Journal of Society of Hospital Epidemiologists of America, 2013 Dec)**

- Candida species also produce a glycocalyx which enhances their ability to colonize catheters
- There is growing evidence that the ability of candida to produce a biofilm enhances its adherence to catheters
- This increases the ability of the pathogen to cause blood stream infections

Scanning electron micrograph of a C. albicans biofilm that has formed in vitro on the surface of a vascular catheter.



Kojic E M , and Darouiche R O Clin. Microbiol. Rev. 2004;17:255-267

Diagnosis of candidal CRBSI

- Infectious Diseases Society of America (IDSA) guidelines suggest that ‘ catheter cultures should be performed when a catheter is removed for suspected CRBSI; catheter cultures should not be performed routinely’ .

- Isolation of Candia sp or Gram-negative organisms from CVC tips should be discussed with the clinical microbiologist as to the appropriateness of investigation and initiation of antimicrobial therapy.

- Central line tips should only be sent to the laboratory if there is clinical suspicion of CRBSI, preferably before commencing antibiotics.

- Central line tips in conjunction with a percutaneous/ peripheral blood cultures are necessary to satisfy the gold standard definition for CRBSI.

- A negative line tip culture in the absence of concomitant negative blood cultures does not definitively out rule CRBSI. When the pretest probability is low the NPV of catheter tip culture is 99%.

- A positive line tip culture result in the absence of concomitant blood cultures has a low PPV for CRBSI and if interpreted incorrectly may lead to unnecessary antimicrobial therapy.

MANAGEMENT OF CANDIDAL CRBSI

REMOVAL OF CATHETER

- Central intravenous catheters should be removed in patients with candidemia
- Clearance of fungemia occurs more quickly when catheters are removed and higher mortality has been documented if catheters remain
- In addition, treatment with an antifungal agent is required. It should never be assumed that removal of a catheter alone is adequate therapy for candidemia.

Several studies, albeit with limitations, have evaluated whether central venous catheter removal is beneficial:

- A retrospective subgroup analysis of two randomized trials of patients with candidemia was performed in order to assess the potential benefit of early central venous catheter removal.
- In the univariate analysis, early removal of the central venous catheter (within 24 or 48 hours) did not improve time to mycologic eradication or rates of persistent of recurrent candidemia but was associated with improved treatment success and survival.
- However, in the multivariate analysis, these benefits were lost.

- A study in cancer patients used a fivefold difference in quantitative cultures taken from the central catheter and a peripheral vein to help define catheter-associated candidemia. Using these criteria, patients with non-catheter sources did not benefit from catheter removal in addition to antifungal agents.

- In contrast to the studies described above, an individual patient-level quantitative review that evaluated observational data gathered from seven randomized treatment trials of candidemia and invasive candidiasis found that removal of a central venous catheter was associated with decreased mortality (odds ratio 0.50, 95% CI 0.35-0.72)

- Despite the controversy, the current consensus, including that noted by the Infectious Diseases Society of America (IDSA) guidelines, remains that in most patients with candidemia, intravascular catheters should be removed, realizing that in some patients this may not be feasible

Choice of initial agent —

- History of recent azole exposure
- Prevalence of different *Candida* species and current antifungal susceptibility data in the clinical unit and medical center
- Severity of illness
- Relevant comorbidities that increase the risk of fluconazole-resistant *Candida* species
- Evidence of involvement of the central nervous system, cardiac valves, eyes, and/or visceral organs
- History of intolerance to an antifungal agent

EMPIRICAL THERAPY

- Nonneutropenic patients with candidemia
- Clinically stable,
- Not been exposed to recent azole therapy,
- In clinical units or medical centers in which C. glabrata or C. krusei are uncommonly isolated (<15 percent of all species causing candidemia),

The suggested initial therapy is fluconazole rather than an echinocandin

- In nonneutropenic patients
- Moderately severe or severe infections
- Who are at increased risk of C. glabrata or C. krusei infection,
- Suggested initial therapy is an echinocandin (caspofungin, micafungin, or anidulafungin) NOT fluconazole

EMPIRICAL THERAPY IN NEUTROPENIC PATIENTS

- Most neutropenic patients with candidemia should be treated with an echinocandin or an amphotericin B formulation.
- Azole drugs have not been studied extensively for treatment of candidemia in this population.
- Also, neutropenic patients who are heavily pretreated with azole drugs as part of prophylactic regimens are at increased risk for fluconazole-resistant Candida spp, such as C. glabrata and C. krusei
- If amphotericin B is used, a lipid formulation is preferred.

