FUNGAL INFECTIONS AND ANTIFUNGAL THERAPY IN THE SURGICAL INTENSIVE CARE UNIT

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The first clinical description of *Candida* infection can be traced to Hippocrates, with Parrot recognizing a link to severe illness. Langenbeck implicated fungus as a source of infection, and Berg established causality between this organism and thrush by inoculating healthy babies with aphthous "membrane material." The first description of a deep infection caused by *Candida albicans* was made by Zenker in 1861, even though it was not named until 1923 by Berkout. On the other hand, the genus *Aspergillus* was first described in 1729 by Michaeli, and the first human cases of aspergillosis were described in the mid-1800s.

Invasive mycoses have emerged as a major cause of morbidity and mortality in hospitalized surgical patients. It is estimated that the incidence of nosocomial candidemia in the United States is about 8 per 100,000 inhabitants. Excess attributable health care costs are approximately $1 billion per year. Average medical costs per episode of candidemia have been estimated at $34,123 for Medicare patients and $44,536 for privately insured patients. In the United States, *Candida* is the fourth most common cause of catheter-related infection. A recent prospective, observational study reported the incidence of fungemia in the surgical intensive care unit (SICU) to be nearly 10 cases per 1000 admissions with an unadjusted mortality rate of 25%–50%.

Fungemia is the fourth most common type of bloodstream infection in the United States. Outside the United States, several studies have reported a rise in candidemia and other forms of *Candida* infections. In Canada, there has been an increase in the number of *Candida* isolates since 1991, where currently it constitutes 6% of all blood isolates. In general, the rates reported from European hospitals are slightly less than those from North America. In a meta-analysis of randomized, placebo-controlled trials with fluconazole prophylaxis, the incidence of fungal infections was significantly reduced; however, there was no survival advantage, raising the issue of the value of prophylaxis.

With the introduction of antibiotics and the subsequent appearance of intensive care units (ICUs), new examples of opportunistic fungal infections have emerged. The use of immunosuppression, organ transplantation, implantable devices, and human immunodeficiency virus infection has also radically changed the spectrum of fungal pathogenicity.

Fungi are ubiquitous heterotrophic eukaryotes, quite resilient to environmental stress and able to thrive in numerous environments. They may belong to the *Chromista* or *Eumycota* kingdom.[1] For identification purposes, the separation of taxa is based on the method of spore production, assisted by molecular biology techniques (rRNA and rDNA) that further refine fungal phylogeny and establish new relationships between groups. The most important human pathogens are the yeasts and the molds (from the Norse *mowlde*, meaning fuzzy). The dual modality of fungal propagation (sexual/teleomorph and asexual/anamorph states) has meant that since the last century there has been a dual nomenclature.

PREDICTORS OF FUNGAL INFECTIONS

The National Nosocomial Infection Surveillance program (NNIS) of the U.S. Centers for Disease Control and Prevention (CDC) has reported that whereas the rate of hospital-acquired fungal infections nearly doubled in the past decade compared with the previous decade, the greatest increase occurred in critically ill surgical patients, making the surgical population in the ICU an extremely high risk group.[2] Several conditions (both patient-dependent and disease-specific) have been recognized as independent predictors for invasive fungal complications during critical illness. ICU length of stay was associated with *Candida* infection as were the degrees of morbidity, alterations of immune response, and the number of medical devices involved. Neutropenia, diabetes mellitus, new-onset hemodialysis, total parenteral nutrition, broad-spectrum antibiotic administration, bladder catheterization, azotemia, diarrhea, use of corticosteroids, and cytotoxic drug utilization are also associated with candidemia.[2-5]

Diabetes Mellitus

Diabetes mellitus is an independent predictor for mucosal candidiasis, invasive candidiasis, and aspergillosis. Diabetic ketoacidosis has a strong association with rhinocerebral mucor (produced by *Zygomycetes*) and other atypical fungal infections, with hyperglycemia being the strongest predictor of candidemia after liver transplantation and cardiac bypass. It has been postulated that hyperglycemia produces several alterations in the normal host response to infection and in the fungus itself, increasing its virulence. Glycosylation of cell surface receptors facilitates fungal binding and subsequent internalization and apoptosis of the targeted cells. Glycosylation of opsonins renders them unable to recognize fungal antigens. Diabetic serum has diminished capacity to bind iron (therefore making it available to the pathogen). There is evidence that altered Th-1 lymphocyte recognition of fungal targets impairs the production of interferon-gamma (IFN-γ), and that *Candida* spp. overexpress a C_3-receptor–like protein that facilitates fungal adhesion to endothelium and mucosal surfaces. Dendritic cells and other antigen-presenting cells have been postulated as crucial in the induction of cell-mediated responses to fungi, and diabetic patient vaccination studies have showed an impaired antigen—T-cell interaction.

Neutropenia

There is a direct correlation between the degree of neutropenia and the risk for developing invasive fungal infections. Although a recent meta-analysis concluded that there is little benefit from prophylaxis or preemptive treatment in neutropenic cancer patients, this is a regular practice in the United States. Empirical antifungal therapy is the standard of care for febrile neutropenia patients after chemotherapy or bone marrow transplantation. When profound neutropenia exists, the risk for breakthrough candidemia (during antifungal therapy) is significantly higher, and the response to voriconazole (and likely other antifungals) is decreased. Novel therapies for the treatment of invasive fungal infections in neutropenic patients include granulocyte transfusions and infusion of IFN-γ.

Organ Transplantation and Immunosuppression

The two most common opportunistic fungal infections in transplant patients are caused by *Candida* spp. and *Aspergillus* spp., generally by the inhalation route (*Aspergillus*) or from gastrointestinal sources (*Candida*). Interestingly, the risk of fungal infection decreases six months after transplantation, unless a rejection episode requires intensification of the immunosuppression. In the solid organ transplant recipient, the graft itself is often affected. In liver transplantation, the risk of fungemia increases with the duration of the surgery and the number of transfusions. Other risk factors include the type of bile duct anastomosis (Roux-en-Y), the presence of tissue ischemia, infection with cytomegalovirus (CMV), and graft-versus-host disease. The most common place of occurrence for *Aspergillus* tracheobronchitis in lung transplant patients is at the bronchial anastomosis. Anastomotic colonization is both a risk factor for subsequent disruption or hemorrhage and a predictor for rejection and diminished graft survival. Surveillance bronchoscopies are recommended in this setting. *Aspergillus* is also the main organism responsible for fungemia after heart transplantation, and second only to CMV as the cause of pneumonia in the first month after operation.

