Antibiotic treatment in acute pancreatitis

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Abstract

Severe acute pancreatitis is characterized by a poor prognosis with local and systemic complications, high morbidity and mortality. From the morphological standpoint, almost all patients suffering from severe forms of acute pancreatitis present various degree of pancreatic necrosis. In these patients the occurrence of infection of pancreatic necrosis certainly represents a very important prognostic factor as it has worldwide accepted as the leading cause of death. In addition, the discovery of an infected necrosis represents a crucial point in the treatment of these patients as it is the only clear-cut shift from medical to surgical treatment in necrotizing pancreatitis. Over the last years, earlier and more precise identification of pancreatic necrosis together with availability of new classes of antibiotics with documented activity against the most commonly involved bacteria and able to reach in therapeutic concentration the pancreatic necrosis give us the opportunity to perform some important controlled clinical trials on antibiotic prophylaxis in necrotizing acute pancreatitis. The great majority of these studies showed the usefulness of a prophylactic regimen (using antibiotics such as fluoroquinolones and carbapenems) in terms of reduction of pancreatic and extrapancreatic infections in comparison with untreated controls. Nevertheless, some questions on this topic still present controversial aspects such as the antibiotic of choice, the duration of treatment, the possible opportunistic infections with fungi and/or resistant strains. Antibiotics may prove very useful in patients with documented infected necrosis and high anaesthesiological risk unfit for surgical debridement and drainage; some initial experiences show the possibility that antibiotic treatment may be curative without surgery in these selected cases.

Key words: acute pancreatitis, pancreatic necrosis, antibiotic prophylaxis, antibiotic treatment, fluoroquinolones, imipenem, meropenem.

Introduction

When we are talking about acute pancreatitis (AP) we are facing with two complete different diseases, i.e. mild and severe AP. Almost all patients with mild disease recovery within few days and they do not require any specific treatment, including antibiotics. For these patients, presenting with *edematous* form of AP, we can observe a spontaneous resolution of the disease; the main clinical problem consist of the correction of the etiological factor to avoid recurrences. On the contrary, severe AP presents a poor prognosis with local and systemic complications, high morbidity and mortality [1]. From the morphological standpoint, severe AP shows various degree of *pancreatic necrosis* in almost all cases. In a recent survey on AP in Italy (1184 patients prospectively enrolled in 2 years), severe forms represent the 14% only of all AP, but mortality (20%) and morbidity (47%) are almost completely confined in this form. Data from other series coming from Europe and USA shows a percentage of severe forms little bit superior – 15 to 25% – with a related mortality up to 50% [2-5]. In these patients the occurrence of pancreatic infection, that means *infection of pancreatic necrosis*, certainly represents a very important prognostic factor as it has worldwide accepted as the leading cause of death. On this context, infection of necrosis accounts for a major cause of death in the late phase of the disease, in general after the second week, when most deaths are the sequel of ongoing sepsis and septic multiple organ failure [6].

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Infection of pancreatic necrosis in severe AP

Pancreatic infection basically occurs in patients with AP presenting pancreatic or peripancreatic necrosis and/or fluid collections. Pancreatic necrosis become infected in a percentage ranging from 20 to 40% and, as a rule, a time dependent increase of the infection rate with the duration of the disease is registered (*Fig. 1*) [6,7]. Patients suffering from AP develop pancreatic infection mainly after the second week of the disease, whereas the most important complications within the first two weeks are the systemic complications related to the organ(s) failure. Our recent data based upon a prospective evaluation of 210 patients with AP observed in four years [8] showed that infection of necrosis developed in 18 of 75 patients (24%) with necrotizing forms. The occurrence of infection of necrosis represents a crucial point in the treatment of these patients as it is the only clear-cut shift from medical to surgical treatment in necrotizing pancreatitis [7,9]. The extent of pancreatic necrosis correlates with the incidence of its infection. As a consequence, strict monitoring of necrotic process, by means of contrast-enhanced computed-tomography and of fine-needle percutaneous aspiration of necrosis for bacteriological examination when clinical suspicion of infection arises, is required [10]. Recognition of bacterial strains at fresh-microscopy of the aspirated material or positive results of the cultural exam indicates surgical debridement as soon as possible.

