

CASE 3: 65-YEAR-OLD WOMAN WITH FEVER AND ACUTE RESPIRATORY INSUFFICIENCY PRESENTED BY MATTEO BASSETTI, MD, PHD



Initial Presentation

A 65-year-old white woman from Genoa, Italy, with no relevant previous medical history, was admitted to the intensive care unit (ICU) in February 2019 for acute respiratory insufficiency. She also presented with fever (39.0 °C/102 °F).

Computerized tomography (CT) showed bilateral alveolar infiltrates. Laboratory results showed neutrophilic leukocytosis, with high serum levels of C-reactive protein (CRP, 213 mg/L) and procalcitonin (PCT, 52 ng/mL). Empirical therapy with ceftriaxone, azithromycin, and oseltamivir was started. After blood cultures were found positive for *Streptococcus pneumoniae*, oseltamivir and azithromycin were discontinued and an 8-day course of ceftriaxone was completed, with patient recovery, normalization of inflammatory markers, and extubation. Discharge to an internal medicine ward was planned on Day 11 from admission.

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On Day 10, the patient presented a novel episode of fever (38.5°C/101.3°F) with reduced blood pressure (85/55 mm Hg), need for vasopressors, and increased serum lactate. There were no signs of novel pulmonary localizations. Serum CRP and PCT were 172 mg/L and 1.3 ng/mL. The patient had a central venous catheter (CVC) in place for more than 48 hours, and she was receiving total parenteral nutrition (TPN). There were no previous isolations of *Candida* spp. from urine, pharyngeal swab, and bronchoalveolar lavage fluid (BAL). An empirical antibacterial regimen with meropenem and daptomycin was initiated based on the local microbiological epidemiology in the hospital and on risk scores for multidrug-resistant bacteria. A course of empirical antifungal therapy is now being considered.

Challenge Question 1. Regarding the consideration of empirical antifungal therapy which of the following clinical rationales do you agree with?

- A. The patient is not at risk of candidemia, so administration of empirical antifungals is not necessary.**
- B. Candidemia usually develops after at least 20 days of ICU stay, so it is unlikely that the patient has candidemia. Consequently, empirical antifungals are discouraged.**
- C. The patient has only a slightly increased PCT value, which is consistent more with candidemia than bacteremia, thus the patient should be treated with empirical antifungals rather than with antibacterials.**
- D. The patient is at risk of candidemia according to risk scores, albeit with a low positive predictive value. Nonetheless, empirical antifungals are worth considering.**

Discussion

- A. The patient is not at risk of candidemia, so administration of empirical antifungals is not necessary.** Risk prediction models based on patient clinical data and/or *Candida* colonization are used for identifying patients without infection who are at risk of subsequent candidemia. These models are also used as early diagnostic tools at the onset of the disease to trigger dedicated diagnostic algorithms and/or guide early therapeutic choices. It is critical to consider that risk scores frequently have a high negative predictive value (NPV), so it would be ok to not initiate empirical antifungals in a patient deemed not at risk according to risk scores. However, in this present case, the patient could be considered at risk. For example, according to the *Candida* score by León, et al¹, a score of >2.5 was proposed as a cut-off for administration of empirical antifungals. In the present case, the score was equal to 3 (1 point for parenteral nutrition and 2 points for severe sepsis). There are several other proposed scores, and most of them have been validated in external cohorts. In general, the other key concept besides their high NPV is that such scores usually have a low positive predictive value (PPV). Consequently, while their NPV may provide a firm indication for when not to initiate antifungals, there is still debate as to whether all patients with positive risk scores should be treated empirically, a question which is deeply intertwined with the search for accurate rapid diagnostic methods.