Infectious complications are the main cause of morbidity and mortality in pancreas and kidney–pancreas transplantation. The most common organisms are gram-positive cocci, closely followed by gram-negative bacilli and *Candida*. Risk factors for fungal infections include bladder drainage (in cases of pancreas transplantation) and use of OKT-3 for rejection treatment. Kidney recipients, of all solid organ transplant recipients, have the lowest incidence of infectious complications. However, the risk is sufficiently high that all solid organ transplant recipients (kidney recipients included) receive fungal prophylaxis with fluconazole.

Solid and Hematological Malignant Tumors

Cancer patients are susceptible to opportunistic infections. Cancer and chemotherapy produce three types of immune dysfunction that render the patient vulnerable to opportunistic infections: neutropenia (see previously), deficits in lymphocyte cell-mediated immunity (e.g., Hodgkin disease and during corticosteroid treatment), and humoral immunodeficiency (e.g., multiple myeloma, Waldenström macroglobulinemia, and after splenectomy). The first two types are the most relevant in terms of fungal vulnerability. As many as one-third of the cases of febrile neutropenia after chemotherapy for malignant disease are due to invasive fungemia (see following treatment discussion). The type of lymphopenia is as important as the nadir of the lymphocyte count: Whereas Th-1 type responses (TNF-α, IFN-γ, and interleukin [IL]-12) confer protection against fungal infections, Th-2 (IL-4 and -10) responses are associated with progression of disease. Corticosteroids have anti-inflammatory properties, related to their inhibitory effects on the activation of various transcription factors, in particular NF-κB. In murine models, steroid treatment increases the production of IL-10 in response to a fungal insult, and decreased the recruitment of mononuclear cells to the site of infection. It does not, however, inhibit recruitment of neutrophils to sites of inflammation (IL-8-mediated).

Long-Term Use of Central Venous Catheters

Numerous studies have shown that many, if not most, episodes of candidemia are catheter-related; one of the largest prospective treatment studies of fungemia implicated a catheter 72% of the time. The isolation of *C. parapsilosis* from blood cultures is strongly associated with central venous catheter infection, parenteral nutrition, or prosthetic devices. The source of the fungal contaminants is different in neutropenic patients when compared with their non-neutropenic counterparts. In non-neutropenic subjects the most common portals of entry for catheter contamination (and subsequent infection) is the skin during catheter placement, manipulation of an indwelling catheter, and cross-infection among ICU patients attributed to hand carriage of microbial flora from health care workers. Other possible sources for primary catheter colonization include contaminated parenteral nutrition solution, multiple medication administration with repetitive violation of the sterile fluid path, and the presence of other medical devices. The secondary route of contamination for intravascular catheters and other foreign bodies in direct contact with the bloodstream (e.g., pacemakers, cardiac valves, orthopedic joint prostheses) is candidemia originating via translocation from the gastrointestinal tract. Endogenous flora are also the most common source in neutropenic and other immunosuppressed patients. Once the catheter becomes contaminated, a well-studied series of events takes place: The yeast adheres to the surface of the catheter and develops hyphal forms that integrate into a matrix of polysaccharides and proteins (biofilm) that increases in size and tridimensional complexity. This biofilm is the main reservoir for candidemia secondary to contaminated medical devices, as it sequesters the fungi from antimycotic medication and against the protective immune response.

In general, the removal of all central venous catheters is indicated following the diagnosis of systemic fungal infections and fungemia. Removal may not be necessary in neutropenic patients in whom the fungi originated from the GI tract. Antifungals in general are continued after the catheter is removed, and it is recommended that *Candida* ocular dissemination be ruled out (see following discussion of endophthalmitis).

Candida Colonization

The overgrowth and recovery of *Candida* spp. from multiple sites (without clinical symptoms of disease) has been linked to a high likelihood of invasive candidiasis, and the cumulative risk of death in these two conditions is similar. Risk factors for the development of *Candida* colonization include prior use of antibiotics or a bacterial infection prior to ICU admission, a prolonged stay in the ICU, and multiple gastrointestinal operations. The source of most of the outbreaks of systemic candidiasis in the context of colonization is frequently the gastrointestinal tract.

Because colonization with *Candida* spp. is not benign in the context of critical illness, it is desirable to identify and characterize patients further in terms of risk for invasive candidiasis. Screening techniques include routine surveillance cultures in ICU patients. The method proposed by Pittet et al., the colonization index, has been validated in surgical patients. A threshold index of 0.5 has been proposed for the initiation of empiric antifungal therapy in critically ill patients (see following treatment section), although some authorities suggest that the presence of multiple *Candida* isolates is an epiphenomenon.[6]

Use of Broad-Spectrum Antibiotics

The use of broad-spectrum antibiotics is one of the best-documented risk factors for fungal overgrowth and invasive infections, but the precise mechanism is not understood completely. In evaluating the effect of antibiotic use, one must consider first the complex interrelations between bacteria and fungi in human disease. At least three experimental models have been created to investigate and characterize possible interactions between bacterial and fungal pathogens. In murine models, ticarcillin-clavulanic acid and ceftriaxone (both of which have some antianaerobic therapy) are associated with substantial increases in colony counts of yeast flora of the gut. On the other hand, antibiotics with poor anaerobic activity are less likely to produce this effect (examples

are ceftazidime and aztreonam). This observation was validated in a clinical review of the quantitative colonization of stool in immunocompromised patients treated with those antibiotics. However, this interaction between fungi overgrowth and anaerobic suppression is different from the well-studied model of *Escherichia coli* and *Bacteroides fragilis* in intra-abdominal abscess formation. The work of Sawyer et al. showed that *C. albicans* induces bacterial translocation into abscesses, but the relationship is one of direct competency, rather than synergy or cooperation.[7,8] This is different than the cooperation between *C. albicans* and *Staphylococcus aureus, Serratia marcescens,* and *Enterococcus faecalis,* where an amplification-type interaction has been documented. A number of immunomodulatory and immunosuppressive viruses have been shown to facilitate superinfections with opportunistic fungi, the most notable examples being CMV and human herpes virus (HHV)-6, because they induce the production of immunosuppressive cytokines. It seems that *C. albicans* thrives in situations where immunocompromise is present and adds virulence and mortality to existent bacterial infections in a species-specific manner. This hypothesis has been validated from clinical observations, where antifungal treatment adds little to the therapeutic effect of antibacterial agents alone. Thus, the use of antibiotics (three or more), especially those with anti-anaerobic properties, constitute a risk factor for fungal colonization and overgrowth, which in turn is a predictor for systemic fungal infections. The precise mechanism of action for this observation is unknown but is probably related to fungi-to-microbe competence and growth suppression. *Candida* may enhance the pathogenicity of certain bacteria, but not others, and this interaction remains to be elucidated.[7]