Several pathways of bacteria into pancreatic necrosis have been described: a) hematogenous, *via* the blood circulation; b) ascending infection from the duodenum via the pancreatic duct; c) from the portal vein and the liver *via* the biliary duct system; d) transcolonic migration *via* the lymphatics [11]. The latter pathway is the most important with many *in vitro* and *in vivo* studies which clearly support this mechanism [1,6]. In AP a reduced gut motility secondary to some mediators such as nitric oxide is reported; this lead to alteration of intestinal microflora and to damage of mucosal barrier with increase of gut permeability (*Fig. 2*). In addition, the impairment of gut microcirculation, local ischemia, and a decrease of immune system response related to cytokine release enforce the mucosal barrier damage, thus leading to the translocation of intestinal bacteria into the bloodstream and to a secondary colonization of pancreatic necrosis. The occurrence that bacteria most frequently isolated from infected necrosis (*Tab. 1*) are mainly Gram-negative strains, typical of intestinal flora, strongly support this pathway. In the great majority of patients the infection is monomicrobial with anaerobes bacteria accounting for 15% of cases. In a recent paper [12] – *Tab. 2* – we reported monomicrobial flora in the

Figure 1. **Infection of pancreatic necrosis in severe acute pancreatitis: the incidence rate is a time dependent, and nearly 70% of this event occurs after the second week of the onset of the disease**

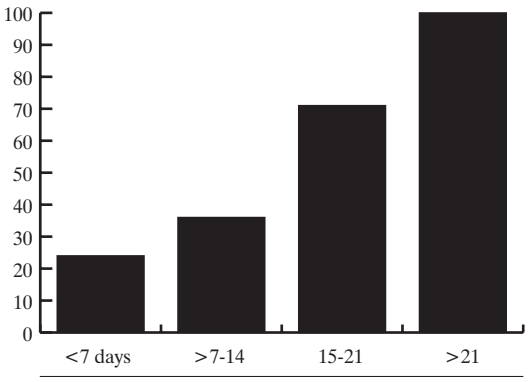


Table 1. **Spectrum of bacteria isolate in infected pancreatic necrosis: mean value from three large series** [16-18]

Monomicrobial flora	60-87%
Escherichia coli	25.9%
Pseudomonas aeruginosa	15.9%
Staphylococcus aeureus	15.3%
Klebsiella spp	10.1%
Proteus mirabilis	10.1%
Streptococcus faecalis	4.4%
Various anaerobes	15.8%

Figure 2. **Bacterial translocation pathway determines colonization of pancreatic necrosis during necrotizing acute pancreatitis (AP) from colon microorganisms (see text)**

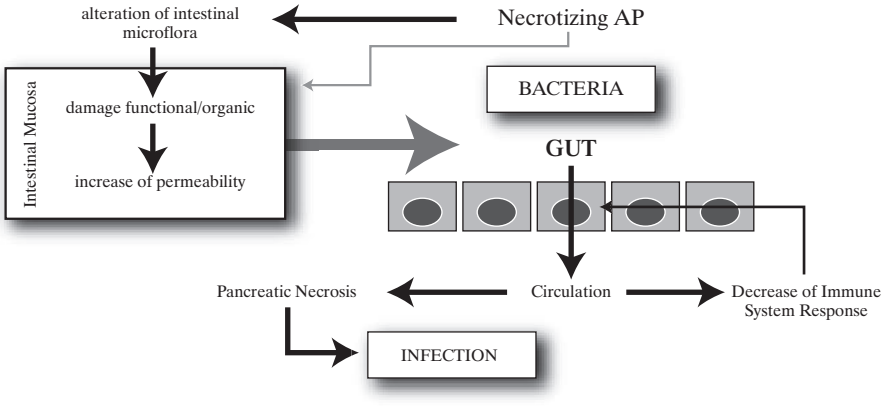


Table 2. **Microbiological isolates in 22 patients presenting severe acute pancreatitis complicated by infection of necrosis – personal experience** [12]

