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Invasive Candidiasis: The Challenges of Diagnosis and Early Therapy CME/CE

Kieren Marr, MD

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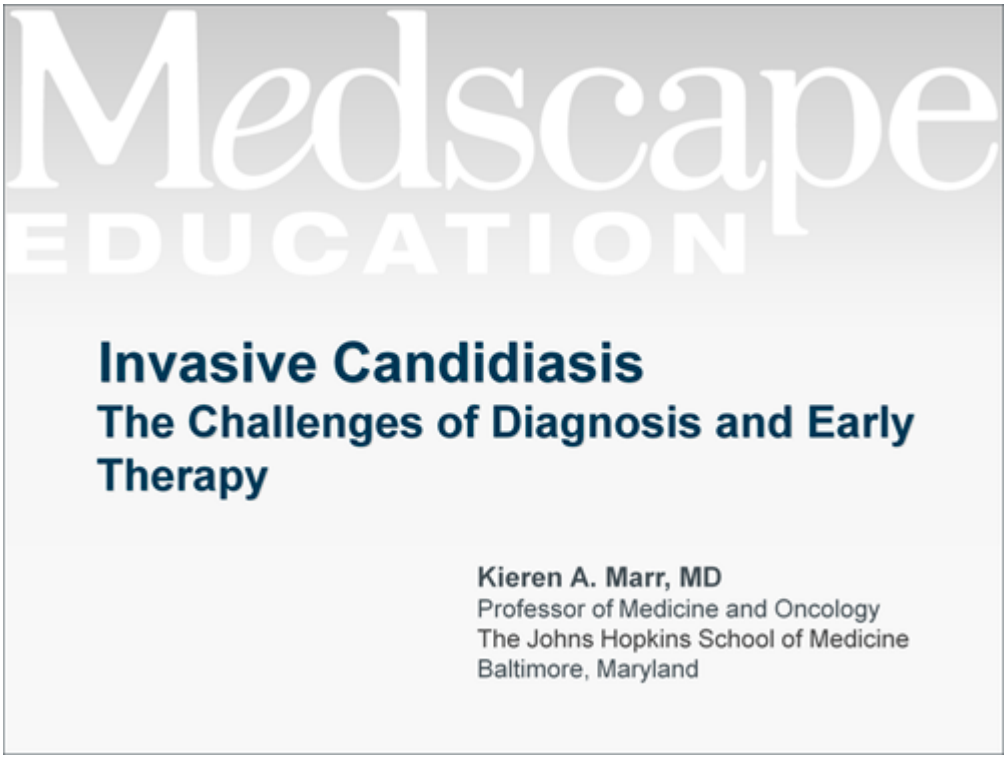
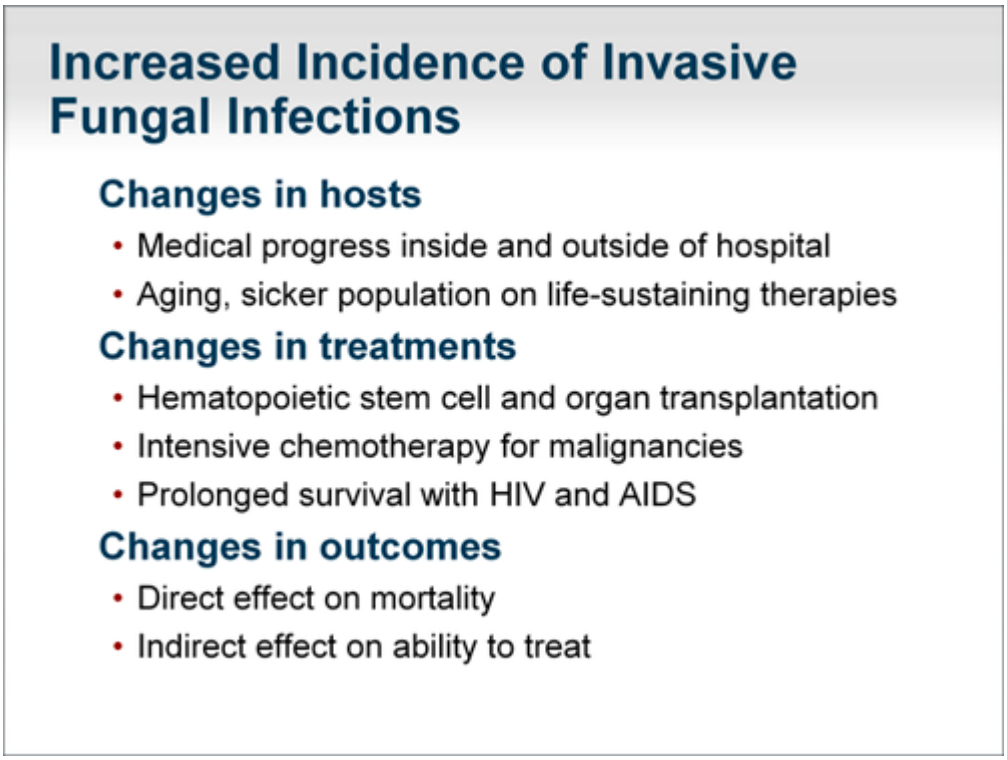


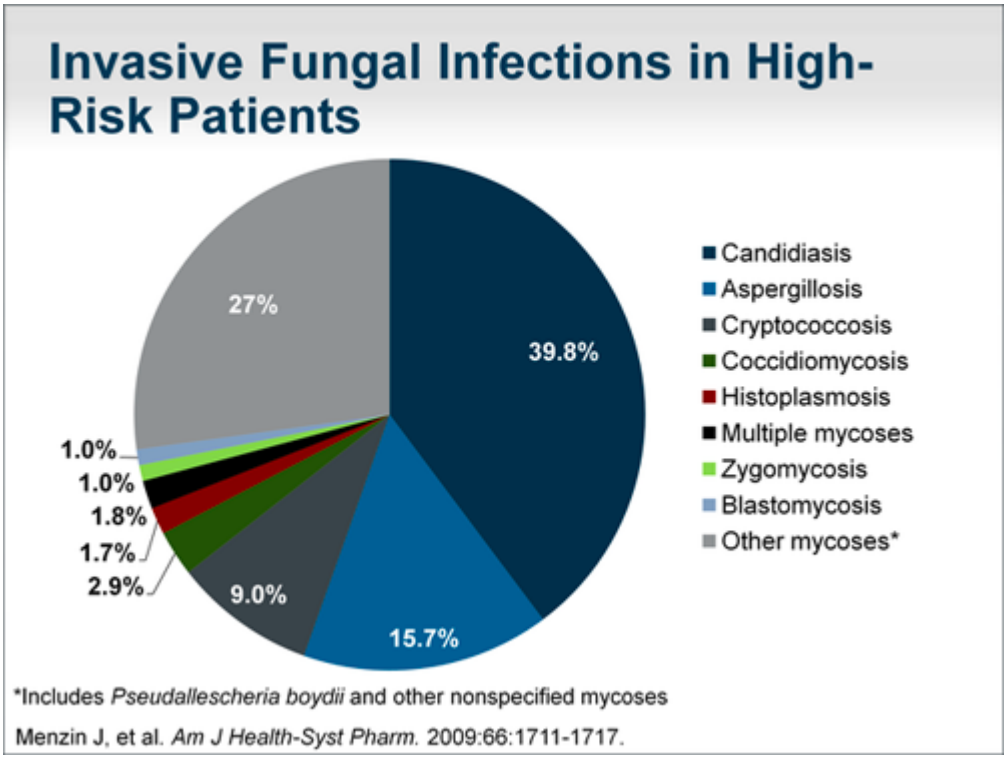
Slide 1.

Dr. Kieren Marr: Hello. I'm Dr. Kieren Marr. I'm Professor of Medicine and Oncology at the Johns Hopkins School of Medicine in Baltimore, Maryland. I would like to welcome you to this CME- and CE-certified activity *Invasive Candidiasis: The Challenge of Diagnosis and Early Therapy*.



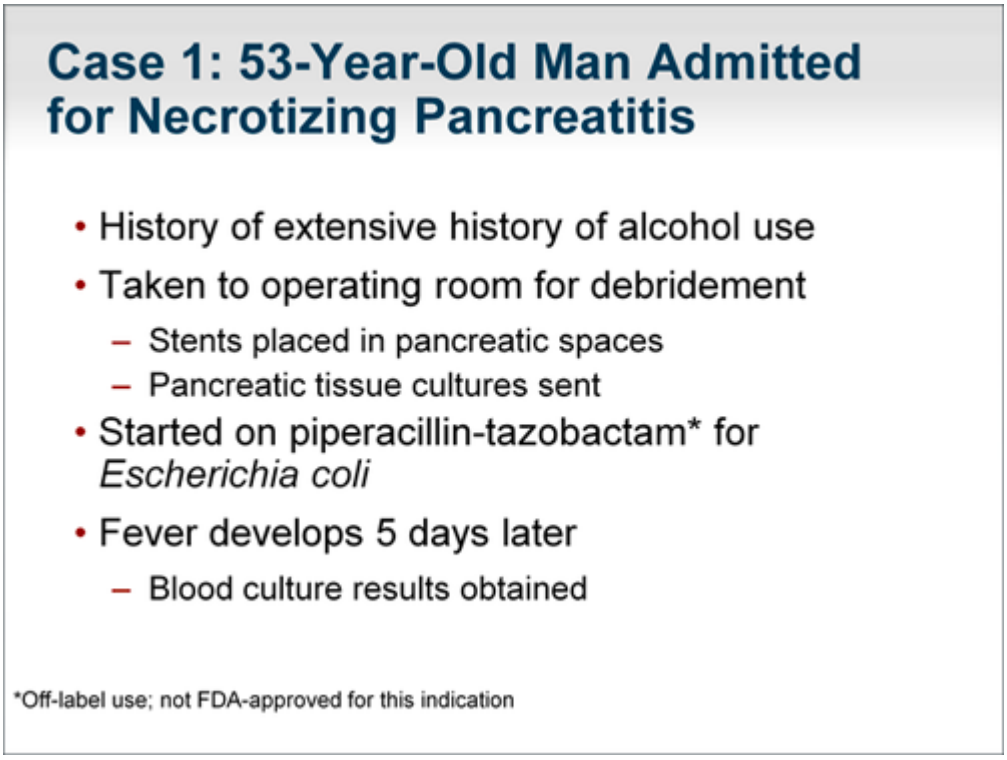
Slide 2.

Invasive fungal infections have increased in incidence over the past several years. In large part this has occurred because of changes in hosts. There has been medical progress inside and outside the hospital, and our patients are in general older and sicker, and many are on life-sustaining therapies. We now perform a lot more stem-cell and organ transplants and administer more intensive chemotherapy for malignancies, and many more people are alive with HIV and AIDS. All of this has led to a change in epidemiology and an increase in infection rates. And unfortunately, we also have poor outcomes, in large part because these infections have a direct effect on mortality and an indirect effect of limiting our therapies for malignancies and underlying diseases.



