Candidemia — An Under-recognized Nosocomial Infection in Indian Hospitals

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Abstract

Objective: To study the occurrence of candidemia as a nosocomial infection in a large Indian teaching hospital and to evaluate the predisposing factors for development of such infections.

Methods: One hundred and one hospitalized patients that developed signs and symptoms of nosocomial bloodstream infections were screened for candidemia and were analyzed for the various predisposing factors like the age of the patient, the duration of hospitalization before the development of fever, neutropenia, use of chemotherapeutic agents, central venous catheters, broad-spectrum antibiotics, infection with HIV, diabetes mellitus, use of corticosteroids, administration of total parenteral nutrition, haemodialysis, use of mechanical ventilation, hematological or other malignancies, underlying disease, and any surgical procedure performed on the patient. Candidemic patients were followed up for outcome and the effect of nosocomial candidemia on mortality was assessed and analyzed statistically.

Results: Out of the 101 patients, seven patients had candidemia, an incidence in study population of 6.9%. Three (42.8%) were infected with albicans and the rest with non-albicans candidemia. All the patients with candidemia were admitted in the Intensive Care Units. Amongst the risk factors, the length of hospitalization (p=0.018), broad-spectrum antibiotics (p=0.045), central venous catheters (p=0.005), mechanical ventilation (p=0.0139) and total parenteral nutrition (p=0.001) were found to be significantly related to acquisition of nosocomial candidemia. Mortality in the candidemic patients was influenced only by the age of the patients (p=0.001). Although the mortality amongst the candidemic patients was twice as much as that of the patients not having this infection, still the difference did not reach significance (p=0.117).

Conclusion: Candidemia is an important problem in Indian hospitals. Diagnostic delays could be shortened by more active screening for candidemia especially in the intensive care settings. The rising incidence of non-albicans candidemia in the United States probably is true here as well. There should be a concerted effort to control known risk factors especially in intensive care units.

INTRODUCTION

Nosocomial infections are a growing problem in hospitals all over the world. Bacteria have been the traditional nosocomial infective agents, but with increasing use of broad-spectrum antibiotics, central venous catheters, abdominal surgeries, chemotherapy, increasing incidence of neutropenia and HIV infection amongst other causes, fungi have become one of the leading cause of nosocomial infections. Candidemia, as a nosocomial infection though widely prevalent in all hospitals, its importance is usually underestimated. Data collected by the National Nosocomial Infections Surveillance System (NNIS) in the United States demonstrated a 487% increase in the bloodstream infection by Candida between 1980 and 1989.1 Candida now ranks as the fourth most common cause2 of systemic nosocomial infection in the United States.

Approximately 200 candida species are known, of which about 10% are recognized to cause infections in humans. So far, candida albicans is the single most common species causing nosocomial infections in humans. In NNIS Hospitals, C. albicans accounted for 76% of 24,227 candida infections during 1980-1990.9 Candida now ranks as the fourth most common cause2 of systemic nosocomial infection in the United States. More recent data show that in the USA and Netherlands,3 73% of all episodes of candidemia were caused by C. albicans. Recent reports suggest a shift in the distribution of infections caused by non-albicans
species like *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis*, *Candida krusei*, and *Candida lusitanae*. A review on candida infections in oncology patients from 1952-1992 reported a wide diversity of candida pathogens identified at various institutions. Invasive fungal infections caused non-albicans species ranged from 14% to 100% and was 46% overall. Candidemia is usually associated with insufficiencies in host defense occurring in intensive care patients. The risk factors for systemic candidiasis described in studies are listed in Table 1.

Various drugs are available for treating candidemia. Fluconazole (400mg/d), Amphotericin B (0.5-1.0mg/kg/d), or Capsofungin (70mg stat fb 50mg/d) can be used. Therapy should be continued for 2 weeks after the patient becomes afebrile. Resistance to azoles is known in various species of candida so amphotericin B is the preferred therapy. Strict monitoring for the side effects of therapy is needed, but with liposomal Amphotericin side effects are rare.

