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World J Gastroenterol 2003;9(11):2619-2621
World Journal of Gastroenterology
 ISSN 1007-9327

• BRIEF REPORTS •

# Prevention and therapy of fungal infection in severe acute pancreatitis: A prospective clinical study

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**Received:** 2003-05-10 **Accepted:** 2003-06-02

## Abstract

**AIM:** To investigate the prevention and therapy of fungal infection in patients with severe acute pancreatitis (SAP).

**METHODS:** Seventy patients with SAP admitted from Jan. 1998 to Dec. 2002 were randomly divided into garlicin prevention group, fluconazole (low dosage) prevention group and control group. The incidence of fungal infection, the fungal clearance and mortality after treatment were compared.

**RESULTS:** The incidence of fungal infection in garlicin group and fluconazole group was lower than that in control group (16 % *vs* 30 %, $P<0.05$ and 9 % *vs* 30 %, $P<0.01$, respectively). Amphotericin B or therapy-dose fluconazole had effects on patients with fungal infection in garlicin group and control group, but had no effects on patients with fungal infection in fluconzole group.

**CONCLUSION:** Prophylactic dosage of antifungal agents (garlicin or low dosage fluconazole) can reduce the incidence of fungal infection in patients with SAP. But once fungal infection occurs, amphotericin B should be used as early as possible if fluconazole is not effective.

He YM, Lv XS, Ai ZL, Liu ZS, Qian Q, Sun Q, Chen JW, Lei DX, Jiang CQ, Yuan YF. Prevention and therapy of fungal infection in severe acute pancreatitis: A prospective clinical study. *World J Gastroenterol* 2003; 9(11): 2619-2621
http://www.wjgnet.com/1007-9327/9/2619.asp

## INTRODUCTION

Severe acute pancreatitis (SAP) accounts for about 20 % of acute pancreatitis. With understanding of the natural course of SAP and advances in critical care medicine, most SAP patients can survive systemic inflammatory response syndrome and accompanying dysfunction of important organs such as the heart, lung, kidney, etc[1]. The major complication in the middle and later phases of SAP is infection, its incidence is 40-50 % and its mortality is 10-20 %. About 80 % of mortality at the later phase of SAP is caused by infection[2]. For the time being, drug resistant bacteria infection, especially fungal infection is obviously increasing, and has become one of the major difficulties in the treatment of SAP[3]. In order to prevent and treat the deep fungal infection of SAP, this clinical research was conducted on fungal infection prevention and treatment by adopting garlicin, fluconazole and amphotericin B for SAP patients admitted from Jan. 1998 to Dec. 2002.

## MATERIALS AND METHODS

### *Selection of cases*

The selected cases accorded with the clinical diagnosis criteria proposed by the Pancreas Surgery Group of the Chinese Medical Association in 1997[4], and were complicated with one of the following predisposing factors of deep fungal infections[5-8], such as gerontism, history of diabetes, dysfunction of one or more organs, non-iatrogenic fasting hyperglycemia ($\geqslant$9 mmol/L), central venous catheter, TPN, retaining urethral catheterization, operation, gastrointestinal fistula, ICU, breathing machine supported$\geqslant$5d, user of glucocorticoid$\geqslant$5d, administration of broad spectrum antibiotics$\geqslant$5d or super broad spectrum antibiotics (such as Tienam, etc.)$\geqslant$3d.

### *Groups and methods*

A total of 70 cases conforming to the above criteria were randomly divided into 3 groups. The garlicin group (25 patients) was given venous instillation of 120 mg garlicin one time per day plus routine treatment. The fluconazole group (22 patients) was given venous instillation of 100 mg fluconazole one time per day plus routine treatment. The control group (23 patients) received routine treatment only. The prophylactic medication for the garlicin and fluconazole groups was applied until relief of the predisposing factors (except gerontism and history of diabetes). The fungal infection treatment protocol was applied when the patients showed signs of deep fungal infection. The clinical data of these three groups are shown in Table 1.

### *Monitoring*

Smears from peritoneal permeated liquid, pus of the infected wounds, throat specimen, sputum, urine and stool were prepared for fungus detection or/and fungal cultivation 2 times per week. If there was fungal infection, smears from the above sources were prepared for fungal identification 3 times per week. If the central venous catheter was suspected as the infection source, it was removed and cultured for fungi. Incidence and mortality of the patients with SAP complicated with deep fungal infection were observed.