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- B. **Candidemia usually develops after at least 20 days of ICU stay, so it is unlikely that the patient has candidemia. Consequently, empirical antifungals are discouraged.** Although it is true that the risk of candidemia is correlated with the length of stay in ICU² and that the risk may still be <5% at Day 10, it is worth noting that this risk is calculated based on the entire population of ICU patients, including both patients with negative risk scores and patients with positive risk scores. Consequently, the risk may be higher and non-negligible for the subgroup of patients with positive scores. Thus, it may be prudent not to exclusively trust length of stay to determine whether to administer empirical antifungals or not.
- C. **The patient has an only slightly increased PCT value, which is consistent more with candidemia than bacteremia, thus the patient should be treated with empirical antifungals rather than with antibacterials.** According to a recent systematic review³, PCT should not be used as a standalone tool for the differential diagnosis between candidemia and bacteremia due to limited supporting evidence and the poor discriminatory performance of PCT as a single marker, despite most studies showing lower PCT values in patients with candidemia than bacteremia. In addition, whether or not low PCT values should support addition of empirical antifungals to empirical antibacterials also remains uncertain due to the suboptimal PPV (68%) and NPV (84%) of PCT used alone for this purpose according to a large retrospective study conducted in 166 ICU patients⁴.
- D. **The patient is at risk of candidemia according to risk scores, albeit with a low positive predictive value. Nonetheless, empirical antifungals are worth considering.** Empirical antifungals should be considered in patients at risk with consistent signs and symptoms of candidemia, in addition to empirical antibacterial due to the indistinguishable clinical presentation and the usually non-negligible baseline risk for bacteremia also in patients with risk factors for candidemia. As reported above, whether or not empirical antifungals should be administered in all patients with positive risk scores remains a matter of debate. A European panel of experts⁵ have proposed consideration of empirical antifungals in (i) patients with positive risk scores plus septic shock and multiorgan failure, and (ii) septic ICU patients with high risk of candidemia (>20–25% according to risk scores) independent of the presence of septic shock.

Correct answer: D is the most appropriate response.

Antifungal Treatment

Eventually, empirical antifungal therapy with an echinocandin was started in addition to meropenem and daptomycin. The following day (Day 11), results of the serum beta-D-glucan assay (BDG) that was performed on Day 10 became available (48 pg/mL, with positivity cut-off of ≥ 80 pg/mL).

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Challenge Question 2. Should antifungal therapy be discontinued?

- A. Yes, discontinue echinocandin treatment and continue empirical antibacterials
- B. No, continue administering both empirical antibacterials and antifungals

Discussion

- A. **Yes, I would discontinue echinocandin treatment and continue empirical antibacterials.** The BDG assays detect the polysaccharide BDG, a cell-wall component of various fungi, including *Candida*. In various observational studies in ICU patients at risk of candidemia, BDG had high NPV (in most cases >95%). Consequently, candidemia is unlikely when BDG is negative.
- B. **No, I would continue administering both empirical antibacterials and antifungals.** There are a few clinical, retrospective experiences that have suggested a possible reduced sensitivity of BDG for candidemia due to *C. parapsilosis* or *C. glabrata*, although this topic certainly deserves further investigation, and should not alone influence the decision of discontinuing empirical antifungals based on a negative BDG. Nonetheless, this suggests that a few cases of false negative results exist, and that they are tricky to detect.

Correct answer: A is likely the appropriate choice on most occasions, although in very selected cases it may be worth waiting for results of blood cultures.

In the present case, antifungals were not discontinued because, while the post-test probability of candidemia in ICU patients at risk with negative BDG was very low, it remained non-negligible in patients with a negative BDG (<80 pg/mL) and a low PCT (<2 ng/mL) in an observational, retrospective study⁴. On this basis, we waited for the results of the blood cultures.

On Day 13, blood cultures turned out positive for extended-spectrum beta-lactamase-producing *Escherichia coli*. Together with the negative BDG, this result further reduced the probability of candidemia, and echinocandin and daptomycin treatment were discontinued. Monotherapy with meropenem was continued.

On Day 17, a novel episode of fever, with novel increases in serum CRP and PCT (80 mg/L and 5.1 ng/mL, respectively), and hypotension were registered. Daptomycin was added again pending blood culture results, and a novel BDG test was ordered.

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Challenge Question 3. While waiting for BDG results, should starting empirical treatment with an antifungal be considered again?

- A. Yes, empirical antifungal treatment should be considered
- B. No, only antibacterials should be continued

Discussion

- A. **Yes, empirical antifungal treatment should be considered.** The probability of candidemia is higher now than the previous episode of sepsis in which antifungals were administered. Besides positive risk scores, two additional well-recognized predictors of candidemia have been identified in several observational studies: prolonged length of hospital stay and possible unresponsiveness to antibacterials^{6,7}.
- B. **No, only antibacterials should be continued.** An antifungal likely should be administered (see reasoning in A).