Few reports documenting the incidence and spectrum of organisms responsible for candidemia in Indian hospitals are available. Even less is known regarding the risk factors for candidemia in Indian critical care settings. Given the escalating clinical importance of nosocomial candidemia, increasing reports of isolates resistant to current antifungal agents and the increased mortality of these patients, we felt that a study of nosocomial candidemia in our institution which is one of the largest teaching hospitals in India, would provide important comparative data for the real significance of candidemia as a nosocomial infection in Indian hospitals.

**MATERIAL AND METHODS**

The study was conducted in the Departments of Medicine and Microbiology, Maulana Azad Medical College and Associated Hospitals.

One hundred and one patients admitted in the medical, surgical wards, and ICUs that developed signs and symptoms of nosocomial bloodstream infection (BSI) were screened for candidemia. Patients <12 years, patients already having candidemia, patients on prophylactic antifungal therapy or patients with <48 hours of stay in hospital were excluded.

All patients were subjected to a detailed history, physical examination and baseline investigations like CBC, B.sugar, B.urea, S.creatinine, LFT, Selectrolytes, Urine analysis. In addition, specific investigations as suggested by history were done when indicated for the underlying disease. Blood samples were taken after taking all aseptic precautions and inoculated in Biphasic media (Brain Heart Infusion Broth and Agar, Sabouraud’s Agar) Blood Agar and/or BACTEC media for fungal isolation. Subsequent subcultures were done for speciation. Candida was identified and speciated by germ tube production, chlamydospore production, sugar assimilation and fermentation tests.

All the patients screened were analyzed for the predisposing factors for the development of candidemia. Candidemic patients were treated with i.v. Amphotericin B and followed up for outcome and the effect of nosocomial candidemia on mortality was assessed.

The baseline investigations and the risk factors were analyzed statistically by using the Students’ t-test, the Mann Whitney U test and by the Chi-square test. In addition, mortality was used as an end point and all the factors were analyzed for their association with mortality.

**RESULTS**

A total of 101 patients were screened over a period of six months. The age of patients screened ranged from 18 years to 80 years with a mean of 43.49 years. The length of hospitalization ranged from 4 to 42 days with a mean of 14.91 days. The patients screened were suffering from a variety of underlying diseases. The patients for the purpose of evaluation of underlying disease were categorized into ten groups according to the organ system involved as summarized in the bar chart given below (Fig. 1).

Out of the 101 patients screened, three were neutropenic, chemotherapy was given to eleven patients, 49 were on CV catheters, 40 were receiving TPN, 64 patients were receiving broad spectrum antibiotics.

**Table 1: Risk factors for systemic candidiasis**

<table>
<thead>
<tr>
<th>Age</th>
<th>Azotemia</th>
<th>Central venous catheters</th>
<th>Colonization</th>
<th>Damaged mucosal barriers</th>
<th>Graft versus host disease</th>
<th>Haemodialysis</th>
<th>Hyperglycemia</th>
<th>Long term broad spectrum antibiotic use</th>
<th>Neutropenia</th>
<th>Parenteral nutrition</th>
<th>Steroids</th>
<th>Surgery (multiple, extended, abdominal)</th>
</tr>
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</table>

Fig. 1: Groups of diseases.
14 were diabetic, 21 were on corticosteroid therapy, seven patients were HIV positive, 54 were on mechanical ventilation, eleven patients had malignant disease and 20 patients had undergone a surgery recently. Amongst these patients, 41 eventually did not survive and 60 had a partial or full recovery and were eventually discharged. The blood cultures showed seven patients to be suffering from Candidemia, three with *Candida albicans*, and one each with *Candida parapsilosis*, *Candida tropicalis*, *Candida famata*, and *Candida catenulata*.

Amongst the seven patients of candidemia, three had ischemic stroke, while there was one patient each of tetanus, intracerebral haematoma, chronic obstructive airway disease, and AIDS with cryptococcal meningitis. The mean length of hospitalization in the candidemic patients was 28.29 days as compared to 13.91 days in the other patients (Fig. 2). In the candidemic group, no patient was neutropenic, no one had received chemotherapy, no one suffered from an underlying malignancy, nor had anyone undergone a surgical procedure. One patient had received corticosteroids, one was on haemodialysis and another one was HIV positive. Two out of the seven patients were diabetic and all the seven patients had CV catheters, had received TPN, broad-spectrum antibiotics and mechanical ventilation.