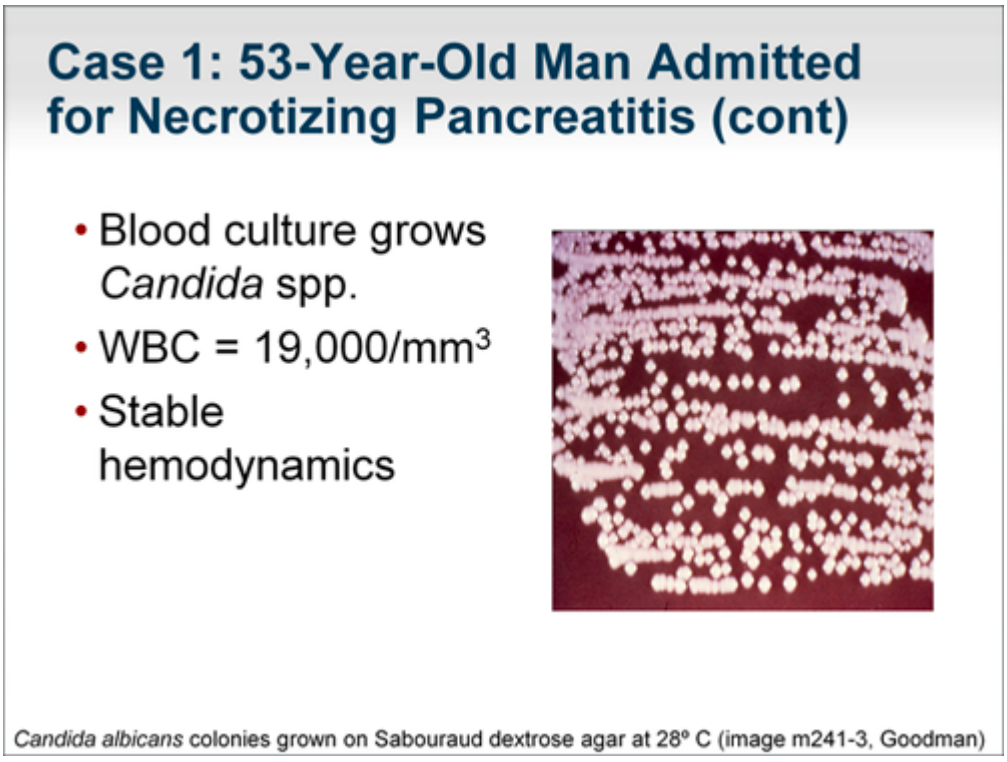
Slide 3.

This slide shows the types of invasive fungal infection that are currently most common in high-risk patients. As you can see, in large part the infections are caused by *Candida* spp. Today I am going to talk about early diagnosis and therapy of *Candida* infections.



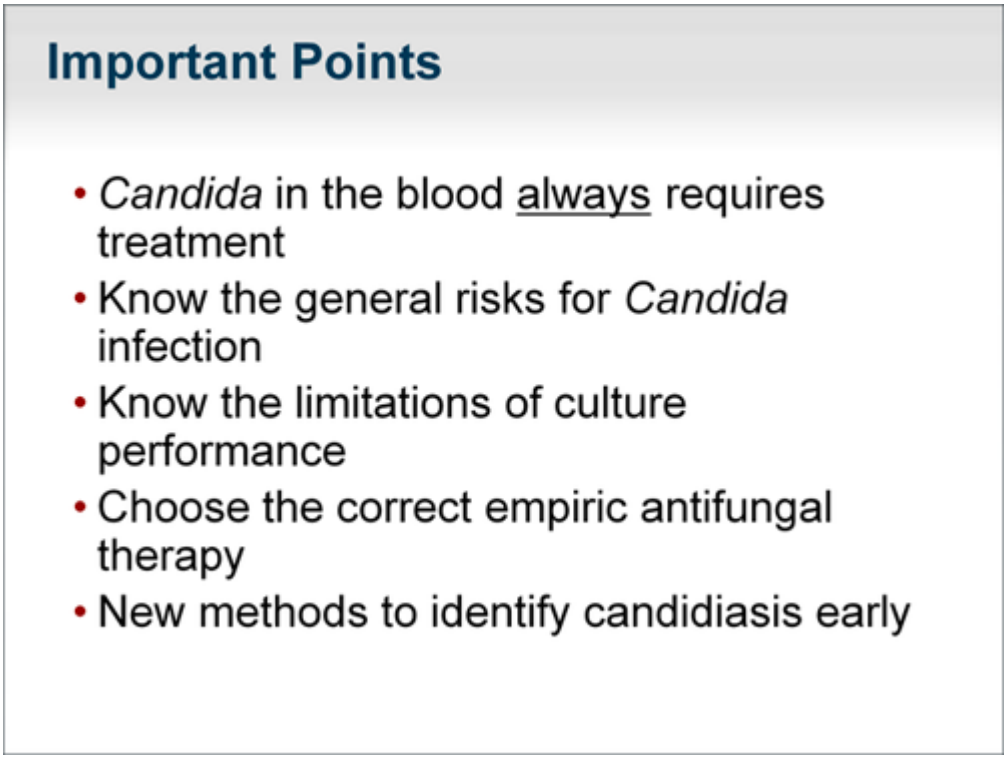
Slide 4.

We are going to take a case-based approach. Let's start with a 53-year-old man who was admitted to our hospital for necrotizing pancreatitis. He has pancreatitis as a result of an extensive history of alcohol use. He was taken to the operating room for debridement and stents were placed around the pancreatic spaces. Tissue cultures revealed *Escherichia coli* and he was appropriately started on piperacillin* and tazobactam.* However, 5 days later in the surgical intensive care unit (ICU), fever developed and blood culture results were obtained.



Slide 5.

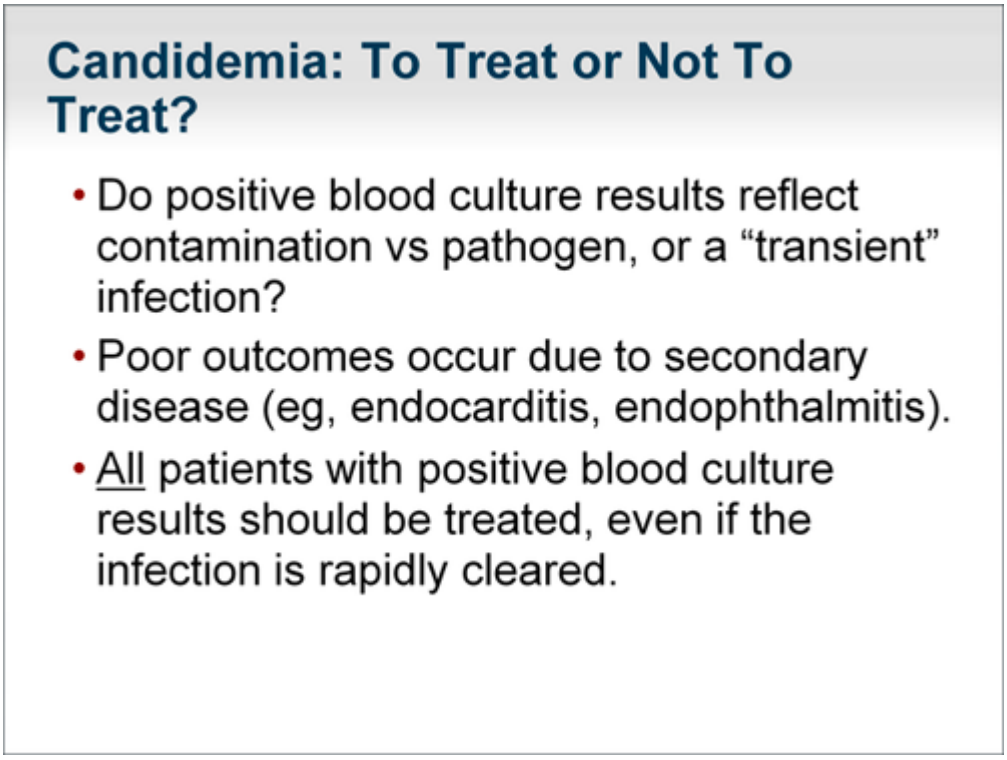
The first blood culture result was initially reported as yeast and potentially *Candida* spp., although it was not identified to the species level. At this point he was hemodynamically stable and he had a white blood cell count of 19,000/mm^3.



Slide 6.

This case illustrates several points. First, is whether *Candida* in the blood always requires treatment. Then, I will discuss the general risks of candidiasis, the limitations of our current culture performance, choosing correct

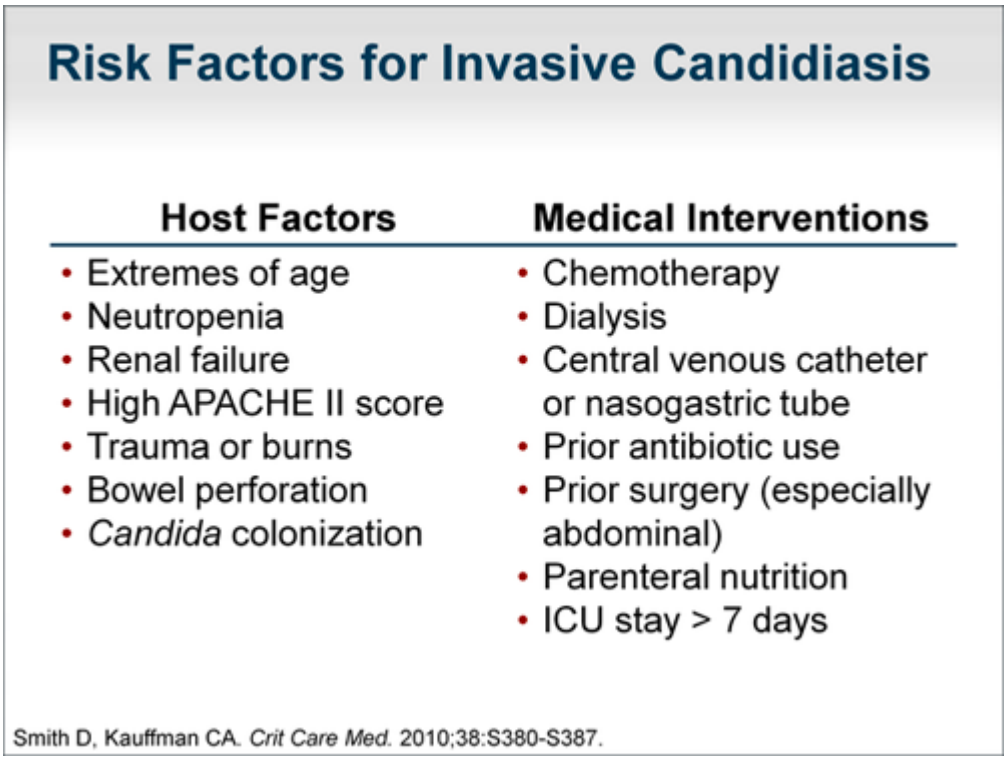
empiric antifungal therapy, and some new methods that we may be able to use to identify candidiasis early.



Slide 7.

First, and I think one of the most important teaching points, is that we need to treat *all* patients in whom candidemia develops. Historically, there was a lot of controversy over whether positive blood culture results reflect a real infection vs contamination or a transient infection that the host could clear, or whether antifungal therapy was required.

We now know poor outcomes occur, largely due to secondary disease, such as endocarditis and endophthalmitis. This has settled the controversy, and you should understand that all patients with positive blood culture results should be treated, even if it appears the patient can rapidly clear that infection.

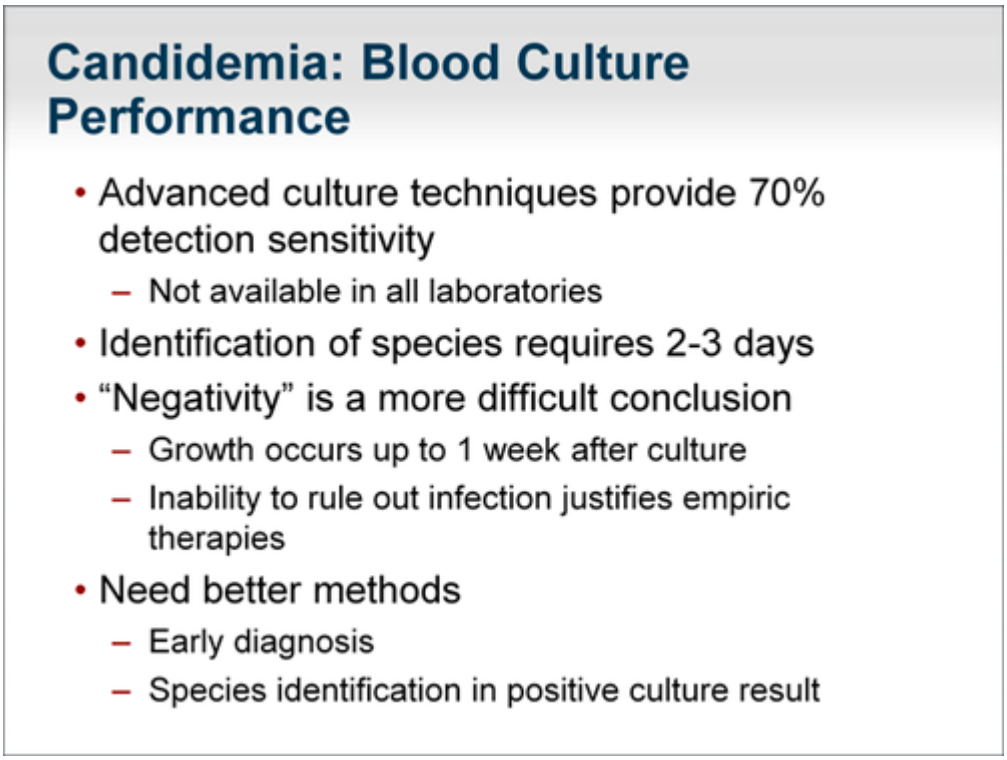


Slide 8.