Correct answer: A is the most appropriate choice in this case.

In the present case, empirical treatment with an echinocandin was started. On Day 18, serum BDG turned out positive (>523 pg/mL).

Challenge Question 4. With these results in mind, what is the next step?

- A. The high BDG value seems to indicate candidemia, but nonetheless check for possible sources of false positivity, and, if present, consider discontinuation
- B. The positive BDG increases the post-test probability of candidemia in a patient at risk, thus continue antifungals
- C. Repeat a second BDG test to confirm positivity
- D. Despite the positive BDG, PCT values are high, clearly indicating bacteremia; therefore, antifungals may be safely discontinued

Discussion

- A. **The high BDG value seems to indicate candidemia, but nonetheless check for possible sources of false positivity, and, if present, consider discontinuation.** There have been many concerns over the years regarding the high number of reasons for a false positive BDG (eg, (i) hemodialysis, (ii) blood or blood derivatives transfusions, (iii) receipt of immunoglobulins or albumin, (iv) bacteremia, (v) *Nocardia* spp. infection, (vi) recent major surgery, (vii) treatment with β -lactams, (viii) use of cellulose containing gauzes, (ix) non-glucan-free laboratory equipment)⁸⁻¹⁰. It is recommended to consider the

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possibility of false positivity in every case, but its weight in influencing therapeutic choices should be based on the context. In this case, the patient should be viewed as belonging to a specific population—that of ICU patients with positive risk scores, prolonged length of stay, and possible unresponsiveness to antibacterial therapy. In such a population, the prevalence of candidemia is reasonably higher than in the entire ICU population, with a consequent increase also in the PPV of the BDG test⁴.

Furthermore, it should be considered that, although non-negligible, the number of false positive BDG results may be lower than in the past or than previously feared, for the following reasons: (i) glucan-free laboratory equipment is now widespread, (ii) BDG is not released by most modern dialysis membranes¹¹, (iii) the risk of false positivity after receiving blood is dependent on the product's BDG concentrations¹² (with the exception of intravenous immunoglobulin preparations, which almost invariably contain BDG), (iv) BDG release from surgery gauzes seems temporary and dependent on the type of gauze used¹³, (v) reduced rates of false positive results were observed in more recent studies of patients receiving beta-lactam antibiotics and/or with bacteremia¹⁴.

- B. **The positive BDG increases the post-test probability of candidemia in a patient at risk, thus continue antifungals.** In an ICU patient deemed at risk and with a consistent clinical picture, the post-test probability of candidemia is increased after a positive BDG⁴. If there was already a suspicion of candidemia (thus performing the BDG test was appropriate), we think a positive BDG should prompt continuation of antifungals.
- C. **Repeat a second BDG test to confirm positivity.** According to the meta-analysis by Lamoth, et al¹⁵, specificity of BDG for invasive fungal diseases (IFD) in hematology patients increased from 91% to 99% when not one but two consecutive positive results were considered. Nonetheless, this was a particular scenario involving screening for early diagnosis and pre-emptive treatment of IFD in a specific population of patients at risk who were without signs and symptoms, not targeted diagnosis in patients at risk with a consistent clinical picture. In this latter scenario, PPV of BDG could be higher, and, in our opinion, a single positive result may be sufficient for deciding to continue antifungal treatment. In addition, if empirical antifungals were not initiated, waiting for another positive BDG before initiation of antifungals in ICU patients with severe sepsis may be in contrast with observational studies¹⁶ reporting an association between delayed administration of antifungals and mortality in true candidemia cases.
- D. **Despite the positive BDG, PCT values are high, clearly indicating bacteremia; therefore, antifungals may be safely discontinued.** As reported above, PCT alone is not a reliable tool for clearly distinguishing between candidemia and bacteremia⁴. In addition, a positive BDG (which is a more specific marker than PCT) supports the possibility of candidemia. Finally, the possibility of mixed infections (eg, bacteremia, which would be in line with high PCT, plus candidemia, which would be in

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line with a positive BDG) should also be considered. In a Spanish study¹⁷, up to 18% of all candidemia episodes were mixed infections. In a similar case, the decision to continue both empirical antibacterials and empirical antifungals (which is the same decision that would be taken on the basis of only the positive BDG, independent of PCT) may be prudent.