### *Statistics analysis*

All data were analyzed with SPSS11.0 software package, and a $P$ value <0.05 was considered statistically significant. The average age, hospitalization duration, APACHE II grading etc, were displayed by $\bar{x}\pm s$, and differences were analysed using analysis of viariance and $F$ test. Sex, etiological factor, death, fungal infection and number of cleared fungi and other data were analyzed using $\chi^2$ or Fisher' s exact test.

**Table 1** General clinical data of three groups

| Group | Cases | | Age | Etiological factor | | | | APACHII |
|---|---|---|---|---|---|---|---|---|
| | Male: | Female | | Biliary | Alcoholemia | Injury | Others | |
| Garlicin | 12: | 13 | 51.4±15.2 | 14 | 6 | 1 | 4 | 11.8±3.8 |
| Fluconazole | 12: | 10 | 48.7±17.3 | 11 | 6 | - | 5 | 13.2±2.5 |
| Control | 13: | 10 | 50.5±20.1 | 11 | 7 | 1 | 4 | 11.6±4.7 |

There were no statistically significant differences in three groups.

## RESULTS

### *Incidence rate of fungal infection*

**Diagnostic criteria for SAP deep fungal infection**[5,6] Doubtful clinical manifestations were fever after the broad spectrum antibiotics treatment with no drug resistant bacteria infection, cough, glue-like mucus or blood streak sputum, pseudo-membrane of the oral cavity or oral ulceration and symptoms of urinary tract stimulation, diarrhea with brown or/and jam-like feces, consciousness changes with unknown reasons, or bleedings irrelevant to pancreatitis such as fistula bleeding of the biliary and digestive tracts.Pathogenic evidences of fungi included positive fungal cultivation of blood, central venous catheter, smears of the fine-needle aspiration before operation, aspiration ascites or necrotic pancreas tissue during the operation, and drained bile, samples of sputum, peritoneal permeated fluid, pus of the infected wounds, throat specimen, sputum, urine and stool. Deep fungal infection could be diagnosed according to the suspicious clinical manifestations together with the same fungi existed in two or more systems.

**Incidence rate of fungal infection** The SAP patients infected with fungi in the garlicin and fluconazole groups were obviously less than those in the control group, and the number infected by fungi was the fewest in the fluconazole group (Table 2).

**Table 2** Incidence rate of fungal infection in 3 groups

| Group | Cases | Rate of fungal infection | Times of fungal infection after SAP(d) |
|---|---|---|---|
| Garlicin | 25 | 4(16%)[a] | 39-57 |
| Fluconazole | 22 | 2(9 %)[b] | 35-62 |
| Control | 23 | 7(30 %) | 24-183 |

[a]$P<0.05$, [b]$P<0.01$ *vs* control.

### *Treatment results of fungal infection*

**Protocol of treatment** For highly suspicious pathogenic proofs of fungi or those with fungal infection, fluconazole was intravenous used to treat fungal infection, 200 mg (double dosage for the initial injection) once per day until the fungi were cleared. Amphotericin B was used for those with fungal infection in the fluconazole group. The dosage was started from 0.1 $mg.kg^{-1}$, and increased by 5 mg daily according to the patient's tolerance, and the treatment was continued till the dosage reached to 0.6 $mg.kg^{-1}$, the total accumulated amount reached 1.5-2 g. If the patients in garlicin and control groups were not sensitive to fluconazole, amphotericin B was then used.

**Treatment results** The fluconazole group had the lowest incidence of fungal infection, and the shortest hospital stay, but amphotericin B could not clear the fungi in fluconazole group, in which the patients were once complicated with fungal infection, they would inevitably died. When fungal infection occurred, the garlicin group had the highest clearance rate of fungi after treatment, and its mortality and average hospital stay were obviously lower or shorter than those in the control group. In the garlicin and control groups, each had one patient infected with fungi who was not cured by fluconazole therapy for 3 days, and their fungi were cleared when they changed to receive amphotericin B and they finally recuperated (Table 3).

**Table 3** Treatment results of fungal infection in 3 groups

| Group | Rate of fungal clearance | Mortality[#] | Times of Hospitalization |
|---|---|---|---|
| Garlicin | 3(75 %)[a] | 1(25 %)[a] | 48.1±30.7[a] |
| Fluconazole | - | 2(100 %) | 43.3±26.9[b] |
| Contrast | 4(57%) | 3(43 %) | 57.4±27.3 |

Note: # Mortality is the percentage (%) of patients who died of fungal septicemia. [a]$P<0.05$, [a]$P<0.01$ *vs* control.