The risks for candidiasis are multiple and they have to do with the underlying host and other therapeutic variables that predict gastrointestinal (GI) tract colonization with *Candid*a spp., as well as the likelihood of acquisition or invasion through the skin, usually via an intravascular catheter.

This slide shows host factors as well as medical interventions that have been shown in multiple epidemiologic studies to increase the risk for *Candida* infections, specifically invasive bloodstream candidiasis. Host factors include the extremes of age -- so the very young as well as the very old. Other host factors include neutropenia, renal failure, high APACHE II (Acute Physiology and Chronic Health Evaluation II) score, extensive burns or trauma, bowel perforation due to any cause, and factors that lead to increased *Candida* colonization, especially in the GI tract.

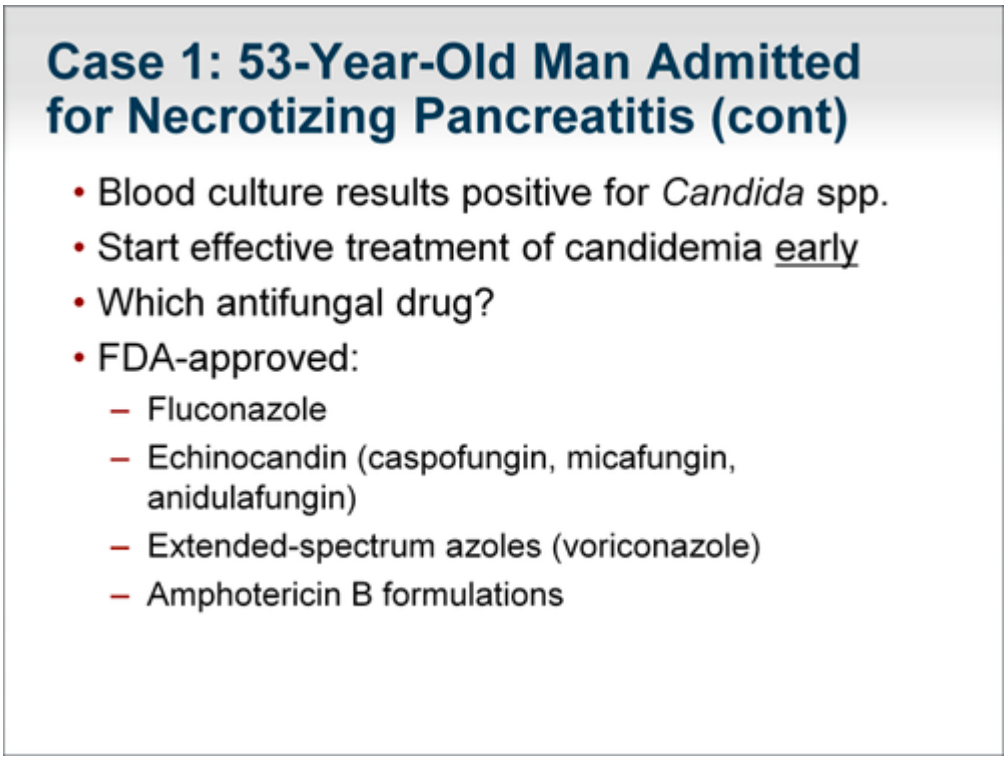
Medical interventions that lead to an increased risk for candidiasis include chemotherapy for cancer (cytotoxic chemotherapy, specifically), dialysis, central venous catheters, and nasogastric tubes. Prior antibiotic use increases risk because this in large part leads to an increase in *Candida* colonization in the gut. Prior surgery increases risk, especially if the surgery involves the abdomen. Parenteral nutrition and an ICU length of stay greater than 7 days also increase risk.



Slide 9.

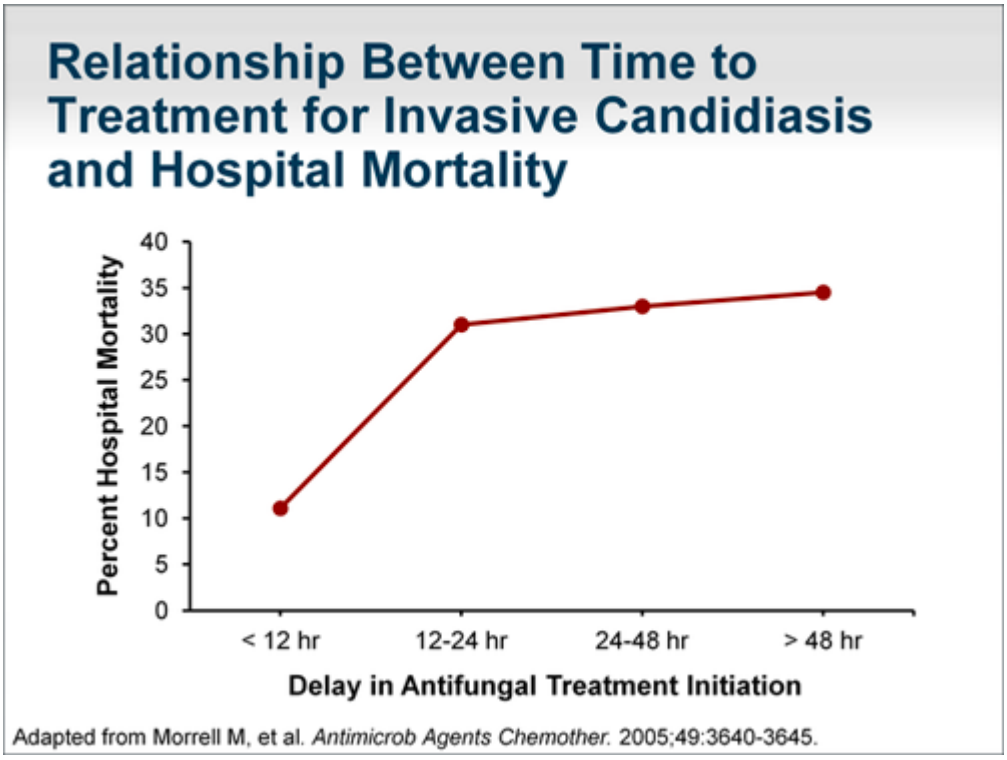
It is also important when you think about the therapies we administer to understand that our blood cultures, even though they are better now than ever before, have limited performance. Advanced culture techniques currently provide a detection sensitivity of about 70%, and importantly, not all hospitals utilize advanced culture techniques.

To make matters worse, confirmation of *Candida* spp. requires about 2-3 days to generate conclusions with regard to antifungal susceptibility profiles and which drugs are appropriate to use. Another important thing to remember is that negativity is a much more difficult conclusion because these organisms can grow in culture for up to a week, and in fact, our inability to rule out infection justifies a lot of the use of empiric therapies. We need better methods to diagnose candidemia early and to identify species in positive culture results.



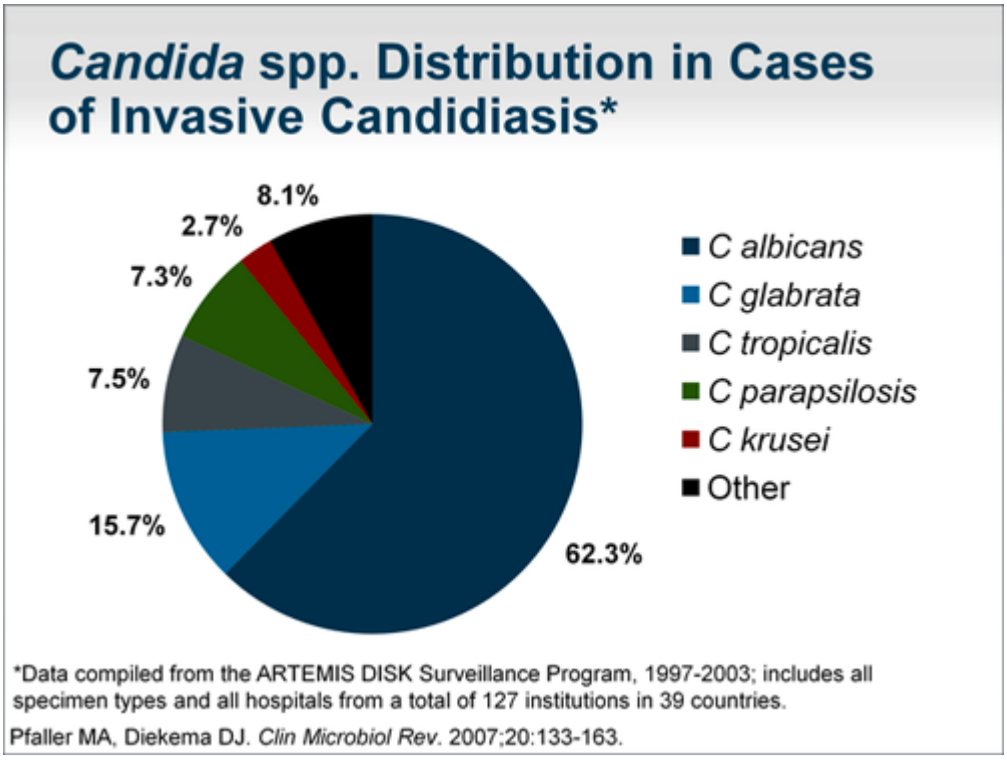
Slide 10.

Now, back to our case; this man's blood culture results were positive for *Candida* spp., but we don't know which species. We want to start effective treatment early, so the first question is which antifungal drug should we use. The United States Food and Drug Administration (FDA) and other agencies have approved multiple drugs for the treatment of *Candida*. Fluconazole, multiple echinocandins (caspofungin, micafungin, anidulafungin), and the extended-spectrum azoles, specifically voriconazole, have all been approved for treatment of candidemia as have amphotericin B formulations. So we have a lot of different drugs to potentially choose from.



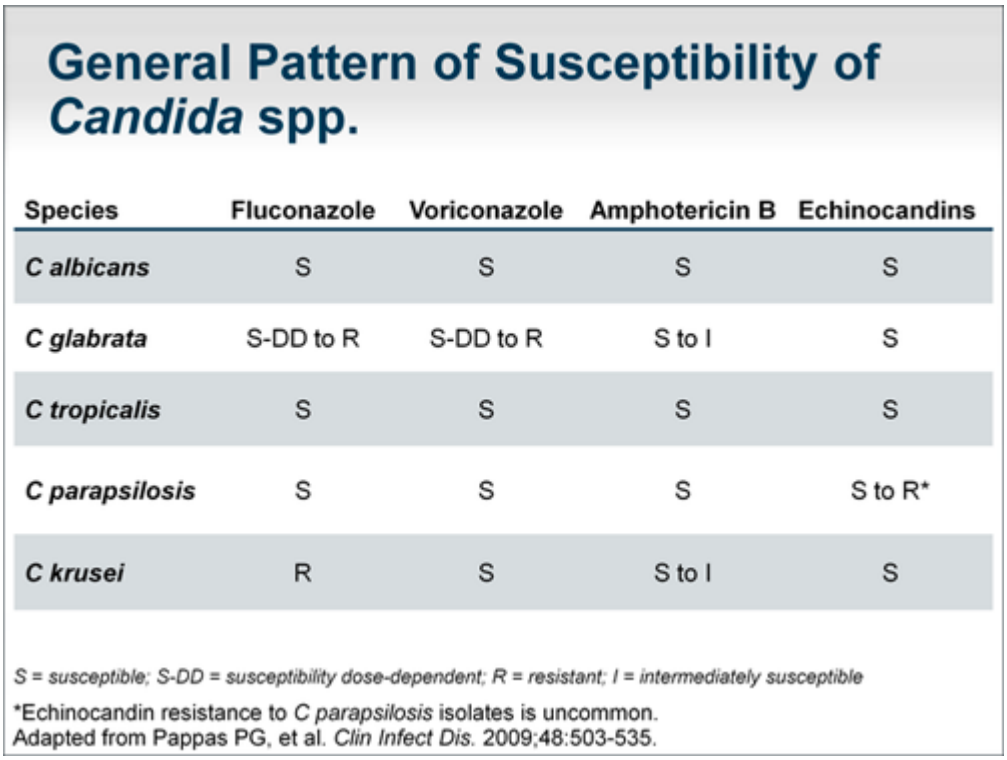
Slide 11.