On statistical analysis neither the age of the patients (p=0.08), nor the baseline investigations were significantly related to candidemia (p>0.05). The length of hospitalization was significantly associated with a P-value of be 0.018 by the Students’ t-test and of 0.002 by the Mann Whitney test. TPN, antibiotics, mechanical ventilation and central catheters were found to be significantly related to candidemia with P-values of 0.001, 0.045, 0.0139 and 0.005 respectively whereas neutropenia (p=0.263), chemotherapy (p=0.338), diabetes (p=0.249), steroid use (p=0.66), haemodialysis (p=0.973), underlying malignant or nonmalignant diagnosis (p=0.853), infection with HIV (p=0.405) or history of recent surgery (p=0.340) were not related significantly. On comparing mortality, only the patient’s age was significantly related to mortality (p=0.001) while the other risk factors and candidemia itself was found not to be having any significant bearing on mortality (p=0.117).

**DISCUSSION**

Rates of blood stream infection by fungi have increased steadily. Candida species and other fungi were there before 1980 but during the last decades these organisms have assumed increasing prominence as major pathogens all over the world. This is not only because of improved detection techniques but also the increased prevalence of all the risk factors described has lead to an actual increase in the rate of acquiring nosocomial fungal infections. Various studies in the past have tried to find out the incidence of nosocomial candidemia. The measured incidence has increased dramatically over the last two decades as shown by Banerjee et al and Emori and Gaynes et al as part of NNIS. There is a lot of variation in the reported incidence of nosocomial candidemia. The National Epidemiology of Mycoses Survey (NEMIS) study defines for the first time the interinstitutional variations in rates of BSI due to candida. Lesser incidence of candidemia has been reported in Asia. A study done in The United Arab Emirates (UAE), an incidence of 0.77 episodes per 100 discharges was observed as compared to rates seen in the USA (3.8-4.9). In the West by the end of 1980s, nosocomial candidemia constituted 5-10% of all nosocomial BSI. Reports from individual Scandinavian centers published between 1989 and 1991 show frequency of less than 1%. In contrast, data collected by the NNIS (180 hospitals) in the US identified candida species as the fourth most common bloodstream isolate in hospitalized patients, accounting for between 10-15% of isolates in many centers. A study done in Taiwan shows an incidence of 0.071/1000 discharges, which is far lesser than the NNIS data. The present study, though does not measure exactly the incidence or prevalence of nosocomial candidemia in all hospitalized patients, still provides a fair idea as to the incidence of candidemia in the study population that consisted of hospitalized patients with nosocomial BSI. The incidence calculated was 6.9% in the study population. This is comparative to the NNIS figures. As such there are no previous studies in our hospital or for that matter in other Indian hospitals and so it can be inferred that nosocomial candidemia is widely prevalent in this hospital, almost as much as in the West. Another point to highlight is that all seven patients were admitted in the ICU. This is not to say that nosocomial candidemia does not occur in non-ICU settings but that the environment of ICU with the various invasive procedures, mechanical ventilation etc, makes it much more conducive for acquiring fungal infections than the general wards. This has been shown by other studies as well. In the United States almost 50% of candida infections are from the ICU compared to 21% in Europe and 27% in the UAE.

Three out of the seven episodes (42.8%) were due to C. *albicans*. This is consistent with the recent trend of
increasing incidence of non-albicans candidemia. The NEMIS\(^\text{13}\) data shows that 48% of episodes of candidemia are from Candida albicans while the rest are due to non-albicans species.

