Review

Pro/con debate: Antifungal prophylaxis is important to prevent fungal infection in patients with acute necrotizing pancreatitis receiving broad-spectrum antibiotics

Philippe Eggimann[1], Saurabh Jamdar[2] and Ajith K Siriwardena[2]

[1]Department of Intensive Care Medicine and Burn Unit, Interdisciplinary Department for Support and Technics, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland
[2]Hepatobiliary Surgery Unit, Department of Surgery, Manchester Royal Infirmary, Manchester, UK

Corresponding author: A Siriwardena, Ajith.Siriwardena@CMMC.nhs.uk

Published: 7 September 2006
This article is online at http://ccforum.com/content/10/5/229

Critical Care 2006, **10:**229 (doi:10.1186/cc5025)

Abstract

When critically ill patients with pancreatitis develop infection of the pancreas, the ongoing management of such patients becomes difficult. Sufficient evidence supports the use of broad-spectrum antibiotic prophylaxis to prevent the development of bacterial infection. Since fungal infection is also a relatively common complication of severe pancreatitis – particularly when broad-spectrum antibiotics are used – it seems logical that fungal prophylaxis may be an important component of management. In this issue of *Critical Care*, two expert groups debate the merits of antifungal prophylaxis in patients with acute necrotizing pancreatitis who are receiving antibiotics.

The scenario

A 47 year old male presents to your intensive care unit with evidence of severe pancreatitis. He develops multi-organ failure, including the need for intubation/mechanical ventilation, inotropes and dialysis. Although the cause of his pancreatitis is not clear, there is evidence of pancreatic necrosis on abdominal imaging. As a result you start broad-spectrum antibiotics and plan on-going management with the surgical team. Given that you understand these patients are at high risk for fungal infection, you wonder about the role of prophylactic antifungal agents.

Pro: Antifungal prophylaxis should be parallel to any antimicrobial prophylaxis

Philippe Eggimann

Acute pancreatitis is severe in only 20% of patients with the disease, but despite continuous advances in supportive treatments, the prognosis for these patients has not improved over the past decades. Necrosis of the pancreatic tissue develops early in 25% to 40% of patients, and for those who survive to an eventual initial multiple organ failure, mortality rates up to 60% have been linked to the high proportion of superinfections [1]. Gram-negative bacteria and fungi progressively colonize the bowel within the first two weeks of the disease and further translocate into necrotic tissues [2]. Bacterial and fungal infections have been documented in patients not exposed to prior antimicrobials at rates of 40% to 70% [3] and 5% to 8% [2,4,5], respectively. Infected pancreatic necrosis or, for some experts, a high suspicion of it requires aggressive surgical debridement, itself associated with further increased morbidity and mortality [6,7].

This vicious circle has prompted the testing of early antimicrobial prophylaxis in acute pancreatitis. The results of at least 12 studies suggest that morbidity and mortality are reduced when prophylaxis is restricted to the most severe cases. Despite considering the same data compiled in several meta-analyses and systematic reviews, experts and scientific organizations have drawn different conclusions and proposed contradictory guidelines [1,6,8]. Nevertheless, antimicrobial prophylaxis has become a standard practice in many institutions. In a UK survey performed in 1997, as many as 90% of surgeons prescribed it, as did, more recently, 73% of 329 members of the European chapter of the International Hepato-Biliary Association [9].

Candida has been found in 15% to 70% of infected necrotic tissues of patients requiring surgery, and these high proportions have been repeatedly related to prior antibiotic exposure, which promotes the overgrowth of unaffected micro-organisms [2,4,7]. In addition, pancreatic fungal infections may be associated with further increased morbidity and mortality [2,4,5,8].

The good safety profile and the excellent bioavailability of triazole compounds in pancreatic tissues make them good candidates for antifungal prophylaxis, but only limited data are

available for their use in severe acute pancreatitis [2,4,10]. In addition, the prophylactic trials in surgical patients that have been carried out have included only a few patients with pancreatitis. Indirect evidence of potential protection comes from trials testing selective digestive decontamination, in which lower candidiasis and mortality rates have been reported [5]. In a unique open randomised study, He and colleagues [11] investigated the effect of prophylaxis in a series of 73 severe acute pancreatitis cases. Compared to controls, garlicin and fluconazole reduced the rates of fungal infections from 30% to 16% ($p < 0.05$) and 9% ($p < 0.01$), respectively.

These data are clearly insufficient to support evidence-based recommendations about antifungal prophylaxis in acute pancreatitis. However, according to the preceding arguments, I would recommend adding antifungal prophylaxis with a triazole compound in any patients receiving antibacterial prophylaxis. This prophylaxis may not only prevent infection of necrotic pancreatic tissue, but also delay the need for surgery. As early surgery within the first 2 weeks has been associated with higher mortality rates, this may have an impact on the outcome of the patients [1,6]. Delayed surgery may allow a more conservative approach, with the use of a minimally invasive procedure, such as extra-abdominal lumbar retroperitoneal debridement on well circumscribed collections, for which promising preliminary results have been reported [6,7].