We also know that choosing the right drug is critically important. There is a very nice relationship between time to treatment of invasive candidiasis and hospital mortality. The hospital mortality rate increases more than 3-fold if initiation of antifungal therapy is delayed more than 12-24 hours. So, early therapy is really quite important, as is choosing the right drug.



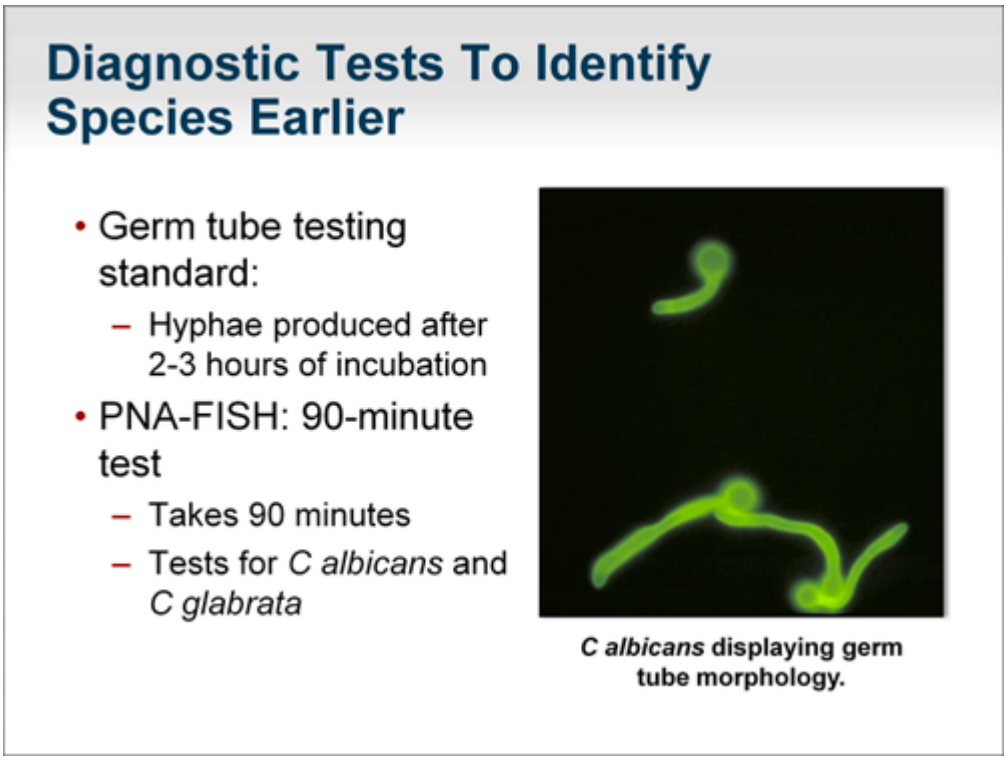
Slide 12.

It is important to understand which species is likely to be causing infection. If you look at the largest population-based studies, the most common species that cause infection in this particular patient population is by far *C albicans,* which as you can see on this graph, constitutes about 62% of the cases of invasive candidiasis that occur right now internationally. Other species, however, are important and potentially of increasing importance, including *C glabrata*, *C tropicalis*, and *C parapsilosis*.



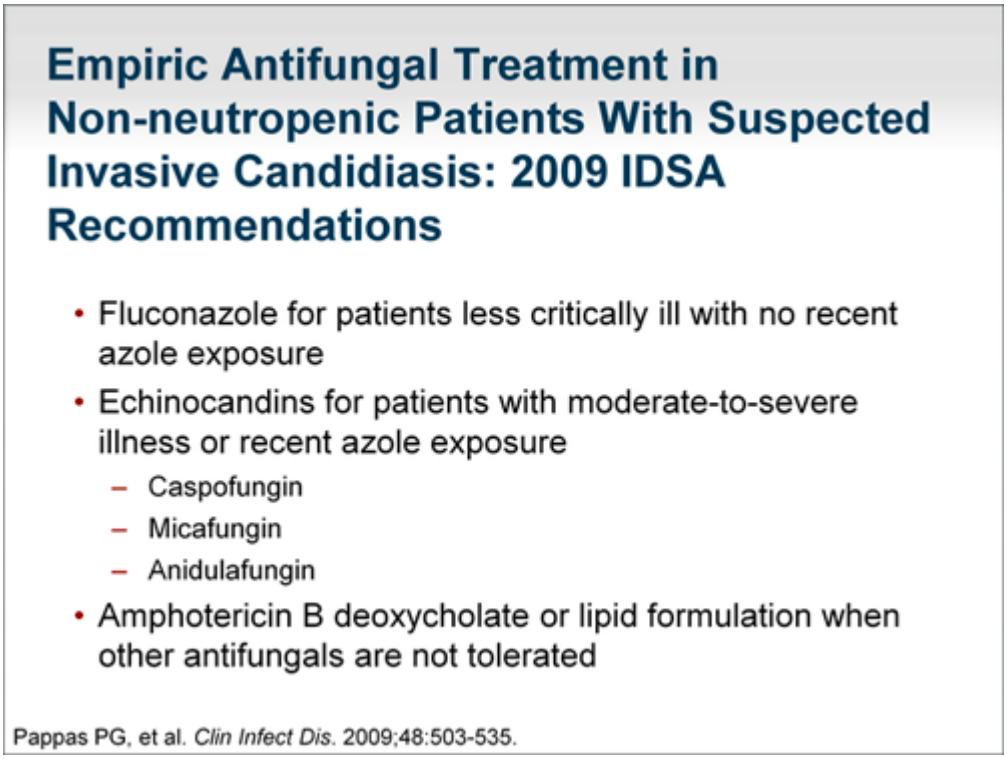
Slide 13.

This table shows the general pattern of susceptibility in *Candida* spp. Look at the species listed in the [rows] as well as the different drugs listed across the top of the columns: fluconazole, voriconazole, amphotericin B, and the echinocandins. You can appreciate that, for the most part, *C albicans* is largely susceptible to all of these drugs, with the rare exceptions being organisms that can gain resistance to azoles over time. In general, most *C albicans* [strains] are susceptible to all of these drugs. *C glabrata* is a little trickier; it demonstrates a dose-dependent susceptibility or resistance profile to azoles, including voriconazole and fluconazole. *C tropicalis* is much like *C albicans* in retaining susceptibility to most of these drugs. *C parapsilosis* as we know it now demonstrates a fairly low susceptibility to echinocandins, and so that is a point that needs to be considered. And the other issue is with *C krusei*; this organism is largely resistant to fluconazole, but susceptible to the other drugs, including voriconazole. Keeping these points in mind, you can guess which drug is likely to be active against the species that is the most likely cause of the infection, but it is very difficult to determine the species early enough.



Slide 14.

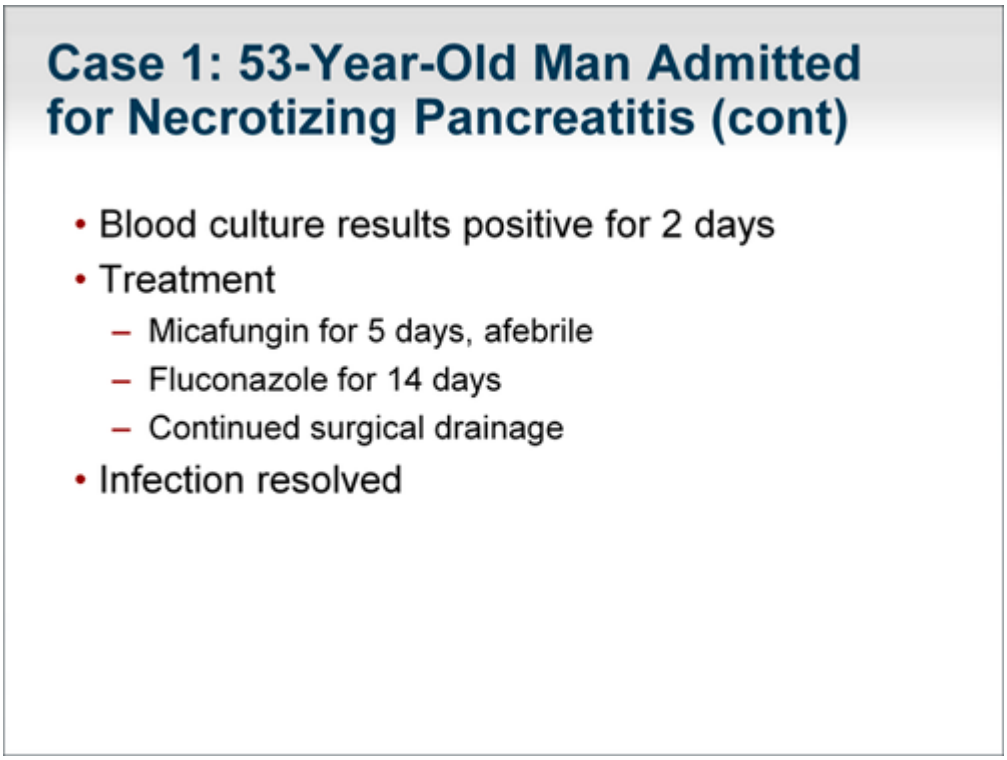
There are diagnostic tests that can be used to identify species earlier. One is the classic germ tube test. Within hours the laboratory tests whether the species of *Candida* can produce pseudohyphae, or some people call them true hyphae, shown on the right. When they are present, the most likely [etiology] is *C albicans.* Another test used by some hospital laboratories is called the PNA FISH (peptide nucleic acid fluorescence in situ hybridization) test. This test will tell you within 90 minutes whether the organism is likely to be *C albicans* or *C glabrata*, so it can be used to employ early therapy as well.



Slide 15.