## DISCUSSION

Deep fungal infection often occurs in patients with impaired immunity, e.g. diabetes, AIDS, malignant tumor and organ transplantation, etc. In recent years, the incidence of SAP deep fungal infection has obviously increased. Before routine administration of prophylactic antibiotics for SAP, the proportion of fungi was 7 % in the bacteria spectrum of SAP infection[9]. After that, the incidence of fungal infection in SAP has increased to 12-41 %[2,3,5,6,8,10-14], which has become an important cause for death and mutilation by SAP[3,5,6,8,10-14]. Since lack of specific manifestations, unrecongizability of symptoms, a long time for fungal cultivation, and apparent relevance between the fungal infection and prognosis, active and effective measures to prevent SAP deep fungal infection will contribute to further decreasing the mortality of SAP.

It has been reported[7] that prophylactic application of fluconazole in patients after bone marrow transplantation or chemotherapy could reduce the incidence of fungal infection. But there was not any systematic or prospective study in preventing SAP fungal infection. This study initially showed that prophylactic application of anti-fungi garlicin or fluconazole could significantly reduce the incidence of deep fungal infection of SAP patients who had some predisposing factors. Garlicin is cheap but good in quality, which not only has anti-fungi effects, but also anti-bacteria and anti-viral effects. The normal prophylactic dosage of garlicin is 1-2 $mg.kg^{-1}.d^{-1}$. With respect to prevention alone, fluconazole is better than garlicin, but we have noticed that once those who used fluconazole to prevent infection were indeed infected by fungi, their treatment might become more difficult and the prognosis was much worse. Once fungal infection occurred, an in-time use of fluconazole could quickly clear fungi, and significantly improve prognosis. Low dosage (100-150 mg/d) of fluconazole is often used in prevention while high dosage (200-600 mg/d) is often used in treatment.

About 80 % of the fungal strains in SAP fungal infection are candida[3,5,6,10-14]. Once fungal infection has been ascertained, anti-fungal drugs should be applied in time. Besides direct application of amphotericin B for mucor infection, fluconazole has be the priority for other fungal infections. Like maphotericin B[15], fluconazole has a good permeability in pancreas. If

fluconazole is not effective, it should change for amphotericin B in time or combined medication. In this research, two patients with fungal infection died in fluconazole group possibly due to delayed treatment besides drug resistance.

Deep fungal infection is different from shallow one, sometimes its diagnosis depends on biopsy, because it is hard to differentiate "passenger" bacterial parasites from real infection under many circumstances. As shown by autopsy statistics, only less than 20 % of the patients with fungal infection received anti-fungal treatment[16]. It is believed that for SAP patients, even "passenger" bacterial parasites may probably develop into infection, the finding of fungi in extra-peritoneal positions has provided clues to fungal infection within abdominal cavity, especially when fungi have been cultured from the peritoneal draining liquid. Hoerauf *et al*[12] reported that anti-fungi chemotherapy could increase survival rate. Aloia *et al*[11] suggested small dosage and short course amphotericin B treatment. Grewe *et al*[10] and Gotzinger *et al*[13] reported that although amphotericin B could quickly clear fungi, it could not improve prognosis. This might be related to the fact that anti-fungi treatment was only started when the blood cultivation became positive. The authors agree with Keiser' s viewpoint[17] that the failure of treatment was unable to be realized in time because the fungi were the pathogenic bacteria, instead they were often regarded as pollution and "passenger" in the infection course of surgery, therefore treatment was delayed.

SAP complicated with fungal infection could be classified into primary infection (fungus found in samples of fine-needle aspiration before operation or the first operation) and secondary infection (no fungus found in samples of fine-needle aspiration before operation or the first operation, and fungal infection happens later)[10,13]. In time clearing and draining of the necrotic tissues should be done for primary fungal infection, conservative treatment is mainly for the secondary infection, operation should be done actively if there is a fungal abscess formation. There is no special clinical manifestation in fungal infection, and repeated fungal cultivation on sputum, urine, stool and peritoneal permeated liquid and blood sample can contribute to in-time diagnosis and treatment. Zhang[18] reported that it was helpful to rapid diagnosis of fungal infection in patients with severe acute pancreatitis by PCR using universal primers targeting the 18s rRNA gene of fungus.