Con: Prevalence and risks of fungal colonisation of pancreatic necrosis

Saurabh Jamdar and Ajith K Siriwardena

Fungal colonisation of pancreatic tissue is a feared complication of severe acute pancreatitis. Invasive candidiasis can be associated with mortality rates in excess of 40% [12] and, once colonised, eradication of fungi from the poorly perfused peri-pancreatic tissues of the retroperitoneum may be difficult.

The risks of fungal colonisation of pancreatic necrosis are brought into focus in contemporary critical care practice as a result of recent trends in antibiotic use and trends in surgical debridement of infected necrosis. Several small randomised trials of antibiotic prophylaxis in severe acute pancreatitis [13-15] together with a meta-analysis [16] and a Cochrane systematic review [17] have indicated an improvement in outcome in those patients receiving antibiotics. This evidence has resulted in antibiotic prophylaxis being recommended in several published guidelines for the treatment of severe acute pancreatitis [8,18,19]. Although the Cochrane systematic review [17] concluded that there was no increased preponderance of fungal infection in patients in the treatment arms compared to placebo, this finding is not necessarily at odds with evidence of increased prevalence of fungal colonization in critically ill surgical patients and, recently, Isenmann and colleagues [5] demonstrated that prolonged antibiotic therapy was associated with a high incidence of Candida-infected pancreatic necrosis. The advent of antibiotic prophylaxis in the management of severe acute pancreatitis has probably also contributed to a significant shift in the profile of pathogenic organisms. The resistant flora encountered following such therapy include multi-resistant Gram-positive cocci, Gram-negative bacilli and fungi.

To date, no randomised trial has examined the role of antifungal prophylaxis in patients with severe acute pancreatitis and practice guidelines must thus be based on extrapolation of current evidence. The Ostrosky-Zeichner clinical prediction rule [20] defines patients with pancreatitis (with central lines and receiving broad spectrum antibiotics) as being at high risk for fungal colonisation. Incorporation of evidence from studies in parallel patient populations is central to the construction of a rational policy for severe acute pancreatitis and the recent detailed meta-analysis of fluconazole prophylaxis in critically ill surgical patients concluded that, although treatment was associated with lower fungal colonisation rates, there was no evidence of a reduction in mortality [21]. In data specific to acute pancreatitis, He and colleagues [11] from Hunan, China, demonstrated in a study of 70 patients that colonisation in individuals receiving fluconazole prophylaxis ($n = 22$) was 9% compared to 23 control patients in whom colonisation rates were 30%. A retrospective analysis of 46 patients with infected pancreatic necrosis demonstrated that the early administration of antifungal therapy (defined as at least 48 hours before surgical intervention) reduced subsequent fungal infection rates but not mortality [22].

Synthesising this evidence into a practical management algorithm would suggest that there are limited grounds for routine antifungal prophylaxis in patients with severe acute pancreatitis even if these patients are receiving antibiotic therapy. The subset of patients with on-going disease requiring prolonged critical care support, where antibiotic prophylaxis has transformed into specific broad-spectrum antimicrobial therapy and, in particular, where trans-abdominal percutaneous drains are in place (in addition to central venous catheters), can be regarded as a subset of critically ill patients with high on-going organ dysfunction scores where antifungal prophylaxis can be considered. Even in this setting, it must be acknowledged that there is little evidence that antifungal prophylaxis is associated with a reduction in mortality and, further, that this intervention may be associated with a higher incidence of resistant candidal species [21].

Pro's response: Both antimicrobial and antifungal prophylaxis should be restricted to a limited number of critically ill patients

Philippe Eggimann

I agree with the outstanding arguments of my opponent.

In addition, recent evidence further supports the generalisation of antimicrobial prophylaxis [23]. While waiting for the results of eventual large randomised studies, we need to propose a simplified pragmatic approach for the daily care of critically ill patients admitted for necrotizing pancreatitis.

Currently, according to the ecological impact of antimicrobial prophylaxis, antifungals should be considered for all patients receiving it. However, my second recommendation will be to strongly restrict both antimicrobial and antifungal prophylaxis to the subset of the most severely ill patients, carefully selected after extensive diagnostic workup [24].

Con's response: Antifungal prophylaxis does not reduce mortality in severe acute pancreatitis

Saurabh Jamdar and Ajith K Siriwardena

Dr Eggiman's key point is that co-prescription of an antifungal at the time of commencement of antibiotic prophylaxis may "delay the need for surgery". There is now broad consensus that surgical intervention for pancreatic necrosis should be deferred, if possible, during the first 21 days. However, there is no suggestion that antifungal therapy helps to defer intervention. In contrast, routine use of antifungal therapy is not only over-used but is likely to encourage the emergence of resistant species in precisely those patients who are eventually most likely to require specific antifungal treatment: patients with severe acute pancreatitis undergoing radiological or surgical intervention.

Competing interests

PE has collaborated on several industry-sponsored clinical trials since 1990. He has served on an advisory board and/or sponsorized meetings and/or lectures for B-Braun, Cook Critical Care, Lilly, Medex, Merck Sharp & Dohme-Chibret, Pfizer, Roche and Wyeth-Lederle.