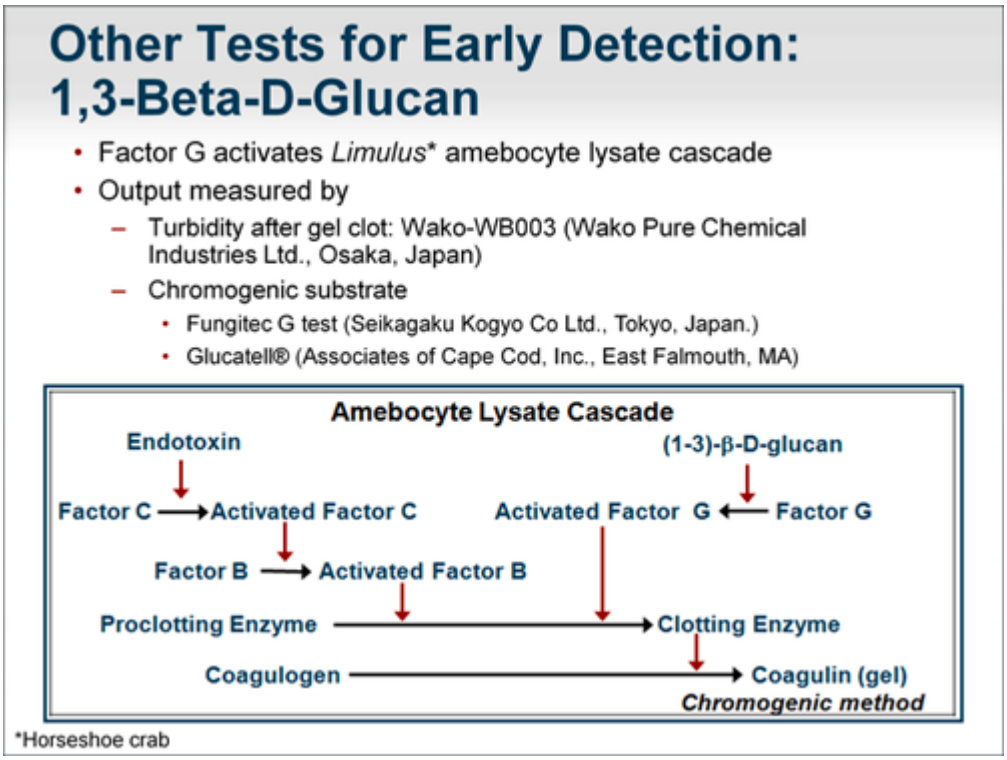
This slide summarizes the recommendations for empiric antifungal treatment of nonneutropenic patients with suspected invasive candidiasis, as developed by an Infectious Diseases Society of America (IDSA) consensus group in 2009.

- An important point is that fluconazole can be used in patients who are less critically ill and have no recent azole exposure -- in that setting, you predict that *C albicans* is the likely cause of infection and susceptible [to fluconazole];
- The second point is that echinocandins can be used in patients with moderate-to-severe illness or recent azole exposure -- all 3 echinocandins (caspofungin, micafungin, or anidulafungin) are considered appropriate choices; and
- The third point is that amphotericin B deoxycholate or the lipid formulation of amphotericin B can be used when the other antifungals are not tolerated, but most people do not turn to these agents as first-line therapy. Typically, either azole therapy or echinocandins are preferred.



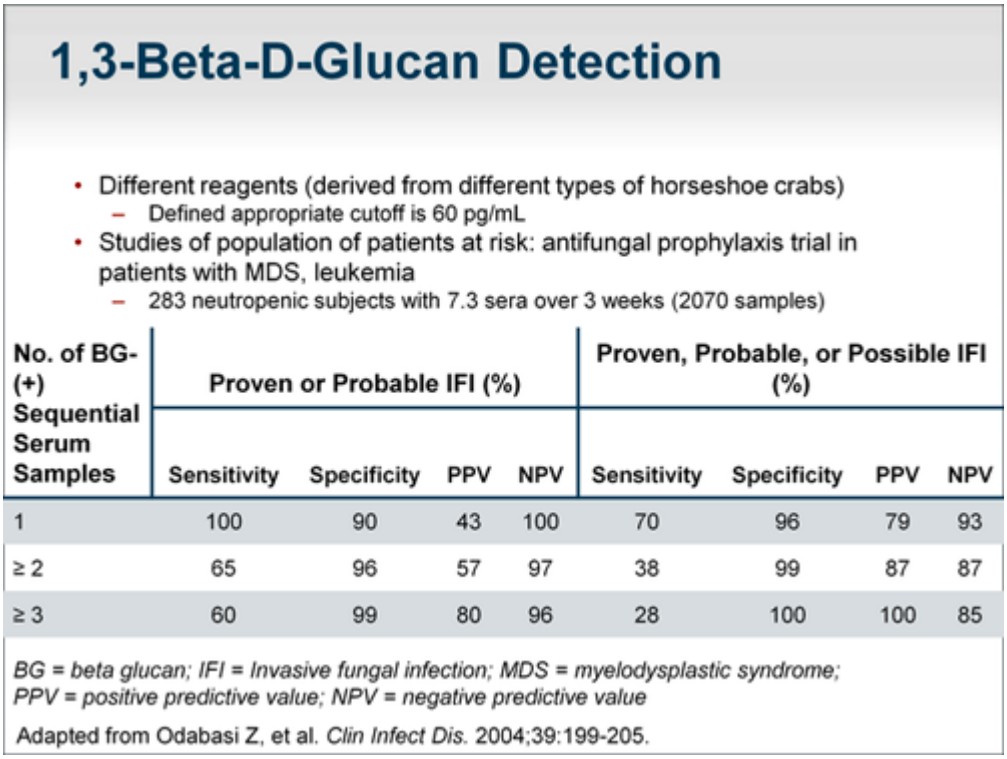
Slide 16.

Let's go back to the patient in our first case. To remind you, he has necrotizing pancreatitis, *Candida* grew in his blood culture, and he has 2 days of positive cultures. He was treated with micafungin for 5 days and he rapidly became afebrile. Then he was treated with fluconazole for 14 days with surgical drainage of the collection around his pancreas, and his infection resolved. Importantly, he was continued on fluconazole for 14 days after the blood cultures cleared. Again, this is to target any other site in which *Candida* may be causing a secondary infection that is not clinically apparent. He did well.



Slide 17.

One of the questions that you might ask is whether there are other tests that can be utilized to detect *Candida* infection earlier. And the exciting answer is yes. Some of these tests rely on detection of antigens rather than culture of *Candida* spp. One is called the 1,3-beta-D-glucan test, which relies on activation of the limulus amebocyte lysate cascade. This is the same cascade that detects endotoxin, but in this case it detects beta-D-glucan, which is a component of *Candida* and multiple other fungi. These tests have been utilized in Japan for a long time. They measure beta-D-glucan using a number of different methods to create output, including the gel coagulability or gel clot method and the chromogenic method.



No. of BG-(+) Sequential Serum Samples	Proven or Probable IFI (%)				Proven, Probable, or Possible IFI (%)			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
1	100	90	43	100	70	96	79	93
≥ 2	65	96	57	97	38	99	87	87
≥ 3	60	99	80	96	28	100	100	85

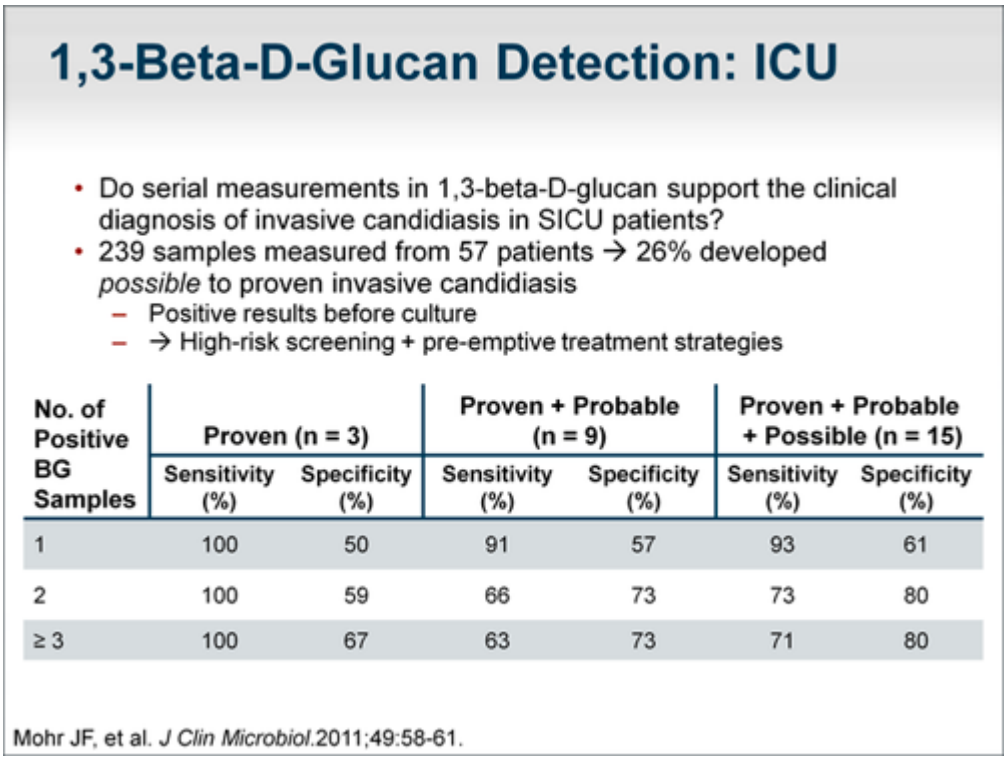
BG = beta glucan; IFI = Invasive fungal infection; MDS = myelodysplastic syndrome; PPV = positive predictive value; NPV = negative predictive value

Adapted from Odabasi Z, et al. *Clin Infect Dis.* 2004;39:199-205.

Slide 18.

A test that is cleared by the FDA and available in the United States (Glucatell®, Associates of Cape Cod, Inc., East Falmouth, Massachusetts)relies on a chromogenic method to detect beta-D-glucan in patients' blood. This test has been studied in a number of different patient populations. The first population studied was high-risk patients with myelodysplastic disorders and leukemia. One thing to keep in mind is that these tests may not be the same from study to study or from country to country because the reagents are derived from different types of horseshoe crabs.

An at-risk leukemic population was studied in which 283 neutropenic subjects had > 7 sera [samples] obtained over a 3-week period, constituting more than 2000 samples. As you can see in the table, the positive-predictive value and the negative-predictive value of detecting either proven or probable invasive fungal infection in the presence of 3 or more serum samples was quite high; the positive-predictive value was 80% and the negative-predictive value exceeded 90%.

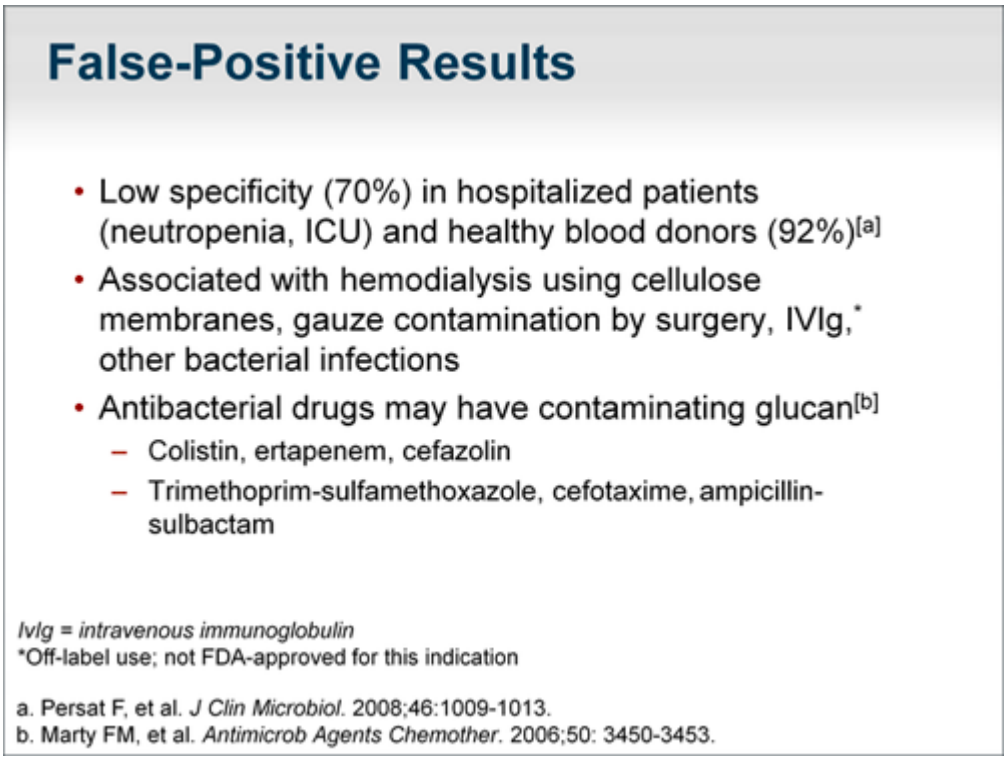


No. of Positive BG Samples	Proven (n = 3)		Proven + Probable (n = 9)		Proven + Probable + Possible (n = 15)	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
1	100	50	91	57	93	61
2	100	59	66	73	73	80
≥ 3	100	67	63	73	71	80

Slide 19.

