

# Topical nystatin powder in severe burns: a new treatment for angioinvasive fungal infections refractory to other topical and systemic agents

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## Abstract

Angioinvasive fungal infections have a significant morbidity and mortality in the immunocompromised host. Massive burns produce a profound derangement in cellular immunity along with a loss of cutaneous barrier function. Treatment of fungal burn wound infections poses a difficult therapeutic challenge. We present a new method of treatment for angioinvasive fungal infections with nystatin powder at a concentration of 6,000,000 units/g. It proved to be efficacious in four consecutive severely burned patients affected by massive angioinvasive fungal infection. Both superficial and deep tissue infections were eradicated without any other therapeutic interventions or adverse effects on wound healing. © 1999 Elsevier Science Ltd and ISBI. All rights reserved.

*Keywords:* burns; *Aspergillus*; *Fusarium*; Nystatin

## 1. Introduction

Fungal infections in immunocompromised burned patients are associated with significant morbidity and mortality [1,2]. The prognosis for severely burned patients has improved in the last two decades. Broad-spectrum antibiotics have had a major role in the control of infections, but have also resulted in the emergence of fungi as prominent opportunistic pathogens [3]. Specifically, angioinvasive infections with *Fusarium* sp and *Aspergillus* sp are difficult to eradicate and are often refractory to conventional antifungal therapy. A marked decline in bacterial wound infection has occurred in the last decade, but fungal wound infection remains a constant threat. Candidiasis, a mycotic infection that has threatened our patients for decades is also declining. Factors that appear to have markedly reduced bacterial burn infection do not appear to have

a similar effect on fungal wound infection. The lack of effective topical chemotherapeutic antifungal agents may explain the prevalence and severity of fungal infections in burn patients [4]. Currently, the best treatment for fungal infections in burned patients is prevention. Identifying patients at risk and maintaining an environment free of fungal spores is extremely important. The treatment for angioinvasive fungal infections in burned patients include amphotericin B and excision of all affected areas. The former, though, is not effective in many instances, since an effective topical treatment to stop the progression of the infection is, at present, not available. Furthermore, susceptibility testing for filamentous fungi is tenuous and difficult to obtain. Determination of sensitivities under these circumstances may take days to weeks. When fungi appear to be resistant to the drugs currently used to treat the infections a systemic spread of the angioinvasive infection may result.

We describe a novel and effective method of topical treatment for angioinvasive fungal infections in severely burned patients.

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## 2. Patients and methods

Four consecutive patients admitted to the Shriners Burns Hospital in Galveston, Texas between March 1998 to September 1998 who presented with invasive fungal burn wound infections were treated with a new regimen of topical treatment with nystatin powder. All full thickness burns were excised within 24 hours after the admission to the burn center. Wounds were autografted with autografts harvested from any available donor site and the rest of the wounds homografted. Patients returned once a week to the operating theater for further autografting thereafter.

Biopsies of wounds were taken at every operative session and from any suspicious area detected on daily wound care. They were sent to the laboratory for quantitative bacteriology and histopathology examination to rule out invasion of bacteria or fungi to living tissues. Antibiotic and antifungal treatments were established accordingly to the results.

In order to test filamentous fungi for susceptibility, aliquots of concentrated antifungal drugs were prepared. Conidia and hyphal fragments from clinical isolates were harvested by washing the mature colonies of the moulds growing on potato dextrose agar with 0.9% sodium chloride solution and then transferring the suspension to a sterile tube. The concentration was adjusted to a 0.5 McFarland standard and counted with a hemacytometer. 0.1 ml of each of the fungal suspensions was inoculated to 0.5 ml of the antifungal aliquots, with an additional tube of sterile saline used as a control. After timed exposure of the inoculum in the aliquot for 5, 10, 15 and 30 min, 100 µl sample of each suspension was inoculated to 10 ml of Sabourand Dextrose Broth and an additional 10 µl into Brain Heart Infusion Agar Plates. Plates and broth were incubated at 30°C and examined once each day. They were kept until 30 days of incubation had passed.

The treatment with nystatin powder was performed as follows. Topical nystatin powder (6,000,000 units/g; Pharma-Tek, Inc, Huntington, NY 11743) was dusted to the area affected. Approximately four to six gram of powder were dusted per extremity affected with care that the powder was uniformly dispensed. Next, a wet to dry dressing with normal saline was applied. The dressing was then changed every six hours with a new application of nystatin powder before the application of the wet to dry dressing.

Procedural pain and anxiety associated with the wet to dry dressing changes was managed with a regimen that included IV morphine sulfate (0.03 mg/kg per dose) and IV lorazepam (0.03 mg/kg per dose).

Data collected included demographics, hospital course, pain and side effects of the treatment, wound healing and outcome.

## 3. Results

The mean age of patients was  $6.5 \pm 2.1$  years and total body surface full thickness burns  $72 \pm 4.5\%$  (mean  $\pm$  SEM). All patients presented in common a large burn size and a delay in the excision of all full thickness burns (patients were initially treated in another facility). On admission to our facility, patients underwent fascial excision of all full thickness burns and the excised areas were treated with auto and homografting. Intraoperative biopsies from the four patients showed invasive fungal infection. Subsequent microbiology cultures grew *Fusarium* sp in three cases and *Aspergillus* sp in the fourth case. Persistent tissue invasion was observed in patients despite aggressive surgical excision, which included amputation of extremities in two patients and systemic treatment with amphotericin B and itraconazole. Susceptibility testing of filamentous fungi showed resistance to amphotericin B, intermediate sensitivity to azoles and intermediate resistance to nystatin at usual concentrations of 100,000 units/g. Due to the progression of the disease, sensitivity patterns and the ominous prognosis of all cases, surgical treatment was stopped and topical nystatin powder application (6,000,000 units/g) with wet to dry dressings was initiated. Systemic antifungal treatment with amphotericin B was stopped and itraconazole continued. During the following two weeks, a continuous improvement of the wound was observed in all cases, with negative cultures and no pathology findings at the end of this period. Previously autografted areas healed nicely under the application of the nystatin powder and open wounds granulated quickly and were successfully autografted. All patients were discharged home in good condition with negative cultures. Patients did not experience pain with the direct application of the nystatin powder and minimal discomfort was noted with dressing changes.