Monomicrobial flora	**17/22 (77.3%)**	
Polimicrobial flora	**5/22 (22.7%)**	
	• Escherichia coli	6
	• Pseudomonas aeruginosa	5
	• Enterococcus faecalis	4
	• Staphylococcus aeureus	3
	• Xanthomonas maltophilia	3
	• Klebsiella oxytocica	2
	• Enterobacteriacee	2
	• Proteus mirabilis	1
	• Streptococcus mitis	1
	• Bacillus species	1

Table 3. **Efficacy factor of various antibiotics in the prophylaxis of infection of pancreatic necrosis in severe acute pancreatitis (AP); efficacy factor represents the ratio between the bacterial spectrum covered and the pancreatic penetration, at least at the minimal inhibitory concentration; the maximum efficacy factor is 1**

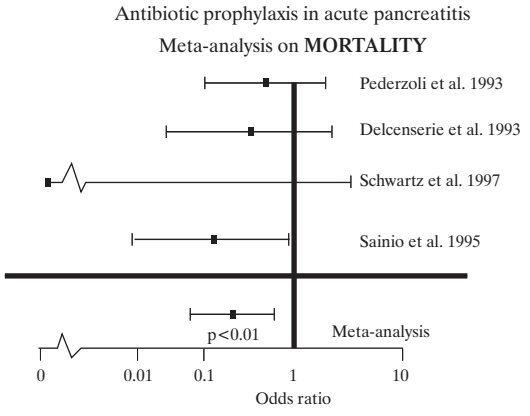
Antibiotics in AP	efficacy factor
Netilmicin	0.14
Tobramycin	0.12
Mezlocillin	0.71
Piperacillin	0.71
Cefotiam	0.75
Ceftizoxime	0.76
Cefotaxime	0.78
Ceftriaxone	0.79
Ciprofloxacin	0.86
Ofloxacin	0.87
Imipenem	0.98
Meropenem	0.98

77% of microbiological isolates from 22 patients with infected necrosis and stressed the clinical relevance of the occurrence of *Xanthomonas malthophilia* pancreatic infection (mortality of 100% in our experience). This Gram-negative organism belongs to the *Pseudomonas* family and it has the peculiarity of growth in plastic devices and of resistance to carbapenem antibiotics we currently use in the prophylaxis of infected necrosis.

Antibiotic prophylaxis to prevent infection of pancreatic necrosis

The history of prophylaxis of pancreatic infection starts near 40 years ago. Earlier studies do not indicate favourable effects on the outcome of AP [13-15]. We can today identify at least three reasons for these negative results: 1) all studies were carried out before the CECT era; as a consequence, no clear criteria were adopted to ascertain the presence of necrosis ant its stratification into two categories, i.e. sterile and infected, was lacking; 2) many of the included patients had edematous pancreatitis; 3) the authors utilize ampicillin that subsequent studies showed

Figure 3. **Meta-analysis on mortality resulted from data of four studies of antibiotic prophylaxis in severe acute pancreatitis** (see text for references)



to be unable to reach pancreatic necrosis. Starting from the 90' years a less empiric approach was utilised, on the basis of more precise identification of pancreatic necrosis, stratification of the disease severity, and deeper knowledge of prognostic relevance of pancreatic infection. In addition, and utmost important, new advances in antibiotic pancreatic penetration, especially during the acute phase of the disease, became available together with broad-spectrum antibiotics with documented pancreatic penetration at therapeutic *minimal inhibitory concentration* (MIC). On this context, today we have to talk about the **efficacy factor** of a specific antibiotic, that means a ratio between the bacterial spectrum covered and the pancreatic penetration, at least in MIC [16-18]. *Tab. 3* shows the efficacy factor of several antibiotics; keeping in mind that the maximum efficacy factor is 1, fluoroquinolones and imipenem present an efficacy factor clearly more advantageous than cephalosporin, ureidopenicillin, and aminoglucosides.