Duration of ICU Care and Invasive Mechanical Ventilation

Epidemiological observations correlating the duration of mechanical ventilation and the amount of intensive care required correlate with the occurrence of both systemic fungal infections and fungal colonization. Other factors involved in the pathogenesis and susceptibility of systemic candidiasis are total parenteral nutrition, use of H_2 blockers, acquired immunodeficiency syndrome (AIDS), radiation therapy, previous bacteremia, abdominal surgery, hemodialysis, extremes of age, recurrent mucocutaneous candidiasis, and duration of cardiopulmonary bypass greater than 120 minutes.[2]

PATHOGENIC ORGANISMS

Candida albicans

The most common fungal pathogen both in the United States and abroad, and ranked among the most common sources of ICU sepsis, *C. albicans* is a common cause of human disease.[9] *Candida albicans* accounts for 59% of *Candida* isolates, followed by *C. glabrata* (15%–25% of all *Candida* infections). Both colonization and invasive candidiasis can be focal or disseminated. Multifocal candidiasis is the simultaneous isolation of *Candida* from two or more of the following locations: respiratory, digestive, urinary, wounds, or drainage. Disseminated candidiasis is microbiological evidence of yeast in fluids from normally sterile sites such as cerebrospinal, pleural, pericardial, or peritoneal fluid, histologic samples from deep organs, or diagnosis of endophthalmitis or candidemia with negative catheter-tip cultures. The incidence of candidemia has increased over the past 30 years, with mortality rates reported in some series to be as high as 80%. The NNIS system of the CDC found *Candida* species responsible for 8%–15% of all nosocomial bloodstream infection episodes in the United States in 1993, which ranked fourth among commonly isolated pathogens in bloodstream infections.

It is well established that a morphological transition in *C. albicans,* from yeast to hyphal forms, is the most important determinant of dissemination, because the mycelial phase is invasive.[10] Both host and pathogen play a role on this dimorphism. The fungus produces several proteins during the hyphal transition, which are currently the focus of research. The thiol-specific antioxidant, or TSA-1, has shown an increased survival capability in an antioxidant environment created by host cells. Host recognition molecules (adhesins), secreted aspartyl proteases and phospholipases, and phenotypic switching accompanied by changes in antigen expression, colony morphology, and tissue affinities are other recognized virulence factors. The inducer mechanisms and the multiple stimuli that trigger this change are unknown.

From the host side, the presence of the enzyme indoleamine 2,3-dioxygenase (IDO) has been linked to antifungal defense mechanisms, by blocking the morphological transition. The enzyme is induced in infectious sites and in dendritic cells by IFN-γ. Interferon serves in a pivotal position in immunity from *C. albicans* invasion. Other immune mechanisms blocking the transformation include salivary histidine, other gastrointestinal inhibitory peptides, and the resident population of dendritic cells. The dimorphic change produces disseminated candidiasis (also known as hepatosplenic candidiasis) and specific end-organ involvement in susceptible hosts. Of those metastatic infections, among the most devastating is fungal endophthalmitis.

Disseminated candidiasis and fungemia can lead to septic shock, similar to that seen with other microorganisms. The dimorphic transition generates shock and end-organ failure in susceptible individuals, and these events are independent of TNF-α. The diagnosis of fungemia as the cause of a patient's sepsis depends on a strong clinical suspicion. Only 50% of blood cultures for invasive candidiasis are positive and bacterial pathogens may interfere with the recovery of *Candida*. There are no reliable laboratory tests to differentiate between *Candida* colonization and invasive candidiasis, and no single site of isolation is superior to others in predicting which patients are likely to have developed systemic infection. The diagnostic criteria for fungemia are a combination of positive tissue cultures (including burn excision cultures and peritoneal cultures), endophthalmitis, osteomyelitis, and candiduria. Purpura fulminans and unexplained myalgias are suggestive of candidiasis in the appropriate clinical context. The presence of three or more colonized sites or two positive blood cultures at least 24 hours apart, with one obtained after the removal of any central venous catheters are strong indicators of fungemia.[10] Whereas asymptomatic recovery of *Candida* in urine rarely requires therapy, candiduria should be treated in symptomatic patients, neutropenic patients, renal transplant patients, and after instrumentation. The removal or at least changing of the Foley catheter is required.

Fungal endophthalmitis usually occurs as a result of hematogenous spread from systemic fungemia. *Candida* spp. are the most common offenders, although *Aspergillus, Cryptococcus, Fusarium, Scedosporium,* and others have been reported to lead to endophthalmitis. Retinal involvement has been diagnosed in 28%–45% of all known candidemic patients, and may actually be the first sign of clinically undetected fungemia. The early initiation of systemic treatment for deep tissue fungal infection appears to decrease dramatically the incidence of endogenous fungal endophthalmitis. It is mandatory for all individuals with systemic candidiasis and fungemia to have a formal ophthalmologic assessment to rule out eye involvement. The observation of a classic three-dimensional retina-based vitreal inflammatory process is virtually diagnostic of endogenous endophthalmitis due to *Candida* spp.

Treatment consists of aggressive intravenous antifungal therapy, and may require intraocular injections of amphotericin B, caspofungin, or voriconazole. In cases where extension to the vitreous or pars anterior are evident, surgical debridement or vitrectomy will be required. Delay in treatment leads frequently to blindness.

