CASE 1: A 70-YEAR-OLD MAN WITH PROSTHETIC VALVE ENDOCARDITIS

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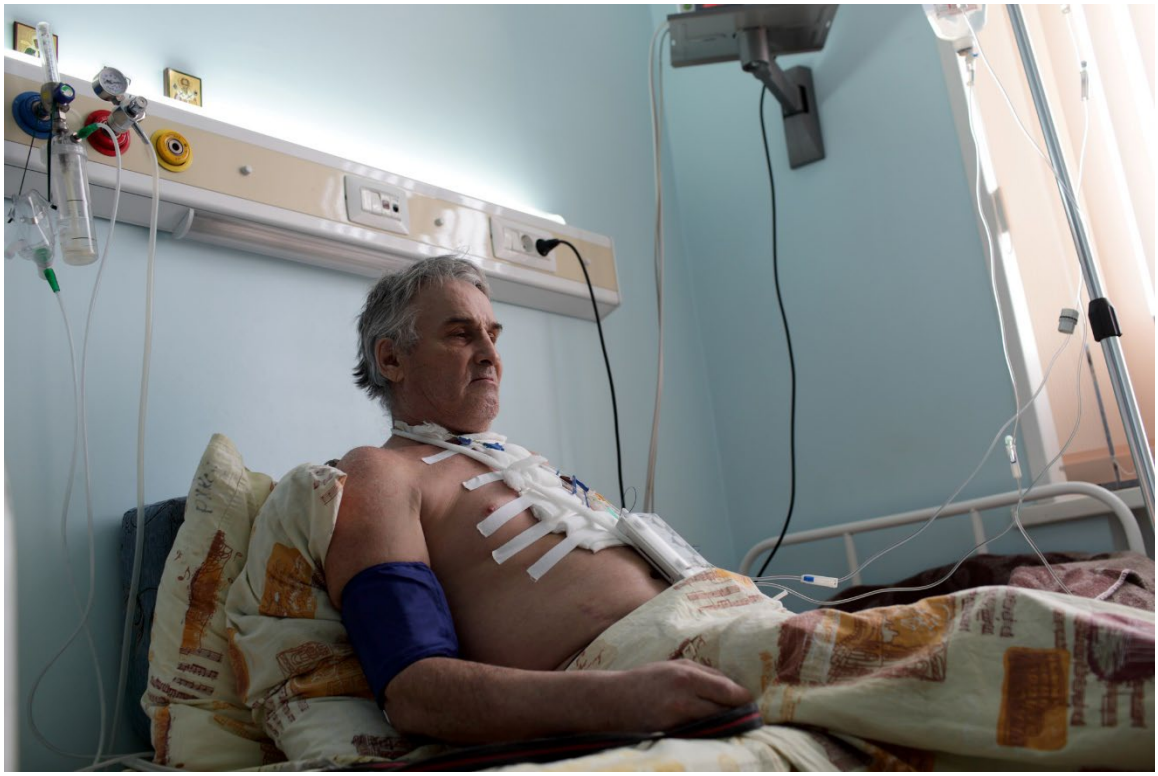

Initial Presentation

A 70-year-old white man from Genoa Italy, with a history of rheumatic attacks in childhood and adolescence, was admitted to the hospital in March 2018 for aortic and mitral valve replacement with mechanical prostheses. He received prophylaxis with one single dose of cefazolin.
During the early post-operative period, there were complications such as pericarditis and ventilator-associated pneumonia due to *Pseudomonas. aeruginosa* treated with piperacillin-tazobactam which started on Day 6 after surgery.

Presentation to Infectious Diseases

On Day 13 after surgery, while receiving treatment with piperacillin-tazobactam, he presented fever with blood pressure (BP) 100/70 mm Hg. His temperature was 39.2˚C (102.6°F). The physical examination revealed the presence of central venous catheter (CVC) in place for 13 days through which he was receiving total

parenteral nutrition (TPN). Surgical wound revealed no signs of infection with no chest pain or sternal dehiscence as well as no purulent or serous secretion from the wound; cardiac auscultation revealed systolic murmur +++/ 4+ in the aortic area and diastolic murmur in the left sternal border. Thoracic auscultation was normal, and the abdomen showed no changes. The patient had no symptoms.
His complete blood count was normal, and his creatinine level was 3.0 mg/dL; his bilirubin level was 2 mg/dL. Lactate level was 1 mmol/L. Chest-X-ray showed no significant changes in comparison with the previous one. Three blood culture sets were performed, and antibiotic treatment was changed to meropenem and daptomycin.