Over the last ten years many studies on antibiotic prophylaxis in AP have been performed. Some of these are single-centre studies [12,19-22], others are multicenter studies [23-29], others are meta-analysis researches [30-32]. Significant advantages on mortality in treated patients in comparison with controls were observed in the meta-analysis studies (*Fig. 3*). In particular, the recent *Cochrane review*, updated March 2003, concluded that there is "strong evidence that intravenous antibiotic prophylactic therapy for 10 to 14 days decreases the risk of superinfection of pancreatic necrosis (Odds ratio 0.51, p=0.04) and decreases mortality (Odds ratio 0.32, p=0.02)" [32]. A general consensus on the usefulness of antibiotic treatment in prophylaxis of infection of pancreatic necrosis in AP appeared in the recent literature as national or international recommendations or guidelines [33-40] – *Tab. 4*. Nevertheless, some questions on this topic require additional comments. The first one concerns the antibiotic of choice. The efficacy factor already discussed shows that the classes of carbapenems (*imipenem*, *meropenem*) and fluorochinolones (*pefloxacin*, *levofloxacin*) represent the best options. Within these two classes, one study from Bassi and co-workers [25] showed significant better results on infected necrosis and extrapancreatic infection rate and lower mortality

Table 4. **International guidelines and recommendations for the antibiotic prophylaxis in Acute Pancreatitis (Cat.: category of evidence)**

American College of Gastroenterology 1997 [33]
…it is reasonable to initiate antibiotic therapy in severe acute pancreatitis
British Society of Gastroenterology 1998 [34]
…there is some evidence to support the use of prophylactic antibiotics
Santorini Consensus Conference 1999 [35]
…prophylactic antibacterial treatment is strongly recommended in severe pancreatitis (Cat. A)
Italian Guidelines 1999 [36]
…antibiotic treatment is indicated in severe acute pancreatitis
German Guidelines 2000 [37]
…antibiotic prophylaxis is not generally recommended; indication could be necrotizing pancreatitis, severe acute pancreatitis (Cat. B)
World Congress Gastroenterology 2002 [38]
…antibiotic prophylaxis is advised in patients with greater 30% necrosis and imipenem is recommended currently (Cat. A)
Japan Guidelines 2002 [39]
…in severe and possibly severe acute pancreatitis broad-spectrum antibiotics should be used prohylactically (Cat. A)
International Association of Pancreatology 2002 [40]
…the use of prophylactic broad-spectrum antibiotics reduces infection rates in CT-proven necrotizing pancreatitis (Cat. A)

Table 5. **Results of a recent randomized trial of our group in which comparison of prophylactic treatment with meropenem vs imipenem was performed; all patients (n=176) suffering from severe necrotizing acute pancreatitis** [12]

	Meropenem	**Imipenem**
patients (n)	**88**	**88**
daily dosage (i.v.)	**500 mg x 3**	**500 mg x 4**
Necrosis <30/30-50/>50%	51/25/12	54/21/13
Infection of necrosis	10 (11.4%)	12 (13.6%)
Extrapancreatic sepsis	19 (21.6%)	13 (23.9%)
Multi-organ-failure	6 (6.8%)	8 (9%)
Systemic complications	30 (34.1%)	33 (37.5%)
Local complications	28 (31.8%)	30 (34.1%)
Surgery	15 (17%)	16 (18.1%)
Deaths	12 (13.6%)	10 (11.3%)
Hospitalization (days)	24 (7-90)	23.3 (6-80)