Non-albicans Candida

The incidence of non-*Candida* fungemia and sepsis syndrome has been increasing in recent years, accounting for up to one-half of non-*albicans Candida* adult ICU infections. The reasons for this are likely multifactorial. Undoubtedly, one explanation for the emergence of *C. glabrata* and *C. krusei* is the selection of less-susceptible species by the pressure of antifungal agents.[11] Other species of yeast are related to specific events, such as the presence of an indwelling central venous catheter and *C. parapsilosis*. The increased incidence of *C. tropicalis* in oncology patients is secondary to the increased invasiveness of the organism, especially in damaged gastrointestinal mucosa. The clinical features of this infection are indistinguishable from *C. albicans*.

Aspergillus

The noninvasive types of aspergillosis include allergic bronchopulmonary aspergillosis (a form of hypersensitivity reaction in asthmatics) and aspergilloma. These entities, without tissue invasion, usually do not require antifungal therapy. Invasive aspergillosis has experienced an increased incidence over the last decade, and has become a major cause of death among patients with liquid tumors. Although invasive *Aspergillus* infections usually occur via inhalation of conidia, the fungus is also frequently present on food (i.e., pepper, regular and herbal tea bags, fruits, corn, and rice). The thermotolerant spores of *Aspergillus* and other fungi present are difficult to eradicate, and represent a threat to the immunocompromised host. Conidia that fail to be cleared by alveolar macrophages germinate in the alveolar space, and hyphal forms invade the pulmonary parenchyma, with prominent vascular invasion and early dissemination (Figures 1 through 3).[12]

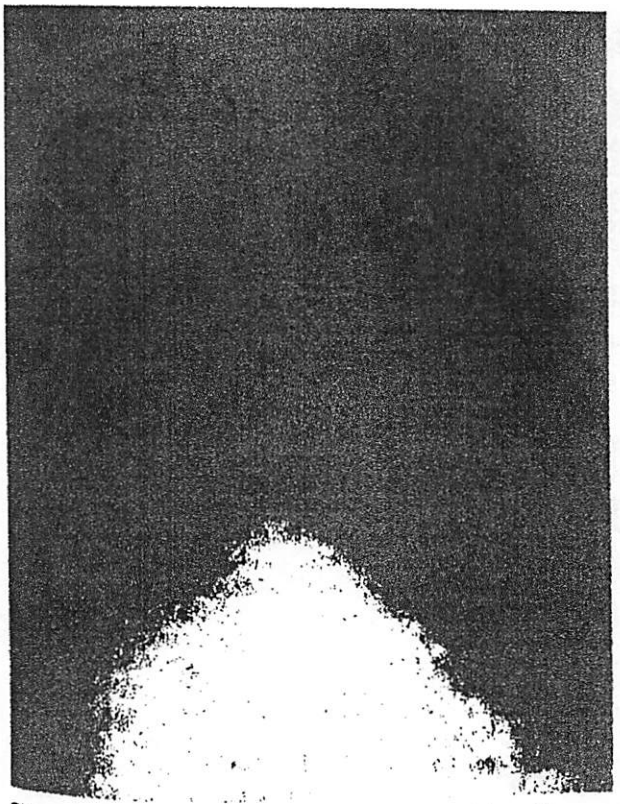

Figure 1 Chest x-ray of a patient with disseminated *Aspergillus* infection and pneumonia. The image is identical to that of acute respiratory distress syndrome. *(Courtesy of Smith-Singares E, Barie PS, Eachempati SR: The Anne and Max A. Cohen Surgical Intensive Care Unit, New York-Presbyterian Hospital-Weill Cornell Medical College.)*

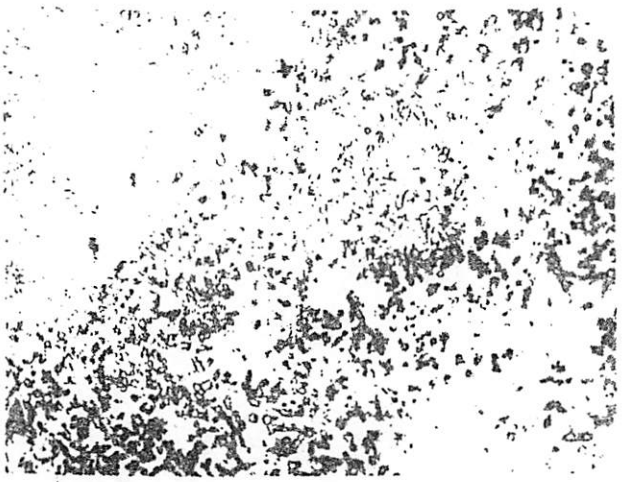

Figure 2 Microphotograph of invasive *Aspergillus* infection in the lungs of the patient in Figure 1. *(Courtesy Minick CR, Loyd E, Amin B: Department of Pathology and Laboratory Medicine, NewYork-Presbyterian Hospital-Weill Cornell Medical College.)*

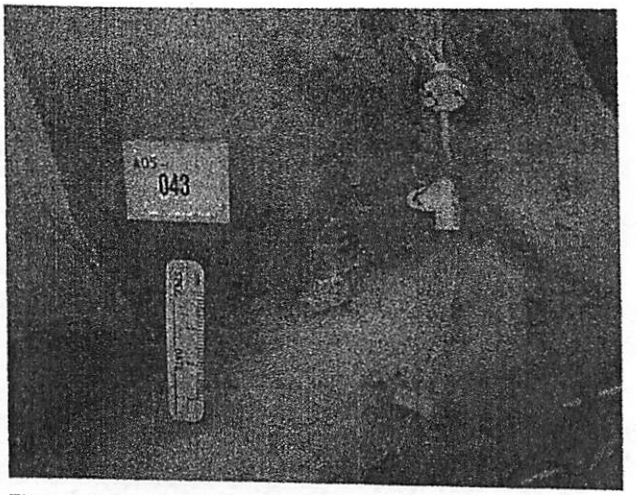

Figure 3 Purpura fulminans in a victim of hepatosplenic candidiasis. *(Courtesy Minick CR, Loyd E, Amin B: Department of Pathology and Laboratory Medicine, NewYork-Presbyterian Hospital-Weill Cornell Medical College.)*

Other Emerging Fungal Pathogens

Zygomycetes (mucor) are becoming increasingly important in ICU patients. The portal of entry in the immunocompromised host is usually inhalation of aerosolized, thermotolerant spores, although percutaneous exposure (i.e., surgical or traumatic wounds and burns) has been reported. The source of these spores is usually decaying organic matter in the soil, but they can be found in hospital food, including fruit, bread, sweet biscuits, regular and herbal tea, and pepper. The major risk factors for mucormycosis are diabetic ketoacidosis, neutropenia, iron overload, deferoxamine therapy, and protein-calorie malnutrition. Treatment includes surgical debridement, depending on the extent of the disease.