The risk factors analyzed in this study are essentially those that have been analyzed in previous studies.\(^\text{19}\) The increasing length of hospitalization increases the risk. This does not need any explaining as the contact with hospital environment and health care workers, the invasive procedures increase with increasing length of hospitalization. Use of central venous catheters is significantly related to candidemia. As shown previously these catheters can even act as a portal of entry for fungal infection. Similarly, total parenteral nutrition as it leads to immunosuppression, is usually given through central lines and on patients who are hospitalized for a longer duration, is significantly related to candidemia. Broad-spectrum antibiotics can suppress the endogenous GI flora, decrease the incidence of bacterial infections and can promote the colonization of various mucosal surfaces with fungi and so promote invasive fungal infections. Mechanical ventilation is significantly related as it is an invasive procedure that leads to colonization of the airways with various organisms.

Neutropenia was not found to be significant. This probably was because of the fact that very few of such patients were studied. This sample size is highly inadequate to make any comment on the significance of neutropenia as a contributing factor. Relationship between candidemia and corticosteroid therapy was also not significant. The reasons for this are not absolutely clear but even in previous studies the relationship has never been proven. The underlying diagnosis is not related to acquisition of candidemia. In this study the underlying diagnoses were studied after dividing on the basis of the organ systems involved. This was done because the sample size was not adequate enough to allow comparisons between all the individual underlying diseases separately. If a large-scale study is undertaken, we might be able to find a few conditions with a positive correlation with candidemia. Similarly surgical procedures done on the patients were also not related significantly to candidemia. Candidemia is therefore more related to long-term in-hospital care rather than on single surgical procedure done on the patient. Mortality was most significantly found to be related to the age of the patient. This is undoubtedly true and no studies are needed to prove the association between advancing age and mortality. Candidemia has been shown to increase mortality by various studies. In the present study, five out of seven patients (71.4%) in the culture positive group died as compared to 36 out of 94 (38.2%) patients who expired in the culture negative group. Clearly the mortality is about twice in the patients suffering from candidemia as compared to patients without such infection despite treatment for candidemia with amphotericin B. However, statistically the association was found not to be significant probably because of the small sample size and the very small number (seven) of candidemic patients. Clearly this small number is insufficient to give any information about the relationship with any degree of confidence. Another important reason could be the presence of a number of confounding factors between the two groups. These factors have to be eliminated by matching or otherwise before the data can be interpreted more correctly.

**CONCLUSION**

This study demonstrates that candidemia is an important problem in Indian hospitals. Diagnostic delays could be shortened by more active screening for candidemia especially in the Intensive care settings. The rising incidence of non-albicans candidemia in the United States probably is true here as well. There should be a concerted effort on the part of all treating physicians to restrict risk factors like use of antibiotics, central venous lines, total parenteral nutrition, mechanical ventilation, and long stay in the hospital especially in intensive care.

**REFERENCES**

Book Review

The Bhopal Saga
Causes and Consequences of the World’s Largest Industrial Disaster

Ingrid Eckerman

The Bhopal Saga is an incisive analysis of one of the worst industrial accidents that has taken place in the recent past. On the night of December 2, 1984, while Bhopal slept, 43 tonnes of methylisocyanate and other substances leaked from the Union Carbide factory located in the city. By next morning the place was a graveyard of dead humans and animals. Of the 520,000 people who were exposed to the gases, 8,000 died during the first week and 8,000 later. The impact on the survivors are visible even today. The pesticide plant from where the gas leaked was half-owned by the multinational Union Carbide and half by the Government of India.

This book contains a thorough review of most of what has been written about the incident since 1984. It discusses the conflicting stance of the Union Carbide Corporation and the Governments of India on the moral responsibility for the tragedy. Using the ‘Logical Framework Approach’, Eckerman analyses the disaster. The analysis demonstrates that the two most important factors leading to the mega-gas leak were the design of the plant and the company policy of cutting back on expenses. The same analysis shows that negligence by the company and the authorities have critically affected the impact of the leakage on people’s in lives.

Ingrid Eckerman is a Swedish medical practitioner in family medicine in Nacka, a suburb of Stockholm, employed by the County Council of Stockholm. Since 1992 she has been an active member of Swedish Doctors for the Environment (LfM). In 1994, She became a member of the International Medical Commission on Bhopal and has been visiting Bhopal every year.

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