On Day 14, the microbiology laboratory informs that the blood culture turned positive for yeasts.
A CVC-related candidemia was suspected because patient had a CVC in place and no alternative source of infection were clinically identified.

Challenge Question 1: What approach would be best to assess if the catheter is the origin of infection?

- **A.** Differential quantitative blood cultures
- **B.** Differential time to positivity
- **C.** Superficial cultures permit to rule out the catheter origin if negative
- **D.** None of the above
- **E.** All of the above

Discussion

A. **Differential quantitative blood cultures.** Quantitative methodology is based on lysing red blood cells with different detergents, centrifugation (eg, lysis-centrifugation), and inoculating the sediment into different culture media and atmospheres. This system has shown better results than conventional methods in terms of detection times and specificity, but the sample must be processed within 20-30 minutes of inoculation of the blood into the tube. Moreover, there is some controversy about the cut-off point of differential quantitative blood culture (2:1 versus 5:1)[1] and the techniques are labor intensive and expensive, which makes them less practicable for routine use.

B. **Differential time to positivity.** Generally, positivity of blood cultures obtained through the catheter ≥ 120 min before positivity obtained from a peripheral vein with the same microorganism is highly suggestive of CVC-related bloodstream infection (BSI)[2]. However, an optimal differential time to positivity cut-off for the diagnosis of CVC-related candidemia has not been established. For example, in a study that included patients with bloodstream infections mainly due to *Candida albicans* and *Candida parapsilosis*, the authors found that a differential time to positivity of ≥ 120 min had high sensitivity (94.7%) but low specificity (40%)[3].

C. **Superficial cultures permit to rule out the catheter origin if negative.** Superficial cultures of the skin around the insertion site and catheter hubs are another conservative method for the diagnosis of CVC-related candidemia. However, in a recent prospective study performed in patients with candidemia with a CVC in place at the time of positive blood culture, superficial culture had a sensitivity of 40%, specificity of 75%, positive predictive value (PPV) of 57.1% and negative predictive value (NPV) of 60%[4].
D. **None of the above.** According to the aforementioned study[4], there are no individual classic tests for evaluating catheter-related bloodstream infections that can exclude catheter-related candidemia before catheter withdrawal.
E. **All of the above.** This is incorrect since none of the classic tests can assess if the catheter is the origin of infection without catheter removal.

Correct answer: D is the most appropriate response.

The microbiological results informed that blood cultures were positive for *C. parapsilosis*. Antibiotic therapy was stopped and treatment with echinocandin was started.

Challenge Question 2. When should the catheter be removed?

A. You pull the line only when the catheter is clearly proven to be the origin of infection
B. You always pull the line immediately
C. You generally pull the line, but not always immediately
D. Lock-therapy permits now to save many catheters colonized with *Candida*

Discussion

A. **You pull the line only when the catheter is clearly proven to be the origin of infection.** In recent years, the combination of prompt adequate antifungal therapy together with CVC withdrawal has been considered the cornerstone for adequate management of patients with candidemia. In two previous multicenter European[5] and US studies[6] including patients with septic shock, authors have shown a close relationship between combination measures and survival. However, conflicting data exist regarding the most appropriate time for catheter withdrawal, or the population of patients that would benefit most from such intervention. Diverse studies have concluded that, in patients with *Candida* BSIs, early catheter removal is associated with a reduction in the death risk, while others concluded that timing of catheter withdrawal does not influence the outcome. These conflicting results could be explained by significant aspects in the management of patients with candidemia. For example, Garnacho-Montero, et al[7] reported no clinical benefit of early CVC

removal if the catheter was not the origin of candidemia, whereas Nucci, et al[8] did not report clinical benefit of early CVC removal in adults treated with anti-biofilm drugs.

B. **You always pull the line immediately.** In accordance with current guidelines, we believe that early CVC removal should always be attempted in all critically ill patients developing an episode of candidemia[9].
C. **You generally pull the line, but not always immediately. This is not true.** As stated above, the line should be pulled immediately in accordance with current guidelines.
D. **Lock-therapy permits now to save many catheters colonized with *Candida.*** While there has been some success observed with lock-therapy[10], this is not the best answer.

Correct answer: B because you always pull the line immediately.

Case Continued

The CVC was removed, and the catheter tip was positive for *Candida parapsilosis* susceptible to fluconazole (culture positive >15 colony forming units). So, the final diagnosis was catheter related candidemia due to *C. parapsilosis* occurring in a patient with recent mitral and aortic valve replacement.

His follow-up blood cultures were positive on Day +2 after CVC removal and +2 after starting antifungal therapy. Following follow-up blood cultures (BCs) performed on Day +4 were positive and +6 were negative. A transesophageal echocardiogram performed in Day +5 was negative for vegetations as well as ophthalmoscopy.