DURATION OF DEFINITIVE THERAPY

- The appropriate duration of therapy for candidemia has not been studied.
- A minimum of two weeks of therapy after blood cultures become negative has been used in most clinical trials and is the recommended duration in the 2009 Infectious Diseases Society of America (IDSA) guidelines

- Daily blood cultures should be performed after initiating therapy in order to determine the date of sterilization.

- If blood cultures remain positive, then a search for a metastatic focus, such as an abscess or endocarditis, must be undertaken.
- In addition, all patients should have resolution of symptoms attributable to candidemia and resolution of neutropenia (e.g., absolute neutrophil count >500 cells/microL and showing a consistent increasing trend) before antifungal therapy is discontinued

DOSES

- The usual dose of fluconazole is an 800 mg loading dose followed by 400 mg orally daily.
- Caspofungin is given at an initial dose of 70 mg on the first day of treatment, followed by 50 mg daily; dose reduction is required with hepatic dysfunction.
- Anidulafungin is given at an initial dose of 200 mg on the first day, followed by 100 mg daily.
- Micafungin is given at a dose of 100 mg daily for candidemia; no loading dose is needed.

COMBINATION THERAPY....?

- Whether more than one antifungal agent should be used together for the treatment of candidemia has not been established, although combination therapy is **generally not given** for the treatment of candidemia.
- A controlled trial randomly assigned 219 nonneutropenic patients with candidemia to fluconazole (800 mg/day) alone for two weeks or fluconazole (800 mg/day) plus amphotericin B (0.7 mg/kg per day) for the first four to seven days followed by fluconazole alone to finish the two-week course
- There was more rapid clearing of fungemia with initial combination therapy, but the success rates overall were similar in the two groups.

PROPHYLAXIS….?

- Several trials have looked into whether antifungal prophylaxis would benefit ICU patients
- However considering the risk of azole resistance, most ICU's refrain from routine antifungal prophylaxis of ICU patients
- Only those at the highest risk should be selected for prophylaxis
- These groups include those with central venous catheter, TPN, recent surgery, recurrent transfusions, and multiple long term antibiotic therapy

PROGNOSIS

- Untreated candidemia has a mortality rate of over 60 percent
- With treatment, the overall mortality of candidemia is approximately 30 to 40 percent
- A delay in treatment can increase mortality
- In one retrospective cohort study of 230 patients with candidemia, the number of days that passed from notification of the first positive culture for yeast to the initiation of fluconazole correlated with increased mortality rates as follows: day 0 (15 percent); day 1 (24 percent); day 2 (37 percent); day 3 (41 percent)

Summary and recommendations

- For nonneutropenic patients with candidemia who are clinically stable, fluconozaole should be used. (Grade 2B).

- Fluconazole should also be used for the uncommon neutropenic patients who meet these criteria (Grade 2B).

- For nonneutropenic and neutropenic patients with candidemia who are clinically unstable or in patients who have risks for infection with azole-resistant organisms, an eichinocandin should be used. (Grade 2B).

- Blood cultures should be checked daily after initiating antifungal therapy until they become negative.
- All patients who have candidemia, whether or not they have ocular symptoms, should undergo an ophthalmologic examination by an ophthalmologist to look for evidence of endophthalmitis.
- In the patient with candidemia alone, treatment should be continued for 14 days after blood cultures have yielded no yeast.
- In addition, all patients should have resolution of symptoms attributable to candidemia **and** resolution of neutropenia before antifungal therapy is discontinued.

- Central intravenous catheters should be removed in patients with candidemia, when feasible.

- Empiric antifungal therapy should not be given to most patients in the intensive care unit (ICU) (Grade 2B).

- However, this approach, using either an echinocandin or fluconazole, is reasonable in a subset of high-risk ICU patients

Acknowldgement

- Significant contribution to the preparation of this presentation made by :

- DR. PARIKSHIT PRAYAG

- PGY3
- Internal Medicine,
- NJ, USA

THANK YOU