## 4. Discussion

Significant advances have been made in recent years in the treatment of neoplastic diseases, prevention of graft rejection in transplant patients and trauma and burn treatment. This has resulted in an increased number of patients affected by an immunocompromised system, which results are much more susceptible to opportunistic infections. Depletion of the number of neutrophils, defects in neutrophil function and T-cell defects all predispose the host to fungal infections. Aspergillosis and hyalohyphomycosis (specifically *Fusarium*) are the most common angioinvasive fungal infections in burn patients.

Aspergillosis, a spectrum of diseases caused by the genus *Aspergillus*, includes toxicosis, allergy, coloniza-

tion and invasion. Aspergilli are widely distributed in nature, in soil, on decomposing vegetation and in dust. Aspergilli have a marked tendency to invade blood vessels producing thrombosis. Dissemination from a colonized wound is not rare and often fatal. Systemic amphotericin B is the treatment of choice.

Fusariosis, an hyalohyphomycosis caused by *Fusarium*, shows a weaker tendency to invasion. It normally only occurs in the compromised host. Species of *Fusarium* are ubiquitous in nature, occurring in water as saprophytes in the soil, on decaying vegetation and as plant pathogens. Amphotericin B is also the drug of choice.

In both fungal infections, excision, when possible, of the affected area, appears to be the most effective therapy. Nevertheless, in all our four cases, excision of the infected areas was not effective, with subsequent progression of the fungal invasion. What is more, cultures showed resistance to amphotericin B and intermediate resistance to other antifungal agents, so all therapies prior to the application of topical nystatin powder failed to stop the disease.

In this series of severely burned children affected by angioinvasive fungal infection, the topical treatment of the wounds with nystatin powder at a concentration of 6,000,000 units/g, proved to be effective in eradicating the invasive fungal infections. This new regimen of topical treatment not only is effective superficially but also eradicates invasive clusters of fungi in deep wound tissues, as documented by pathological examination. The application of the powder is easy and it did not produce pain or discomfort. It did not impair wound healing and all previously autografted areas healed uneventfully.

Nystatin is an antifungal antibiotic that is both fungistatic and fungicidal in vitro. It acts by binding to sterols in the cell membrane of the fungus with a resultant change in permeability. It is a polyene antibiotic obtained from *Streptomyces noursei*. It exhibits no appreciable activity against bacteria. Nystatin is virtually nontoxic and non-sensitizing and is well tolerated by all age groups. This antifungal is not absorbed by the skin or mucosa, but low local absorption is possible in open wounds. This point may explain the success of the present treatment in our patients. Although the fungi presented with intermediate sensitivity to nystatin, the dosage used was by far higher than that tested. Direct application might have helped to stop the progression of the infection in the wound, as a result of the agent's fungistatic and fungicidal properties. We believe that the former, along with the continuation of the systemic itraconazole therapy and the slow improvement of the immunologic response of the patients helped to overcome these aggressive and often lethal infections.

Angioinvasive fungal infections in severely burned

patients are often fatal [1,2]. Different therapeutic approaches have been tried in the management of mycosis in burn patients. The mixture of nystatin with silver sulfadiazine [5] and the administration of nystatin solution as 'swish-and-swallow' [6] produced an important decrease in the rate of candida infections during the last decade. Nevertheless, the rate of fungal infections remains unchanged. Other therapies, such as wound irrigation with a solution of mafenide hydrochloride plus nystatin both during and after the operation, proved to have some effect in the prevention of fungal infections [2]. An appropriate topical agent effective against invasive fungal infections, however, has to be found.

The application of nystatin powder at high concentration was effective to stop the progression and eradicate the invasive fungal infection. Intraoperative biopsies, as determined by pathology examination at the time of excision, were positive for invasive fungal infection. The same areas were clear of infection by pathology findings and cultures two weeks later. No other treatments or surgical interventions were attempted during that period due to the ominous prognosis for the patients. The combination of histologic and mycologic studies in the evaluation of any suspicious wound is very important [7] and rapid frozen sections are necessary for establishing prompt treatment while awaiting definitive diagnosis.

Wounds healed without hindrance in the high nystatin concentration environment. Partially lost autografts healed quickly and open wounds granulated without complications. Boyce et al. found that a combination of nystatin (100 U/ml) with neomycin, mupirocin and polymyxin B was non toxic for topical use with cultured skin on burns [8]. In the present series of patients, nystatin was used alone and at a significantly higher concentration, but, clinically, wound healing was not impaired.

In conclusion, topical treatment with nystatin powder at a concentration of 6,000,000 units/g proved to be effective to eradicate invasive *Aspergillus* and *Fusarium* infections in scores of severely burned pediatric patients. It did not impair wound healing and no complications related to its use were found. Its use should be considered in the treatment of angioinvasive fungal infections refractory to other topical and systemic agents.

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