The patient's treatment switched to fluconazole 200 mg every 24 hours (creatinine clearance 40 mL/min) that continued for 14 days after the first negative follow-up BCs. He was discharged to the hospital on Day 27 after surgery, with the instruction to cardiology rehab only.

However, after 5 months the patient was readmitted with a new episode of fever associated with congestive heart failure. At the emergency department BP was 70/40 mm Hg and his temperature was of 38.2˚C (100.8°F). At the initial work-up, his blood cultures turned positive for *C. parapsilosis*. This isolate matched with the patient's previous strain since they showed exactly the same alleles for all loci analyzed. Accordingly, the recurrent episode was classified as a relapse.

Challenge Question 3. What is true regarding late recurrent candidemia?

A. Recurrent *Candida* BSI is a frequent disease, occurring in about 15%-20% of all patients experiencing an episode of candidemia
B. Late recurrent candidemia is a relatively rare event (1%-4% of all episodes of candidemia) and it is associated with a high mortality rate
C. Genotyping the isolates is a time-wasting procedure because the interval between episodes can help differentiate relapses from reinfections
D. *C. albicans* followed by *C. parapsilosis* are the most frequent species associated with recurrent disease
E. Late recurrent candidemia occurring after 3 months usually suggests an intra-abdominal infection

Discussion

Generally, recurrent BSI are caused by the same microorganism and are uncommon infections that may occur early (<1 month between episodes) or late (>1 month between episodes). Late recurrent candidemia is further classified as relapse or reinfection. Reinfections are usually considered in all episodes caused by different *Candida* species or, if the episode is caused by the same species, when both isolates are genetically different. Relapses are episodes caused by the same genus and species.

A. **Recurrent *Candida* BSI is a frequent disease, occurring in about 15%-20% of all patients experiencing an episode of candidemia**. Few studies have specifically analyzed the incidence of recurrent candidemia and all of them showed a low cumulative incidence of the disease. In a Spanish study performed over 30 years[11], 1219 patients developed candidemia. In this study, only 18 patients fulfilled the criteria for late recurrent candidemia that, accordingly, represents only 1.48% of all candidemic episodes. In another study[12] using a different definition of late recurrence (episodes occurring at least 30 days after the last positive blood cultures as well as all earlier second episodes caused by different species of *Candida*), the cumulative incidence of the infection was higher but still low (about 4.4%).
B. **Late recurrent candidemia is a relatively rare event (1%-4% of all episodes of candidemia) and it is associated with a high mortality rate.** As discussed in option **A**, late recurrent candidemia is a relatively rare event. In addition, the 1-year mortality rate reported in patients with late recurrent episodes is usually higher than that observed in patients with a single episode of candidemia[11]. The high mortality associated with late recurrent candidemia probably reflects the severity of the underlying diseases (eg, neoplasia or cardiovascular disease requiring surgery).
C. Genotyping the isolates is a time-wasting procedure because the interval between episodes can help to differentiate relapses from reinfections. Overall, half of late recurrent episodes are relapses caused by the same original strain and half are reinfections.[11,13] Contrary to what is expected, the interval between episodes does not help clinicians to differentiate relapses from reinfections. However,

previous studies showed a clear pattern of distribution of clinical manifestations over time.[11] If late recurrent candidemia occurs within 3 months of the first episode, then the clinical source of the infection is in most cases a central venous catheter, an endocarditis, or a suppurative thrombophlebitis, independent of the type of recurrence (relapse or reinfection). On the other hand, episodes of late recurrent candidemia occurring after 3 months usually suggests a wider possibility of diagnosis, mainly intra-abdominal infection, infective endocarditis, or urinary tract infection.

D. ***C. albicans* followed by *C. parapsilosis* are the most frequent species associated with recurrent disease.** Previous studies reported a higher probability of recurrence among patients with candidemia due to *C. parapsilosis*. Although the reasons are not clear, *C. parapsilosis* may be associated with a higher risk for recurrence because of its ability to form biofilms on implanted devices,[14] thus suggesting a suppressive—but not curative—role for antifungal drugs during the initial episode.
E. **Late recurrent candidemia occurring after 3 months usually suggests an intra-abdominal infection.** As previously reported, late recurrent candidemia occurring after 3 months usually suggests a wider possibility of diagnosis, mainly intra-abdominal infection, infective endocarditis, or urinary tract infection.

Correct answer: B.

Work-up of Second Episode

A transesophageal echocardiography was performed and showed the presence of a large aortic valve vegetation (diameter 1 cm) with severe aortic valve disfunction.