Correct answer: B is the most appropriate response.

Case Continued

Antifungals and antibacterials were continued until the results of blood cultures became available on Day 21 (all were negative). In the meantime, the patient's conditions had improved, with normal blood pressure and consistent reductions in PCR and PCT values.

Challenge question 5. At this point, which of the following therapeutic strategies should be adopted?

- A. Continuation of empirical daptomycin for a total of 10-14 days, continuation of empirical echinocandin for a total of 14 days, and continuation of meropenem for a total of 10-14 days**
- B. Continuation only of echinocandin treatment on the basis of the positive BDG, with discontinuation of meropenem and daptomycin**
- C. Continuation of empirical daptomycin for a total of 10-14 days, continuation of meropenem for a total of 10-14 days, and monitoring of serum BDG levels with discontinuation of antifungals in case of negative BDG levels**

Discussion

- A. Continuation of empirical daptomycin for a total of 10-14 days, continuation of empirical echinocandin for a total of 14 days, and continuation of meropenem for a total of 10-14 days.** According to guidelines⁶, the length of antifungal therapy of candidemia should be 14 days after the first negative blood culture. In this case, candidemia was suspected and all follow-up cultures turned out negative. In a similar case, it could be reasonable to continue treatment until 14 days since its initiation. In the absence of etiological diagnosis, it seems appropriate also to continue empirical antibacterials.
- B. Continuation only of echinocandin treatment on the basis of the positive BDG, with discontinuation of meropenem and daptomycin.** Although a positive BDG increases the probability of candidemia, the risk of bacteremia usually remains non-negligible (since the baseline prevalence of bacteremia usually remains higher than the baseline prevalence of candidemia). Consequently, despite the increased post-test probability of candidemia, the post-test probability of bacteremia, although reduced, remains

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worth considering⁴. Given these premises, in our opinion, both empirical antibacterials and empirical antifungals should be continued in a similar case and in the absence of etiological diagnosis.

- C. **Continuation of empirical daptomycin for a total of 10-14 days, continuation of meropenem for a total of 10-14 days, and monitoring of serum BDG levels with discontinuation of antifungals in case of negative BDG levels.** Several studies have been conducted to assess the possible association between BDG serum levels and response to antifungals. This idea is based on two overlapping speculations: (i) BDG is released during replication of fungi, thus increased serum levels should reflect high fungal burden; (ii) consequently, decreasing serum levels may reflect a reduced fungal burden and thus a favorable response to treatment. In general, available studies¹⁸ are in line with the fact that decreasing BDG levels could indicate good response to treatment. However, it is noteworthy that in some cases, BDG levels may remain high for several weeks despite clinical cure and absence of metastatic foci of infections¹⁹. Therefore, while we agree that persistently high BDG values should prompt investigation for deep-seated candidiasis, therapeutic decisions regarding length of treatment should not be exclusively based on BDG trends.

Correct answer: A is the most appropriate response.

Case Outcome

On Day 24, the patient was transferred to an internal medicine ward, and subsequently discharged home in good clinical condition.

Summary of Special Issues Regarding Empirical Antifungal Therapy for Potential Candidemia

The present case is an example of clinically and laboratory-guided empirical antifungal therapy in patients at risk of candidemia with consistent clinical picture and negative blood cultures. In such cases, a careful and reasonable translation of diagnostic tests performances from clinical studies to clinical practice is essential. Furthermore, this translation should be dynamic during the early course of the disease. In our opinion, there are three key moments in which choices regarding the administration of antifungals should be made in an individual at-risk patient: (i) at the onset of symptoms (when usually only risk scores results are immediately available), (ii) when the results of rapid, non-culture-based tests become available; (iii) at the time of blood culture results.

In conclusion, diagnosis of candidemia is a complex task dependent on different important pieces of information becoming available at differing times. The future diffusion of other rapid molecular or phenotypical tests may favorably change this picture by increasing the rate of etiological diagnosis. Nonetheless, we think their use would need to be carefully implemented at the most appropriate time in diagnostic algorithms of candidemia in order to maximize the peculiar advantages and minimize the peculiar weaknesses of each specific novel test.

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