## REFERENCES


1 **Beger HG,** Rau B, Mayer J, Pralle U. Natural course of acute pancreatitis. *World J Surg* 1997; **21**: 130-135

2 **Ho HS,** Frey CF. The role of antibiotic prophylaxis in severe acute pancreatitis. *Arch Surg* 1997; **132**: 487-493

3 **Gloor B**, Muller CA, Worni M, Stahel PF, Redaelli C, Uhl W, Buchler MW. Pancreatic infection in severe pancreatitis: the role of fungus and multiresistant organisms. *Arch Surg* 2001; **136**: 592-596

4 **Pancreas Surgery Group of China Medical Association**. Clinical diagnosis and classify standard of acute pancreatitis. *Zhonghua Waike Zazhi* 1997; **35**: 773-775

5 **Lei RQ**, Liu W, Qu HP, Tang YQ, Yuan ZR, Han TQ, Zhang SD. Diagnosis and prophylaxis of fungi infection in severe acute pancreatitis. *Zongguo Shiyong Waike Zazhi* 1999; **19**: 544-545

6 **He YM**, Lu XS, Huang JH, Ai ZL, Liu ZS, Lei DX, Qian Q, Sun Q, Wang BY, Jiang CQ, Yuan YF. Fungal infection in severe acute pancreatitis (a report of 40 cases). *Zhongguo Putong Waike Zazhi* 2002; **11**: 135-138

7 **Edwards JE Jr**, Bodey GP, Bowden RA, Buchner T, de Pauw BE, Filler SG, Ghannoum MA, Glauser M, Herbrecht R, Kauffman CA, Kohno S, Martino P, Meunier F, Mori T, Pfaller MA, Rex JH, Rogers TR, Rubin RH, Solomkin J, Viscoli C, Walsh TJ, White M. International conference for the development of a consensus on the management and prevention of severe candidal infections. *Clin Infect Dis* 1997; **25**: 43-59

8 **Qin S**, Tang YQ, Qu HP, Liu W, Mao EQ. Study on the risk factors of fungal infection in severe acute pancreatitis. *Waike LiLun yu Shijian* 2001; **6**: 96-99

9 **Beger HG,** Bittner R, Block S, Buchler M. Bacterial contamination of pancreatic necrosis: A prospective clinical study. *Gastroenterology* 1986; **91**: 433-438

10 **Grewe M,** Tsiotos GG, Luque de-Leon E, Sarr MG. Fungal infection in acute necrotizing pancreatitis. *J Am Coll Surg* 1999; **188**: 408-414

11 **Aloia T**, Solomkin J, Fink AS, Nussbaum MS, Bjornson S, Bell RH, Sewak L, Mc Fadden DW. Candida in pancreatic infection: a clinical experience. *Am Surg* 1994; **60**: 793-796

12 **Hoerauf A,** Hammer S, Muller-Myhsok B, Rupprecht H. Intra-abdominal Candida infection during acute necrotizing pancreatitis has a high prevalence and is associated with increased mortality. *Crit Care Med* 1998; **26**: 2010-2015

13 **Gotzinger P**, Wamser P, Barian M, Sautner T, Jakesz R, Fugger R. Candida infection of local necrosis in severe acute pancreatitis is associated with increased mortality. *Shock* 2000; **14**: 320-324

14 **Isenmann R**, Schwarz M, Rau B, Trautmann M, Schober W, Beger HG. Characteristics of infection with Candida species in patients with necrotizing pancreatitis. *World J Surg* 2002; **26**: 372-376

15 **Shrikhande S**, Friess H, Issenegger C, Martignoni ME, Yong H, Gloor B, Yeates R, Kleeff J, Buchler MW. Fluconazole penetration into the pancreas. *Antimicrob Agents Chemother* 2000; **44**: 2569-2571

16 **Du B**, Zhang H, Chen D. Invasive fungal infection in 3447 autopsy cases. *Zhonghua Yixue Zazhi* 1996; **76**: 352-354

17 **Keiser P,** Keay S. Candidal pancreatic abscesses: report of two cases and review. *Clin Infect Dis* 1992; **14**: 884-888

18 **Zhang WZ**, Han TQ, Tang YQ, Zhang SD. Rapid diagnosis of fungal infection in patients with acute necrotizing pancreatitis by polymerase chain reaction. *Asian J Surg* 2002; **25**: 209-213


**Edited by** Zhang JZ and Wang XL