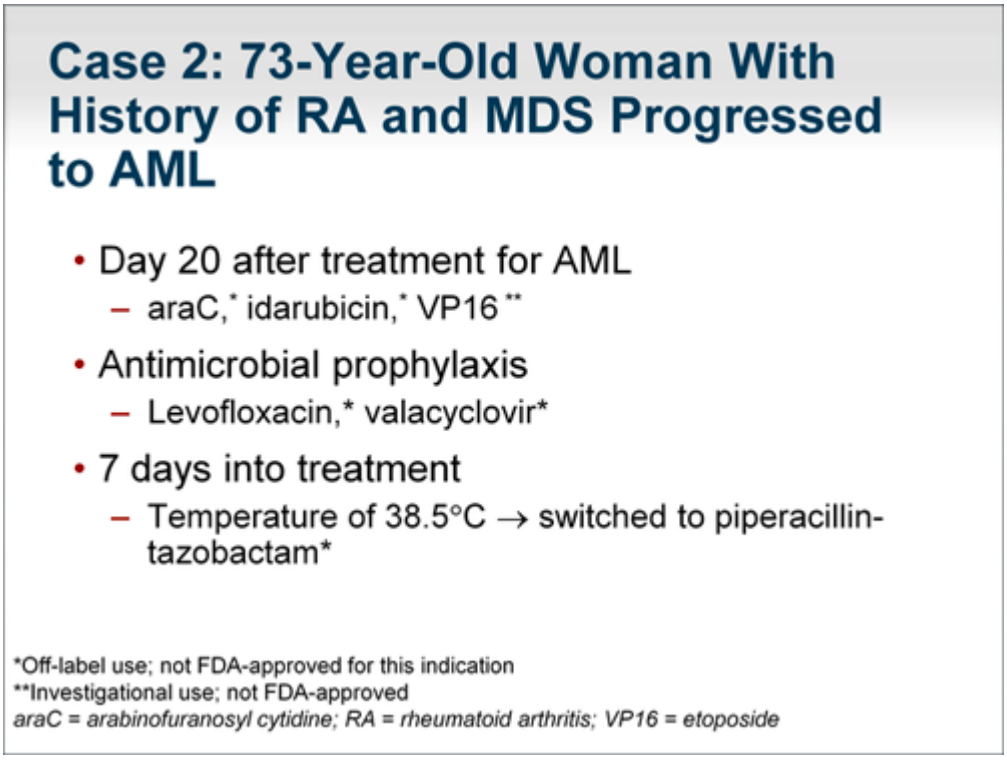
This diagnostic test was also evaluated this year in ICU patients. The question that this study addressed was: Do serial measurements of beta-D-glucan support the clinical diagnosis of invasive candidiasis in patients who are in the surgical ICU? In this study, 239 samples obtained from 57 patients were evaluated; 26% of the patients were considered to have either proven invasive candidiasis or a possible infection. The inclusion of a "possible infection" category in evaluating the outcomes is an important caveat because, in fact, possible infection is not proven infection. That is important to keep in mind because it is a potential limitation of the study.

The results of this rather large analysis are shown in the table. For proven or probable infection, the sensitivity of the assay with more than 3 samples was 63% and the specificity was 73%. In that setting, positive results from the assay were obtained before the culture generated the organism. So it may be possible to give an antifungal drug as a pre-emptive strategy when the beta-D-glucan assay is positive. Because of these results the authors concluded that a high-risk screening strategy, in other words, obtaining serial samples on patients that are known to be at high risk and then employing an antifungal agent that should be effective preemptively, may be a good way to prevent disease progression in surgical intensive care unit (SICU) patients.



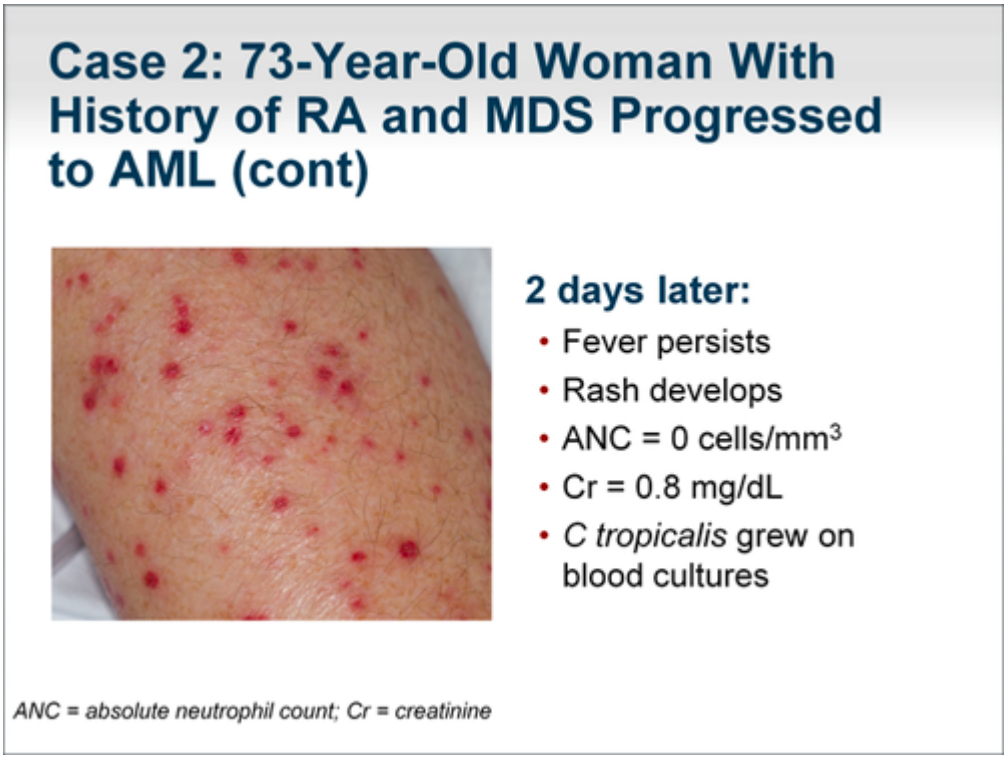
Slide 20.

There are a couple of caveats with regard to these diagnostic tests. One is that there may be problems with false positivity. Specificity has been shown to be rather low in hospitalized patients who are neutropenic or in the ICU. Even healthy blood donors had an almost 8% false-positive test result rate in some studies. There appears to be an association with hemodialysis, and specifically with cellulose membranes that are used for hemodialysis. Gauze contamination from surgery, intravenous immunoglobulins,* and possibly other bacterial infections can also lead to false-positive results. It is important to keep in mind that beta-D-glucan may be found in many different things, including many other treatments. For example, some antibacterial drugs contain glucan contaminant. Drugs found to result in a positive beta glucan test in vitro are shown on this slide.



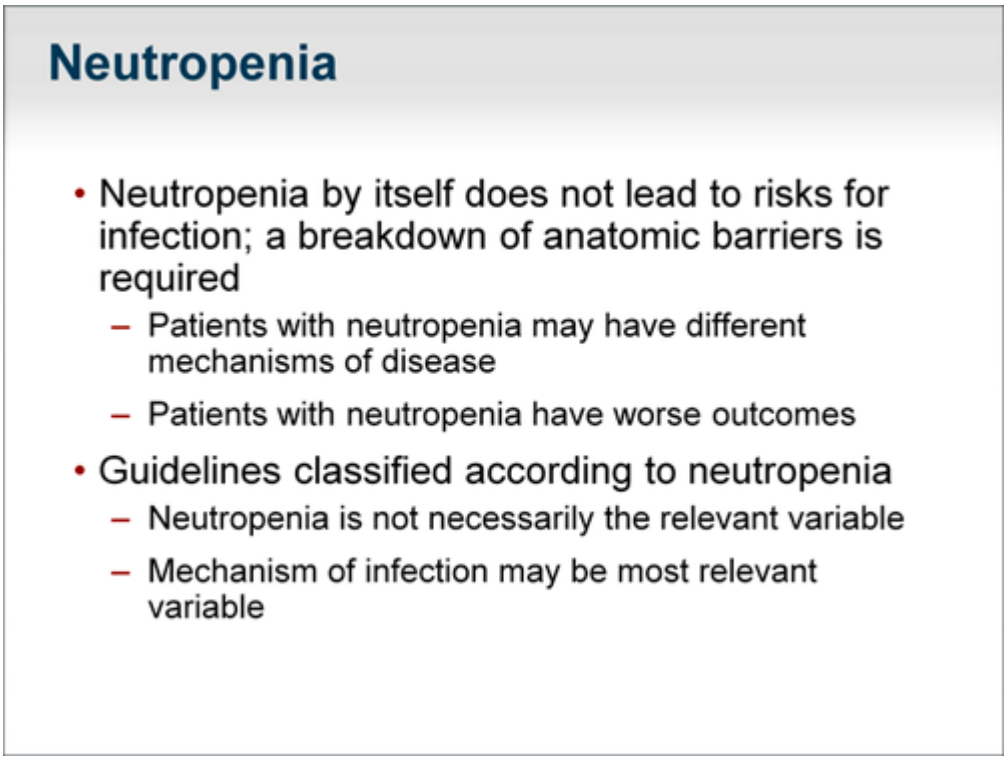
Slide 21.

There are different types of patients that we have to consider, and so I would like to switch to another case. This is a 73-year-old woman with a history of rheumatoid arthritis and a myelodysplastic syndrome that has progressed to acute myelogenous leukemia (AML). She is currently at day 20 after her treatment for AML. She is being treated prophylactically with levofloxacin* and valacyclovir. However, 7 days into treatment, despite prophylaxis, a temperature of 38.5°C developed, and the patient's levofloxacin* was switched to piperacillin/tazobactam.*



Slide 22.

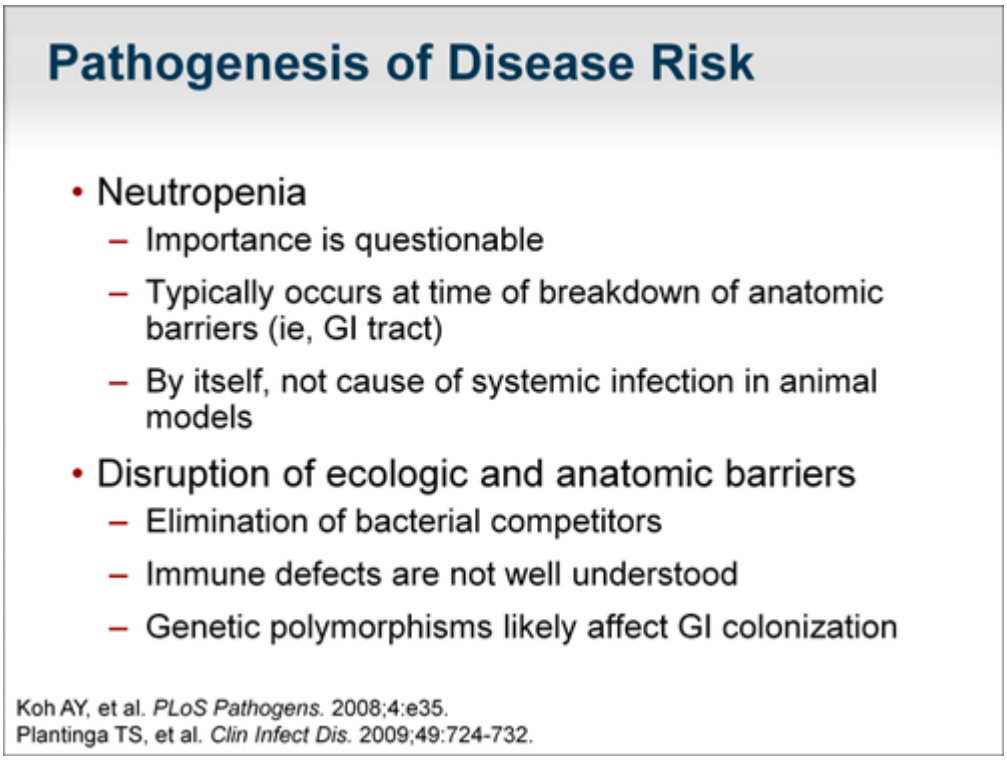
Now, unfortunately, 2 days later, her fever progressed and a rash developed with very small and tender erythematous papules all over her body, but more on her forearms than anywhere else. At this point, she had an absolute neutrophil count of 0. Her creatinine level was 0.8 mg/dL, so her kidneys were working fairly well. Blood culture results rapidly became positive for *C tropicalis*.