PRINCIPLES OF THERAPY

The past 10 years has seen a major expansion in the repertoire of antifungal agents with the introduction of less-toxic formulations of amphotericin B, improved triazoles, echinocandins, and other agents that

target the fungal cell wall. As described by Flanagan and Barnes, therapy for fungal infections in the ICU can be directed using four different strategies: prophylactic, preemptive, empiric, and definitive. Some data suggest a decrease in invasive fungal infections with prophylactic antifungal therapy in non-neutropenic critically ill surgical patients with *Candida* isolates from sites other than blood and the presence of risk factors mentioned previously. Others have suggested that use of antifungal prophylaxis in unselected SICU patients increases mortality, length of stay, and the appearance of resistance in previously susceptible fungi, not to mention the increase in cost this approach generates.[13] Prophylactic fluconazole treatment in the SICU leads to secondary mycoses, with up to 80% of the pathogens resistant to fluconazole.[14,15] Tables 1 and 2 and Figures 4 and 5 show one schema used in the SICU at NewYork-Presbyterian Hospital-Weill Cornell Medical Center. Independent of the species, infection by fluconazole-resistant *Candida* doubles the mortality rate. The colonization index developed by Pittet et al. and Ostrosky-Zeichner suggests that high-risk patients are those who remain in the ICU for 4 days or more and who either have a central venous catheter in place or are treated with antibiotics in addition to two of the following: use of total parenteral nutrition, need for dialysis, recent major surgery, diagnosis of pancreatitis, and treatment with systemic corticosteroids or other immunosuppressive agents.[15,16] Studies have documented the lack of benefit for fluconazole prophylaxis in unselected trauma patients, and in ICU patients, for whom the contribution of mortality by candidemia is surpassed by that of age and severity of illness.[17,18]

Table 3 presents a list of available antifungal agents. Amphotericin B is a natural polyene macrolide that binds primarily to ergosterol, the principal sterol in the fungal cell membrane, leading to disruption of ion channels, production of oxygen free radicals, and apoptosis. It is active against most fungi, including in cerebrospinal fluid. Due to its high level of protein binding, tissue concentrations are not usually affected by hemodialysis. Infusion-related reactions can occur in up to 73% of patients with the first dose and often diminish during continued therapy. Amphotericin B–associated nephrotoxicity can lead to azotemia and hypokalemia, although acute potassium release with rapid infusion can occur and lead to cardiac arrest. Amphotericin B lipid formulations allow for higher dose administration with lessened nephrotoxicity, but whether outcomes are enhanced is unproved. Nystatin is a polyene similar in structure to amphotericin B, and is currently used topically for *C. albicans*. A parenteral formulation is under investigation. Flucytosine is a fluorinated pyrimidine analog that is converted to 5-fluorouracil, which causes RNA miscoding and inhibits DNA synthesis. It is available in the United States in oral form only and has been used with amphotericin B for synergism against *Candida* spp.

The azoles inhibit the cytochrome P_{450}–dependent enzyme, 14-alpha reductase, altering fungal cell membranes through accumulation of abnormal 14-alphamethyl sterols. Ketoconazole comes only in tablet form and is indicated for candidiasis and candiduria. Fluconazole and itraconazole are available in oral and parenteral formulations and are active against *Candida* spp. except *C. krusei*, and *Fusarium* spp. Itraconazole is active against *Aspergillus* spp. As mentioned previously, *C. glabrata* and *C. krusei* resistance has been seen with fluconazole. The tissue concentration of both drugs is influenced by many agents such as antacids, H_2-antagonists, isoniazid, phenytoin, and phenobarbitol.

Table 1: Usual Susceptibilities of *Candida* Species to Selected Antifungal Agents

Candida spp.	Fluconazole	Itraconazole	Voriconazole (not standardized)	Amphotericin B	Caspofungin (not standardized)
C. albicans	S	S	S	S	S
C. tropicalis	S	S	S	S	S
C. parapsilosis	S	S	S	S	S to I (?R)
C. glabrata	S-DD to R	S-DD to R	S to I	S to I	S
C. krusei	R	S-DD to R	S to I	S to I	S
C. lusitaniae	S	S	S	S to R	S

I, Intermediate; *R*, resistant; *S*, susceptible; *S-DD*, susceptible-dose dependent (increased MIC may be overcome by higher dosing, such as 12 mg/kg/day fluconazole).

Modified from Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ, Edwards JE: Guidelines for treatment of candidiasis. *Clin Infect Dis* 38(2): 161–189, 2004.

Table 2: Approximate Antifungal Daily Costs, 2005

Antifungal	Approximate Cost/Dose	Usual Adult Dose	Approximate Cost/Day
Fluconazole 400 mg IV	$30	400 mg IV daily	$30
Fluconazole 400 mg PO	$1	400 mg PO daily	$1
Itraconazole 200 mg PO solution	$17	200 mg PO twice daily	$34
Voriconazole 400 mg IV	$195	400 mg IV twice daily (load)	$390
Voriconazole 280 mg IV	$136	280 mg IV twice daily (maintenance)	$272
Caspofungin 70 mg IV	$440	70 mg IV daily (load)	$440
Caspofungin 50 mg IV	$345	50 mg IV daily (maintenance)	$345
Amphotericin B conventional 70 mg IV	$26	70 mg IV daily	$26
Amphotericin B lipid (Abelcet®)	$292	350 mg IV daily	$292