References

1. Whitcomb DC: **Clinical practice. Acute pancreatitis.** *N Engl J Med* 2006, **354:**2142-2150.
2. Shanmugam N, Isenmann R, Barkin JS, Beger HG: **Pancreatic fungal infection.** *Pancreas* 2003, **27:**133-138.
3. Beger HG, Rau B, Mayer J, Pralle U: **Natural course of acute pancreatitis.** *World J Surg* 1997, **21:**130-135.
6. Beattie GC, Mason J, Swan D, Madhavan KK, Siriwardena AK: **Outcome of necrosectomy in acute pancreatitis: the case for continued vigilance.** *Scand J Gastroenterol* 2002, **37:**1449-1453.
7. Besselink MG, de Bruijn MT, Rutten JP, Boermeester MA, Hofker HS, Gooszen HG: **Surgical intervention in patients with necrotizing pancreatitis.** *Br J Surg* 2006, **93:**593-599.
8. Nathens AB, Curtis JR, Beale RJ, Cook DJ, Moreno RP, Romand JA, Skerrett SJ, Stapleton RD, Ware L, Waldmann CS: **Management of the critically ill patient with severe acute pancreatitis.** *Crit Care Med* 2004, **32:**2524-2536.
9. King NK, Siriwardena AK: **European survey of surgical strategies for the management of severe acute pancreatitis.** *Am J Gastroenterol* 2004, **99:**719-728.
4. De Waele JJ, Vogelaers D, Blot S, Colardyn F: **Fungal infections in patients with severe acute pancreatitis and the use of prophylactic therapy.** *Clin Infect Dis* 2003, **37:**208-213.
5. 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.
10. Shrikhande S, Friess H, Issenegger C, Martignoni ME, Yong H, Gloor B, Yeates R, Kleeff J, Büchler M: **Fluconazole penetration into the pancreas.** *Antimicrob Agents Chemother* 2000, **44:** 2569-2571.
11. 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:**2619-2621.
12. Eggimann P, Francioli P, Bille J, Schneider R, Wu MM, Chapuis G, Chiolero R, Pannatier A, Schilling J, Geroulanos S, *et al.*: **Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients.** *Crit Care Med* 1999, **27:**1066-1072.
13. Pederzoli P, Bassi C, Vesentini S, Camedelli A: **A randomised multicentre clinical trial of antibiotic prophylaxis of septic complications in acute pancreatitis with impenem.** *Surg Gynecol Obstet* 1993, **176:**480-483.
14. Sainio V, Kemppainen E, Puolakkainen P, Taavitsainen M, Kivisaari L, Valtonen V, Haapiainen R, Schroder T, Kivilaakso E: **Early antibiotic treatment in acute necrotising pancreatitis.** *Lancet* 1995, **346:**663-667.
15. Delcenserie R, Yzet T, Ducroix JP: **Prophylactic antibiotics in treatment of severe acute pancreatitis.** *Pancreas* 1996, **13:** 198-201.
16. Sharma VK, Howden CW: **Prophylactic antibiotic administration reduces sepsis and mortality in acute necrotizing pancreatitis: a meta-analysis.** *Pancreas* 2001, **22:**28-31.
17. Bassi C, Larvin M, Villatoro E: **Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis.** *Cochrane Database Syst Rev* 2003, **4:**CD002941.
18. Working party of the British Society of Gastroenterology; Association of Surgeons of Great Britain and Ireland; Pancreatic Society of Great Britain and Ireland; Association of Upper GI Surgeons of Great Britain and Ireland: **UK guidelines for the management of acute pancreatitis.** *Gut* 2005, **54(Suppl 3):**iii1-9.
19. Uhl W, Warshaw A, Imrie C, Bassi C, McKay CJ, Lankisch PG, Carter R, Di Magno E, Banks PA, Whitcomb DC, *et al.*; International Association of Pancreatology: **IAP Guidelines for the surgical management of acute pancreatitis.** *Pancreatology* 2002, **2:**565-573.

20. Paphitou NI, Ostrosky-Zeichner L, Rex JH: **Rules for identifying patients at increased risk for candidal infections in the surgical intensive care unit: approach to developing practical criteria for systematic use in antifungal prophylaxis trials.** *Med Mycol* 2005, **43:**235-243.
21. Shorr AF, Chung K, Jackson WL, Waterman PE, Kollef MH: **Fluconazole prophylaxis in critically ill surgical patients: a meta-analysis.** *Crit Care Med* 2005, **33:**1928-1935.
22. King NK, Siriwardana HP, Wood B, Siriwardena AK: **Trends in fungal colonization of pancreatic necrosis in patients undergoing necrosectomy for acute pancreatitis.** *HPB* 2005, **7:**120-123.
23. Moyshenyat I, Mandell E, Tenner S: **Antibiotic prophylaxis of pancreatic infection in patients with necrotizing pancreatitis: rationale, evidence, and recommendations.** *Curr Gastroenterol Rep* 2006, **8:**121-126.
24. Eggimann P, Garbino J, Pittet D: **Management of *Candida* species infections in critically ill patient.** *Lancet Infect Dis* 2003, **3:**772-785.