Slide 23.

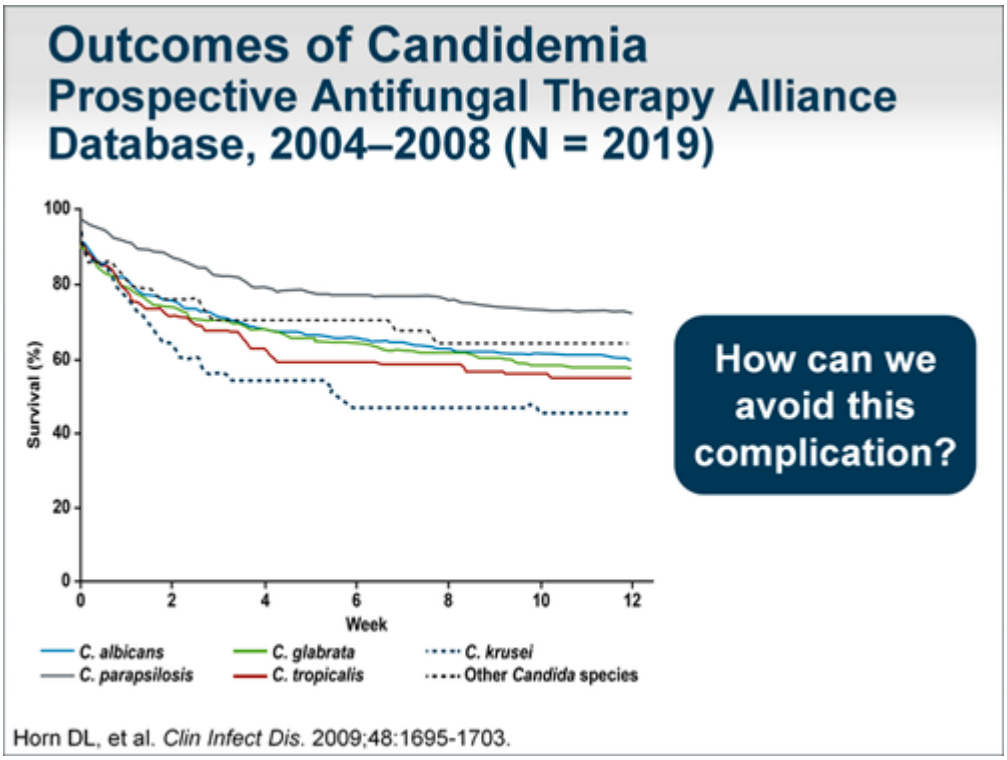
This is a classic neutropenic patient in whom *Candida* infection and disseminated candidiasis develop very quickly. It is important that we understand the nuances of treating neutropenic patients differently from ICU patients. Neutropenia by itself does not lead to increased risk for infection; rather, infection requires a breakdown of anatomic barriers. Disease develops in most as a result of dissemination of infection through their GI tracts.

However, neutropenic patients may have different mechanisms of disease, either dissemination through the GI tract or through the skin. They also have worse outcomes. It is interesting, though, that the treatment guidelines for candidemia are broken out by presence or absence of neutropenia. I don't think this is necessarily the relevant variable. I think the mechanism of infection is the most relevant variable, even though neutropenic patients do worse in outcome models.



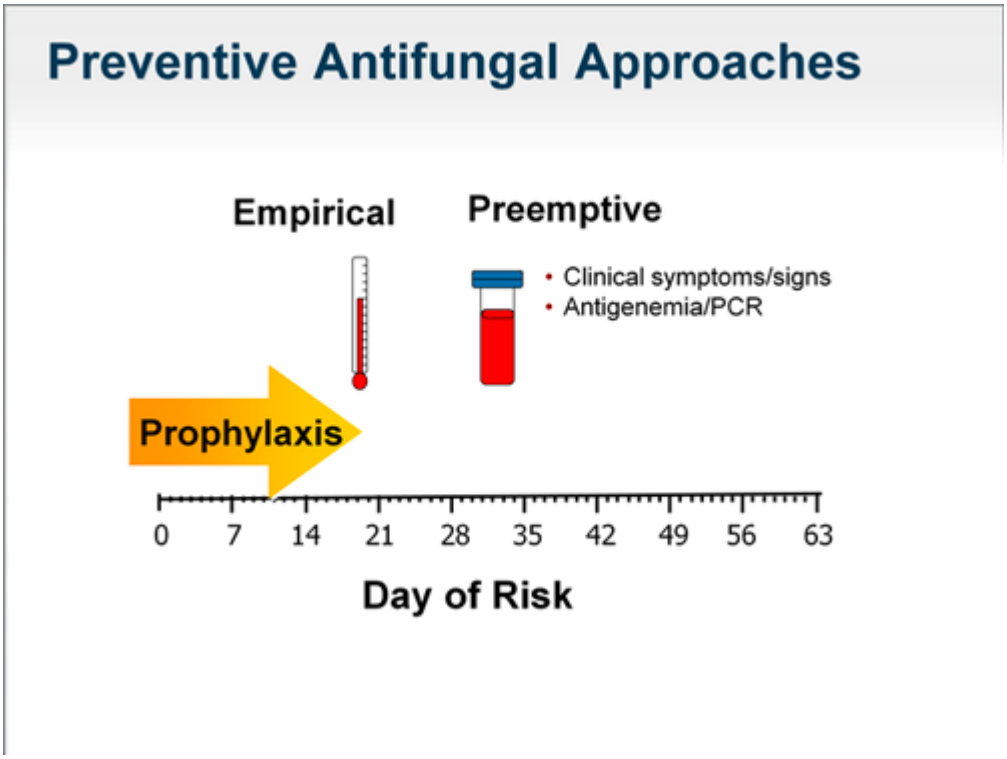
Slide 24.

It is important to understand the pathogenesis and disease risk. As I said, the importance of neutropenia per se is questionable and some of what we are learning about this is coming out of research using [new] animal models that show that the presence of neutropenia does not lead to infection without a breakdown in barriers and transmission through the GI tract. The risks are disruption of ecologic and anatomic barriers, resulting largely in this patient population from elimination of bacterial competitors in the GI tract. That is where other antibiotics come into the mix. Elimination of good organisms in the gut leads to rapid dissemination, but the role of immune defects is not well understood. One of the big questions is: Why does candidemia never develop in so many people who have these risks -- GI tract breakdown and neutropenia? It is probably because there are genetic polymorphisms that encourage GI tract colonization that we are just now starting to appreciate.



Slide 25.

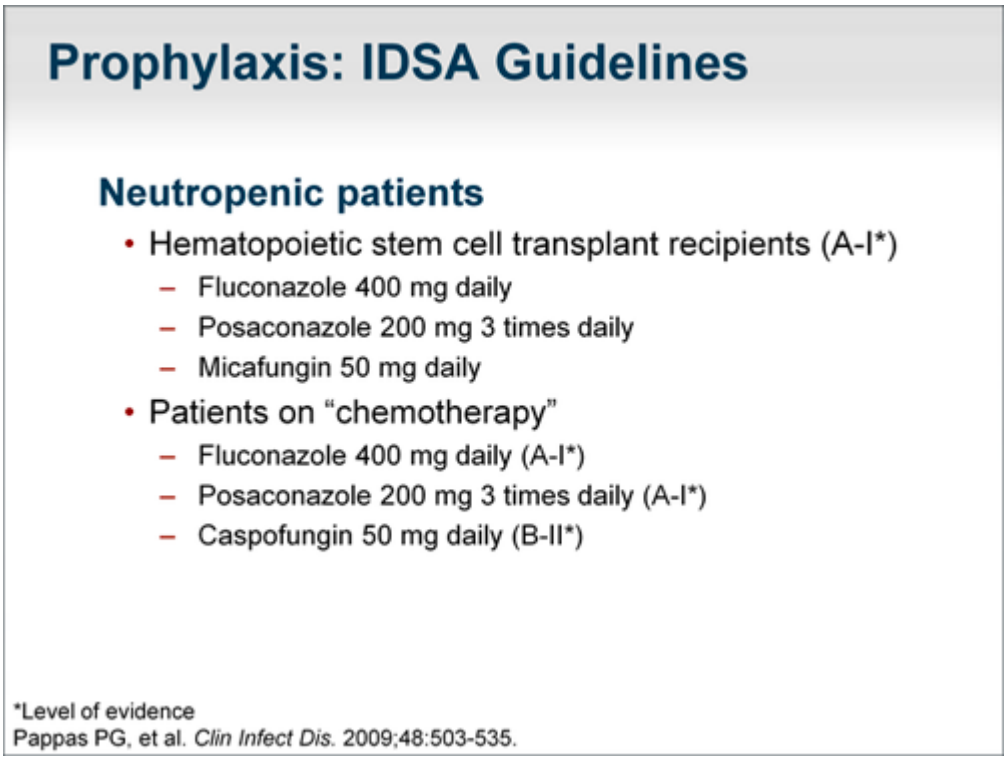
We know from large outcome studies that these patients usually do poorly. This is a Kaplan-Meier survival analysis 12 weeks after infection with various *Candida* spp. The data set included more than 2000 patients in whom candidemia developed in the United States between 2004 and 2008. Patients who did the worst were those with *C krusei* or *C tropicalis* infections. It is very difficult to make conclusions concerning the virulence of these organisms because, in fact, *C krusei* infections developed in the sickest patients. Suffice it to say, the outcomes are very, very poor, and so we should be asking the very important question -- How we can avoid this complication, or candidemia, from the start?



Slide 26.

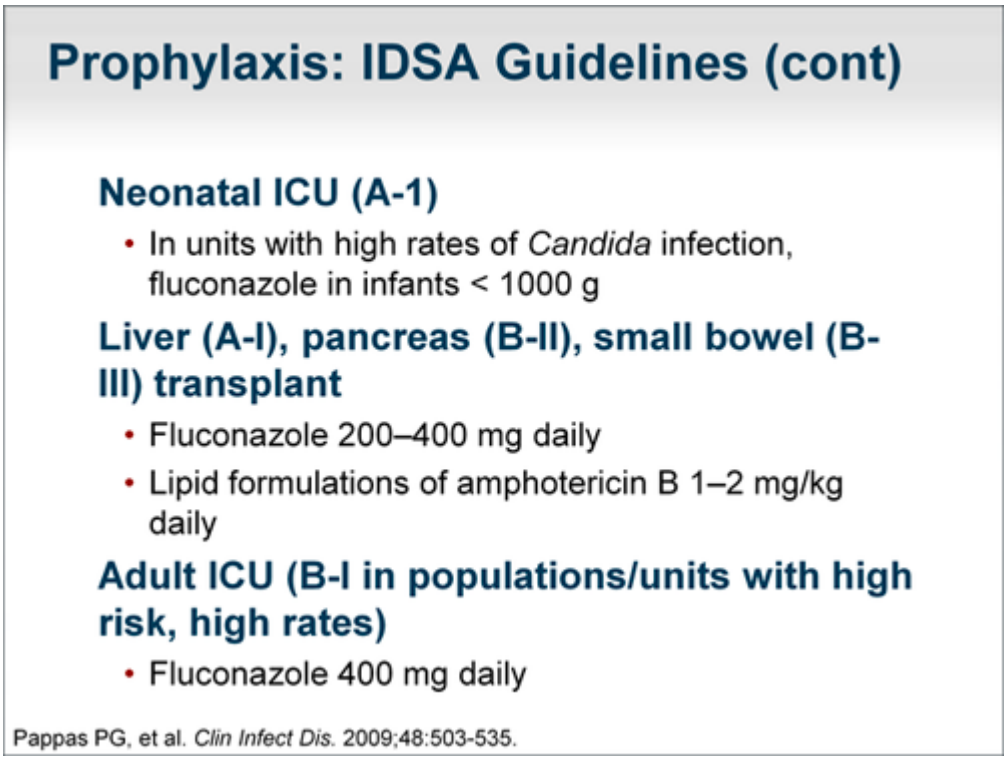
This slide shows all of the preventive antifungal approaches that we classically think about. These includes prophylaxis, or giving a drug during a certain period considered to be high risk for neutropenic patients; empiric therapy, or treating a fever when no other source of the fever is documented; and a preemptive strategy, which relies on detection of some component of the fungus, either from a positive antigen result or from a PCR (polymerase chain reaction) result. By far, the most studied area currently is prophylaxis, where a lot of different drugs are being evaluated for their ability to prevent *Candida* and other fungal infections.