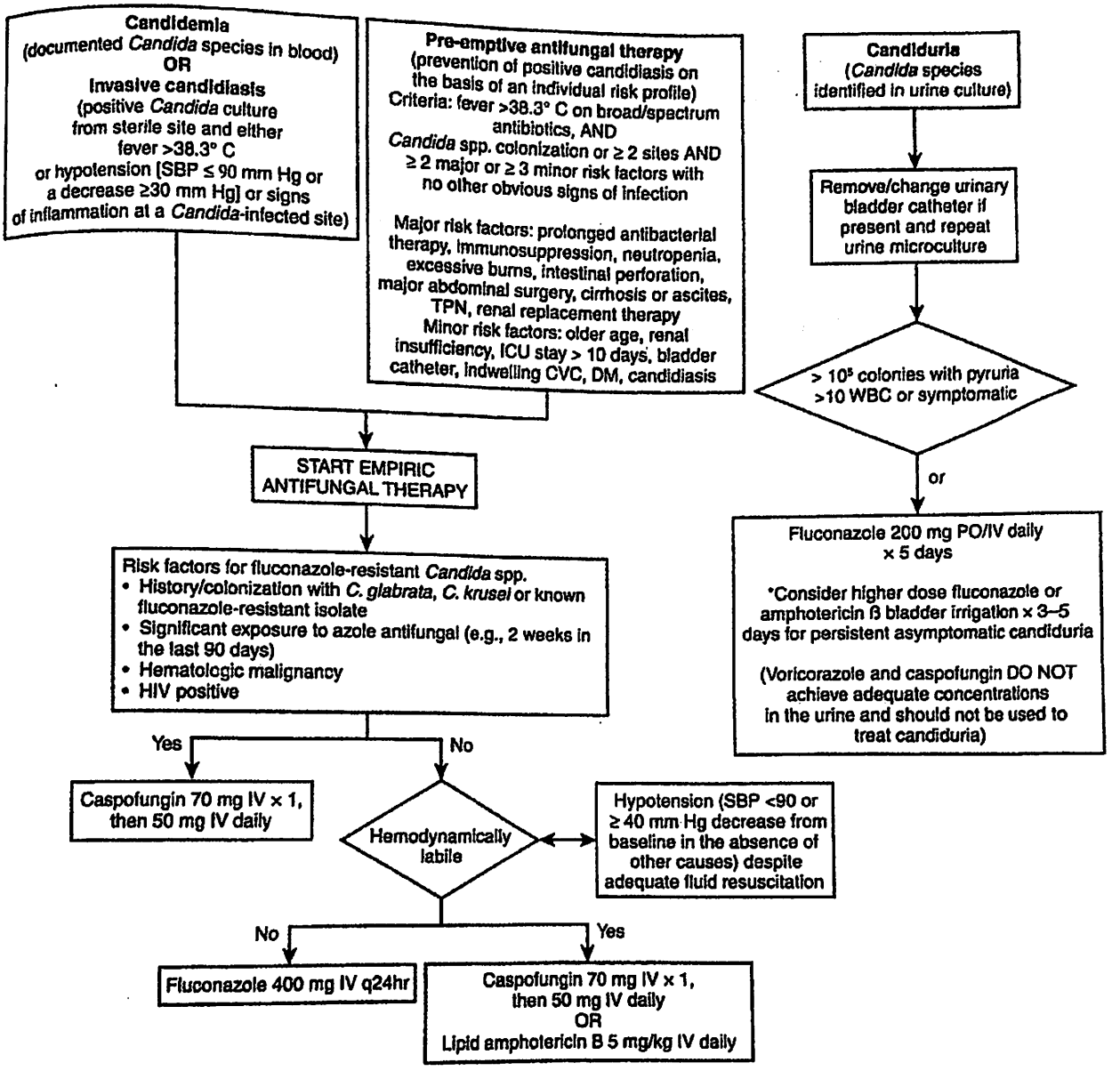

Figure 4 Antifungal therapy for the treatment of infections caused by *Candida* species in adult patients.

Second-generation antifungal triazoles include posaconazole, ravuconazole, and voriconazole. They are active against *Candida* spp., including fluconazole-resistant strains, and *Aspergillus* spp. For the latter, voriconazole is emerging as the treatment of choice.[19,20]

The echinocandins include caspofungin, micafungin, and anidulafungin, each of which is approved therapy for candidiasis and candidemia, but third-line treatment for invasive aspergillosis. Due to their distinct mechanism of action, disrupting the fungal cell wall by inhibiting β(1,3)-D-glucan synthesis, the echinocandins can theoretically be used in combination with other standard antifungal agents. The echinocandins have activity against *Candida* spp. and *Aspergillus* spp., but are not reliably active against other fungi. Echinocandin activity is excellent against most *Candida* spp., but moderate against *C. parapsilosis*, *C. guilliermondi*, and *C. lusitaniae*. Echinocandins exhibit no cross-resistance with azoles or polyenes.[21]

Invasive fungal infections in non-neutropenic ICU patients are treated if histology or cytopathology show yeast cells or pseudohyphae from a needle aspiration or biopsy (excluding mucous membranes), a positive culture obtained aseptically from a normally sterile and clinically or radiologically abnormal site consistent with infection (excluding urine, sinuses, and mucous membranes), or positive percutaneous blood culture in patients with temporally related clinical signs and symptoms compatible with the relevant organism.

Neutropenic Patients and Preemptive Therapy

A novel approach in the use of antifungal therapy in patients who do not exhibit clinical evidence of systemic candidiasis is the concept of preemptive therapy.[16] Being more than just semantics, prophylaxis is defined as treatment triggered by risk stratification (thus directed at patients with "possible" fungal infection), whereas preemptive therapy is the early treatment of identified infection, without clinical signs, detected by the use of surrogate markers or