The diagnosis of the second episode is clear. The patient has *Candida* prosthetic aortic valve endocarditis.

Challenge Question 4. What management is best for this patient?

A. Start treatment with echinocandin at standard dosage
B. Start lipid formulation amphotericin B, 3–5 mg/kg daily, with or without flucytosine, 25 mg/kg 4 times daily
C. Start fluconazole alone at higher than recommended dosage
D. There is no difference in terms of antifungal class since only surgery is needed
E. A and C are both correct

Discussion

In the last decade, the incidence of *Candida* endocarditis has increased concurrent with the general increase in *Candida* infections[15]. Most episodes occur following cardiac valvular surgery, but other risk factors include injection drug use, cancer chemotherapy, prolonged presence of CVCs, and prior bacterial endocarditis. Management can be challenging, and the options provided below illustrate the current thinking for managing these infections.

A. **Start treatment with echinocandin at standard dosage.** Echinocandins have shown a significant role in the treatment of endocarditis, but higher dosages are thought to be necessary to treat endocarditis[9,16].
B. **Start lipid formulation amphotericin B, 3–5 mg/kg daily, with or without flucytosine, 25 mg/kg 4 times daily.** Most clinical evidence regarding treatment of *Candida* endocarditis is based on case reports or very few case series and cohort studies. In most cases, patients were treated with amphotericin B with or without flucytosine[9,16]. This combination currently represents the first choice for treatment of *Candida* prosthetic valve endocarditis. In a recent retrospective study of patients with Candida prosthetic endocarditis, patients receiving initial therapy with liposomal amphotericin B (L-AmB) had a better 6-month survival rate in comparison with those who received initial echinocandin therapy (adjusted OR, 13.52; 95% CI, 1.03-838.10)[17].
C. **Start fluconazole alone at higher than recommended dosage.** Fluconazole monotherapy is associated with an unacceptably high rate of relapse and mortality[9,16,17]. However, it is useful for step-down therapy, a situation in which the drug led to minor adverse effects.
D. **There is no difference in terms of antifungal class since only surgery is needed**. As discussed above, antifungal therapy has a benefit, and the choice of therapy is important.
E. **A and C are both correct.** This is not correct since both A and C are incorrect.

Correct answer: B.

Antifungal Treatment

Treatment with L-AmB 3–5 mg/kg daily was started.

Challenge Question 5. Which is your opinion regarding cardiothoracic surgery for patients with prosthetic valve endocarditis (PVE)?

A. Perform surgical valve replacement in all patients with *Candida* PVE unless contraindicated
B. Perform surgical valve replacement in all patients with *Candida* PVE even if contraindicated. Patients have no alternative to survive

C. You start with antifungal therapy and perform surgery only if vegetation size does not reduce

Discussion

A. Perform surgical valve replacement in all patients with *Candida* PVE unless contraindicated. Several guidelines have consistently recommended surgery as first line in patients with fungal endocarditis. Surgery for *Candida* endocarditis should be performed within days in patients with prosthetic valve *Candida* endocarditis with the intention to cure. Medical therapy of *Candida* endocarditis is usually considered insufficient and the optimum therapy for PVE is a combination of valve replacement with a long course of antifungal therapy[9,17,18].

B. Perform surgical valve replacement in all patients with *Candida* PVE even if contraindicated. Patients have no alternative to survive. Historically, *Candida* endocarditis has always required surgical management. However, with new antifungal agents (L-AmB and echinocandins), there are studies showing some success with medical therapy alone for patients with absolute contraindications to surgery[19].

C. You start with antifungal therapy and perform surgery only if vegetation size does not reduce. As previously stated, surgical replacement should always be performed if indicated and as soon as possible. As a matter of fact, one of the surgical challenges in fungal endocarditis surgery is the increased prevalence of embolic phenomenon in fungal endocarditis, which complicates 60% of cases and leads to embolic hemorrhagic or ischemic stroke[19]. Anticoagulation used during cardiopulmonary bypass can lead to hemorrhagic conversion of these areas and an increase in the size of hemorrhagic stroke.

Correct answer: A is the correct answer, but ultimately the decision to perform surgery in patients with fungal endocarditis is complex and requires the consideration of many factors.

Case Outcomes

A cardiosurgical intervention of prosthetic aortic valve replacement was performed during the first week of hospital admission. Cultures and 18s PCR performed on prosthetic valve were both positive for *Candida parapsilosis*. The initial therapy with liposomal amphotericin B was subsequently switched to lifelong suppressive therapy with fluconazole.

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