In general, [prophylaxis] is a very successful approach, but success relies on a balance between doing a good thing (preventing infection) and potentially doing a bad thing (introducing a drug that can lead to drug toxicities, such as liver or kidney toxicity, as well as drug interactions that ultimately affect that balance).



Slide 27.

Multiple drugs are considered reasonable therapy for a prophylactic indication. This slide summarizes the IDSA guidelines on treating and preventing *Candida* infections according to host state. In general, neutropenic patients have a good outcome with a prophylactic therapy. Giving prophylactic antifungals -- posaconazole, fluconazole, or micafungin -- is an A-I indication (supported by large randomized trials), especially in patients who have received a hematopoietic stem cell transplant, and specifically an allogeneic stem cell transplant in the setting of chemotherapy. This is a very heterogeneous group of patients and multiple drugs have been studied in this group, including fluconazole, posaconazole, and caspofungin. These drugs are considered to be efficacious and rather safe for preventing *Candida* infections.

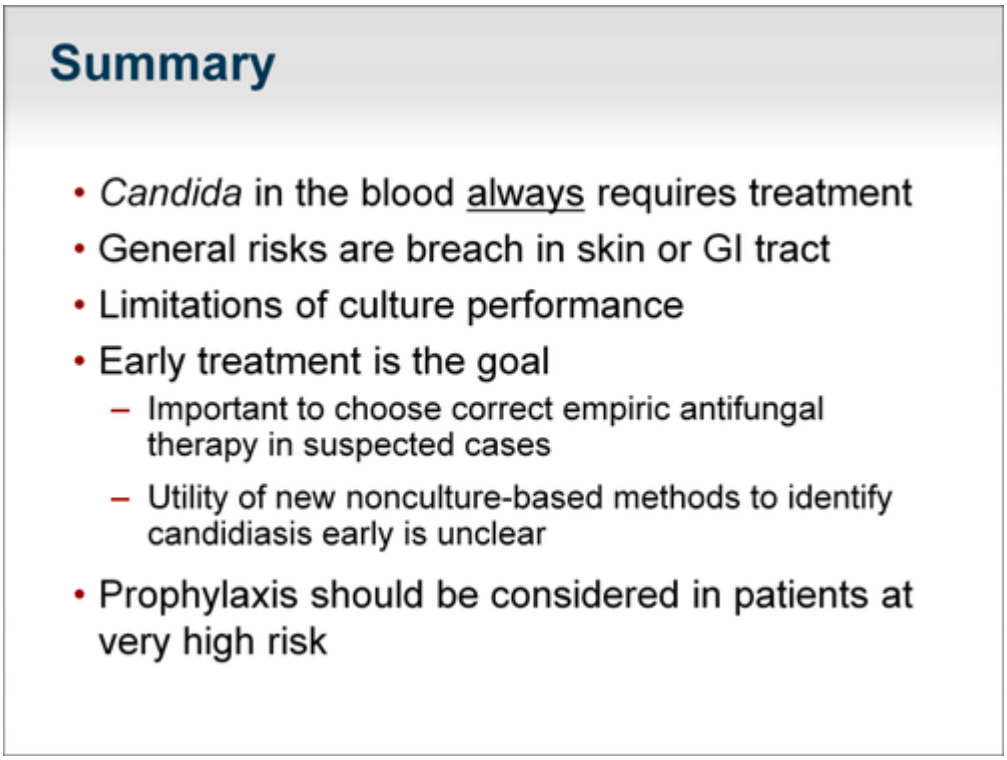


Slide 28.

Another population that has been studied is patients in the neonatal ICU. In that setting, fluconazole given to high-risk infants (< 1000 g) and infants in neonatal ICUs with particularly high rates of *Candida* infections, is supported by good randomized data.

The other populations are more controversial, although there are some large studies of liver, pancreas, and small bowel transplant recipients. Patients with a surgical disruption in the GI tract are at high risk for *Candida* infections. Fluconazole and lipid formulations of amphotericin B at low doses have been shown to be effective at preventing *Candida* infections in these patients.

The last population (as in our first patient case), is adult patients in the ICU. Fluconazole used for prophylaxis is a B-I indication in populations at high risk, as well as those in ICUs with high rates of infections. Some units use it, some units don't; there are a lot of different practice patterns with regard to antifungal strategies in the ICU, but these are the conclusions from the IDSA consensus group.



Slide 29.

I'm going to summarize the points that I think are the most important things to think about in diagnosis and early treatment of *Candida* infections:

- The most important is that *Candida* infection always requires treatment, even if it appears that the host has been transiently infected or has cleared the infection, because you don't know where else *Candida* is causing a secondary infection that may become apparent later on.
- The general risks for infection include breaches in the skin as well as in the GI tract, and then everything that leads to an increase in GI tract colonization.
- It is important to understand the limitations of culture performance; they are better than they used to be, but they are not 100% perfect. This is the observation that suggests that we need to use empiric therapy and early treatment in patients at high risk.
- Choosing the right empiric antifungal therapy in suspected cases requires that you think about what species would be the most common in that setting. However, some of the new nonculture-based methods allow us to potentially identify invasive candidiasis earlier. Their utility is not entirely clear and more randomized trials need to be done.
- Prophylaxis should be considered in patients at very high risk because ultimately, preventing disease in this setting proves to be the best thing that you can do.

Slide 30.

Thank you for participating in this activity. To proceed to the online CME test, click on the Earn CME credit link on this page. Thanks very much.

*Off-label use: Not FDA-approved for this indication.

Post-Assessment: Measuring Educational Impact

Thank you for participating in the CME activity. Please take a few moments to read the following cases and complete the questions that follow to help us assess the effectiveness of this medical education activity.

In your experience, which of the following is the most significant barrier to the optimal diagnosis of patients with invasive candidiasis?

- ☐ Lack of awareness of tests for early detection of invasive candidiasis
- ☐ Limited performance of currently available blood culture testing methods
- ☐ Limited access to tests for early detection of invasive fungal disease
- ☐ Amount of time required to identify *Candida* spp creates the need for an "educated" guess about the most appropriate early treatment

In your experience, which of the following is the most significant barrier to the optimal choice of antifungal agent for invasive candidiasis?

- ☐ General lack of knowledge about how to appropriately select from multiple treatment options
- ☐ Concerns about drug interactions and adverse events associated with antifungal therapy
- ☐ Uncertainty about how to individualize antifungal treatment based on illness severity
- ☐ Uncertainty about how to individualize antifungal treatment based on neutrophil count

(neutropenic vs nonneutropenic)

- Uncertainty about how to individualize treatment based on susceptibility profiles of *Candida* spp
- Resistance of some *Candida* spp to antifungal therapy options

In your experience, which of the following is the most significant barrier to the optimal timing of treatment initiation for invasive candidiasis?

- Uncertainty about when to initiate prophylactic treatment
- Uncertainty about when to initiate empiric treatment
- Uncertainty about when to initiate preemptive treatment
- Amount of time required to determine *Candida* spp

Case #1: Twenty days after undergoing a coronary artery bypass graft, a 59-year-old man presents with mediastinitis, requiring a return to the operating room for sternal debridement and placement of an internal jugular central line. Intraoperative culture specimens isolated from the mediastinum grow methicillin-resistant *Staphylococcus aureus* and vancomycin is started. On postoperative day 3, while recovering in the ICU, a temperature up to 38.1°C develops. His blood pressure is 140/80 mm Hg and his heart rate is 92 bpm. His white blood cell count is 17.5 x 10^3 cells/µL. A single blood culture specimen grows *Candida albicans*; however, his fever quickly abates and subsequent blood culture results are negative.

In addition to central line removal, would you treat this patient with an antifungal agent at this time, and what would be the rationale for your decision?

- Yes, it is likely that he has a secondary infection
- Yes, all patients with a positive blood culture should be treated
- No, It is likely that *C albicans* was a contaminant
- No, it is likely that his candidemia is transient

Using your knowledge about the susceptibility pattern of *C albicans*, which of the following classes of antifungal therapy would you choose from for the treatment of this patient's disease?

- Azoles and extended-spectrum azoles
- Amphotericins and echinocandins
- Extended-spectrum azoles, echinocandins, and amphotericins
- Azoles, extended-spectrum azoles, echinocandins, and amphotericins

Case #1 cont: The patient's vital signs are now within normal limits, and you make the decision to initiate empiric treatment with an antifungal agent, based on the 2009 guidelines of the IDSA for nonneutropenic patients who are less critically ill.

Which of the following agents would you use for empiric therapy?

- Caspofungin
- Fluconazole
- Amphotericin B lipid formulation
- Voriconazole

Case #1 cont: A colleague questions your decision to initiate antifungal therapy. She points out that only 1 blood culture result was positive for yeast, while subsequent blood cultures were negative. You defend your decision by citing the sensitivity of advanced blood culture techniques

and the possibility that the subsequent negative blood culture results may have yielded false-negative results.

Which of the following most closely approximates the sensitivity of advanced blood culture techniques in the detection of *Candida* spp?

- 30%
- 50%
- 70%
- 90%

Case #2: A 53-year-old woman with poorly-controlled type 2 diabetes and end-stage renal disease on hemodialysis is admitted to the ICU after undergoing an open gastric bypass. On postoperative day 13, severe hypotension and a temperature of 39.5°C develop. On physical examination, you discover 6 small nontender, erythematous, pustular lesions localized to her trunk. Blood culture specimens are drawn. You are concerned that your patient may have invasive candidiasis and you initiate empiric therapy. She was recently treated with fluconazole for uncomplicated candidal vulvovaginitis. You receive a call from the laboratory that yeast has grown from 2 of your patient's blood culture specimens.

Based on the 2009 IDSA guidelines, which of the following would be your preferred empiric therapy for the treatment of this patient?

- Micafungin
- Fluconazole
- Amphotericin B lipid formulation
- Voriconazole

Case #3: A 42-year-old woman is diagnosed with acute myelogenous leukemia and undergoes induction chemotherapy through a central venous catheter. She receives prophylactic levofloxacin and trimethoprim-sulfamethoxazole. Fourteen days into therapy, a temperature of 38.8°C, severe diarrhea, and oral sores develop. Her absolute neutrophil count is 0.2 cells/mm^3.

Which of the following would guide your decision about initiating antifungal prophylaxis?

- In general, outcomes of prophylaxis are poor
- In general, outcomes of antifungal prophylaxis in neutropenic patients are good
- All ICU patients should receive antifungal prophylaxis
- The choices are limited

Please indicate how relevant this CME activity is to your practice: approximately how many patients with invasive fungal infections do you see each week?

- 0
- 1-5
- 6-10
- 11-20
- 21-30
- 31-40

Please indicate your practice setting:

- Hospital

Outpatient clinic

Save and Proceed

Supported by an independent educational grant from Astellas.

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Suggested Reading

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