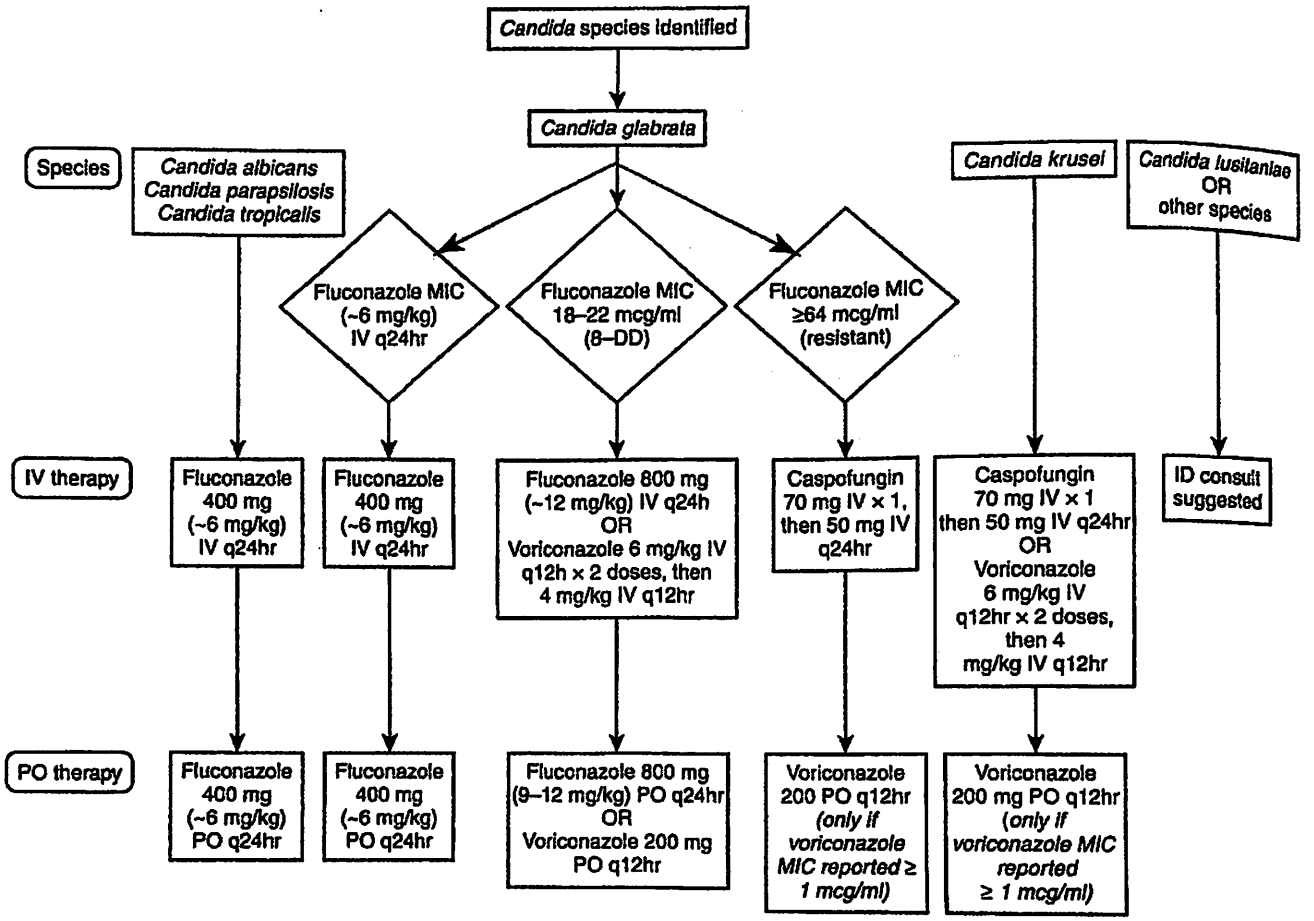

Figure 5 Treatment algorithm when *Candida* spp. are identified.

non–culture-based methods. The appeal of preemptive therapy (for patients with "probable" fungal infection) is that it theoretically combines the best of the evidence for fungal prophylaxis with the benefits of early treatment, mitigating against the increase in fungal resistance and recovery of resistant strains. Given that there is little evidence that prophylactic use of fluconazole confers benefit in the management of nonfebrile neutropenic patients, the development of new protocols using frequent surveillance and screening (instead of therapy) for patients at high risk is imperative.

Antifungal Prophylaxis in Solid Organ Transplant Recipients

Invasive fungal infections remain a frequent complication among the recipients of solid organs. The risk is greater during the early post-transplant period, decreasing after six months from the date of the operation. Liver transplantation carries the highest risk, followed by heart and lung. Other risk factors have been identified, including hepatic and renal dysfunction, retransplantation, rejection, surgical complications, and CMV infections. Fluconazole is effective for prevention of invasive fungal infections, but without any reduction in mortality. In liver transplant patients, the number necessary to treat (NNT) in order to prevent one infection is 14, given an incidence of 10%. Meta-analysis also concluded that, for lower-risk recipients (i.e., renal homograft recipients), the NNT increases to 28. Prophylaxis should be reserved for those patients with a higher stratified risk and in settings where fungal complications are highly prevalent. For those immunosuppressed patients who have developed a noncandidal systemic fungal infection, prolonged suppressive antifungal therapy may be required to prevent a relapse.

Acquired Immunodeficiency Syndrome and Empiric Antifungal Therapy

The incidence of invasive candidiasis is low in the acquired immunodeficiency syndrome (AIDS), which is surprising considering the almost ubiquitous presence of mucocutaneous candidiasis in HIV-infected patients. This underscores that the host defense mechanisms required for resistance against mucocutaneous and invasive candidiasis are different. Therefore, patients who develop AIDS and associated *Candida* infections frequently have additional risk factors, such as parenteral nutrition catheters, broad-spectrum antibiotics, or neutropenia due to HIV-related lymphoma or cytotoxic therapy. The use of empiric fluconazole for these patients is not cost effective, and should be discouraged.

Therapy Tailored to Specific Risk Factors and Likely Offending Organisms

The New York–Presbyterian Hospital, Weill Cornell Medical Center has developed algorithms and guidelines for the use of antifungal agents (see Tables 1 and 2, Figures 4 and 5) based on epidemiological considerations. Table 3 lists the antifungal agents most

Table 3: Antifungal Agents

Antifungal Agent	Indications	Routes/Dosage
Amphotericin B	*Candida albicans* (>95%) *C. glabrata* (95%), *C. parapsilosis* (>95%) *C. krusei* (>95%), *C. tropicalis* (99%) *C. guillermondi*; *C. lusitaniae* Variable activity: *Aspergillus* spp., ferrous *Trichosporon beigelii* *Fusarium* spp., *Blastomyces dermatidis*	IV: 0.5 mg/kg/day over 2–4 hours Oral: 1 ml oral suspension, swish and swallow 4× daily, times 2 weeks
Amphotericin B liposomal (less nephrotoxicity)	*C. albicans* (>95%), *C. glabrata* (>95%) *C. parapsilosis* (>95%), *C. krusei* (>95%) *C. tropicalis* (99%), *C. guillermondi*, *C. lusitaniae* Variable activity: *Aspergillus*	IV: 3–5 mg/kg/day
Amphotericin B colloidal dispersion (more infusional)	*C. albicans* (>95%), *C. glabrata* (>95%) *C. parapsilosis* (>95%), *C. krusei* (>95%) *C. tropicalis* (99%), *C. guillermondi*, *C. lusitaniae* Variable activity: *Aspergillus*	IV: 3–4 mg/kg/day
Amphotericin B Lipid Complex	*C. albicans* (>95%), *C. glabrata* (>95%) *C. parapsilosis* (>95%), *C. krusei* (>95%) *C. tropicalis* (99%), *C. guillermondi*, *C. lusitaniae* Variable activity: *Aspergillus*	IV: 5 mg/kg/day
Ketoconazole	*C. albicans*	PO: 200–400 mg/daily
Voriconazole	*Aspergillus*, *Fusarium* spp., *C. albicans* (99%) *C. glabrata* (99%), *C. parapsilosis* (99%) *C. tropicalis* (99%), *C. krusei* (99%), *C. guillermondi* (>95%) *C. lusitaniae* (95%)	IV: 6 mg/kg Q12 ×2, then 4 mg/kg IV every 12 hours PO: >40 kg, 200 mg every 12 hours <40 kg, 100 mg every 12 hours
Fluconazole	*C. albicans* (97%) *C. glabrata* (85%–90% resistant/intermediate) *C. parapsilosis* (99%) *C. tropicalis* (98%) *C. krusei* (5%) Fungistatic against *Aspergillus*	Candidiasis: Prophylaxis (IV or oral): 100–400 mg/day Invasive: 400–800 mg/day Oropharyngeal: 200 mg day 1, then 100 daily × 2 weeks
Itraconazole	Fungicidal to *Aspergillus*, *C. albicans* (93%) *C. glabrata* (50%), *C. parapsilosis* (45%), *C. tropicalis* (58%), *C. krusei* (69%), *C. guillermondi*, *C. lusitaniae* Blastomycoses, histoplasmosis, chromomycosis	IV: Load 200 mg IV 2× daily × 4 doses, then 200 mg 4× daily maximum 14 days Oral: 200 mg every daily or 2× daily Life-threatening: load 600–800/day × 3–5/days then 400–600 mg/day
Caspofungin	*C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, *C. guillermondi*, *C. lusitaniae*	IV: 70 mg IV, then 50 mg IV every day
Flucytosine	Not effective for *C. krusei* Effective for *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. lusitaniae*	PO: 50–150 mg/kg/day divided QID
Nystatin	*C. albicans*	100,000 units swish and swallow QID
Clotrimazole	Thrush	Oral troches 5× daily × 14 days

commonly in use in the United States. Several studies have demonstrated that azole antifungals have immunosuppressive activity in that imidazoles interfere with neutrophil and lymphocyte function. Ketoconazole has been used to attempt to reduce the frequency of the acute respiratory distress syndrome in high-risk patients, possibly as a thromboxane synthase inhibitor. Itraconazole and miconazole are potent inhibitors of 5-lipoxygenase. Fluconazole, which has no effect on plasma thromboxane and leukotriene concentrations, has been shown in animals and in vitro to augment the bactericidal activity of neutrophils, suggesting a possible role in treating patients with sepsis.

Fungi as an Epiphenomenon

Recent advances in critical care have produced a selected population of very ill individuals that in previous years would have succumbed to their disease processes. Many of these improvements in survival have preceded (and in some cases paralleled) the explosive growth of fungal colonization and infection in ICU patients, and the availability of antifungal therapy. As antibiotic choice has become more complex and resistance has developed, so too has the complexity of fungal infections and the expanded multimodality therapy. Whereas there is little argument that invasive fungal infections are associated

with increased mortality, morbidity, and length of stay (both in the ICU and hospital), the mortality attributable to these infections remains controversial. More problematic is the fact that, although antifungal prophylaxis is effective in preventing fungal colonization and invasive infections, this does not translate into a difference in mortality. Data on length of stay are also contradictory, with staunch supporters for both sides of the debate. Localized fungal infections and colonization have different natural histories depending on the severity of illness, but they remain predictors of invasive infection in very ill patients as defined by higher APACHE scores.

SUMMARY

Fungal infections are increasingly prevalent among ICU patients. The most common offending fungi are *C. albicans*, other *Candida* spp., and *Aspergillus* spp. Therapy should be directed toward patients' specific risk factors, but the use of antifungal prophylaxis is controversial. Empiric antifungal therapy is discouraged in non-neutropenic patients, as well as the treatment of isolated positive non-blood cultures.

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PREOPERATIVE AND POSTOPERATIVE NUTRITIONAL SUPPORT: STRATEGIES FOR ENTERAL AND PARENTERAL THERAPIES

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Nutritional support is an integral part of trauma and critical care management. Its role has undergone a dramatic evolution over the past two decades as we have developed a deeper understanding of the complex inflammatory and metabolic pathways that accompany surgical stress. The manipulation of this stress response and its inherent catabolic reaction is the focus of emerging nutritional therapies.

MALNUTRITION

Malnutrition may be defined as a state of relative nutrient deprivation and metabolic perturbation that compromises host defenses and increases the risk of complications and death. For years, protein-calorie malnutrition has been characterized by weight loss, hypoalbuminemia, decreased skeletal muscle mass, reduced fat stores, and decreased total lymphocyte counts. In 1936, Hiram O. Studley first identified preoperative malnutrition as a specific operative risk factor in patients with peptic ulcer disease. He noted a ten-fold increase in mortality in patients who had lost over 20% of their body weight, and wondered if this might be reversible with a preoperative method for overcoming this deficit. Multiple studies performed since his time have confirmed that malnutrition results in poor wound healing, increased infection rates, and prolonged postoperative ileus with resultant lengthened hospital stays and increased mortality.