in patients treated with imipenem (29 cases) in comparison with the group of patients treated with pefloxacin (27 cases). Our group have recently published the results of another trial [12] in which imipenem treatment (2000 mg i.v./day) was compared with meropenem schedule (1500 mg i.v./day). Considering all series of patients (176 cases), we found subsequent infection of necrosis in a percentage of 12% only. This strongly confirms the opportunity of the antibiotic prophylaxis in these patients. No difference was observed between patients treated with meropenem and those treated with imipenem in terms of incidence of pancreatic infection, extrapancreatic infection and clinical outcome – *Tab. 5*. Meropenem resulted as effective as imipenem in preventing septic complications of patients with severe AP; one advantage resulted from the financial analysis as meropenem treatment, at the time of the study, resulted cheaper than imipenem one [12]. The second question about antibiotic prophylaxis in AP is related to the duration of treatment. No doubt exists as regards the opportunity to start the treatment as soon as possible but the its duration is less clear. In the clinical practice, treatment period isn't hardly ever shorter than three or four weeks, but some patients can require a longer time [35,41]. Another question arising on this topic concerns the possible occurrence of complications of antibiotic prophylaxis. Generally speaking, presumptive risk and problems of prophylactic antibiotic application still remain a controversial issue [42]. One aspect is related to a change into the bacterial spectrum and to a selection of resistant strains induced by a prolonged antibiotic treatment. Resistance of carbapenems was recently reported in limited series of patients with AP and it yielded a significant risk factor for a fatal outcome [43]. Another point regards a presumptive increase of the incidence of fungal infection, in particular of Candida infection [44,45]. The clinical significance in terms of severity of this occurrence has been likely overestimated [46]; the recent *Cochrane review*, updated March 2003 [32], concluded that there is not an increased preponderance of fungi infection with antibiotics (Odds 0.83, p=0.7). In our recent experience [12], we did not find fungi in 22 patients with documented infected pancreatic necrosis, also in 3 of them with *Candida albicans* colonization of central venous catheter. The last point requiring an additional comment on this field is related to the possibility of the enhancement of the power of antibiotic treatment by other medications. Olah and co-workers [47] have recently published the results of a randomised trial in whom early jejunal feeding combined with prophylactic imipenem showed significant better results (in terms of reduction of the septic complication rate) when compared with parenteral nutrition plus the same antibiotic regimen in patients with necrotizing AP. All the same, one can strongly speculate on the potential role of probiotics coupled with antibiotic prophylaxis and a randomised large trial on this topic seems to be timely today [48].

Antibiotic for the treatment of infected pancreatic necrosis

To the best of our present knowledge the discovery of infection of pancreatic necrosis in severe AP indicates a surgical approach as soon as possible; in general this means necrosectomy, debridement and multiple drainage catheters [1,3,5,9]. This option is efficacious and relatively safe but it can result less feasible in some patients presenting high anesthesiological risk for advanced age and/or severe co-morbidities [49,50]. On this context, the rising question could be: can the antibiotic therapy be *curative* in pancreatic necrosis already infected? While there is a general consensus regarding the usefulness of antibiotics for the prophylaxis in patients with severe AP, the role of antibiotics in the treatment of infection of pancreatic necrosis represents a controversial issue. Very few data are available in the literature [7,32,41] regarding this argument. Nordback and co-workers [22] report a very interesting results in a recent trial on the utilization of antibiotics (imipenem 3 g/day) for the prophylaxis

of pancreatic infection. They found a significant reduction of the pancreatic infection rate in the treated group (8% vs 42% of the control group) but, more interesting, 9 out of 14 patients without prophylaxis who develop an infection were cured with imipenem without surgical debridement. Our group also made a favourable experience on this topic. During the period January 1998 – December 2003 we observed 101 patients suffering from necrotizing AP with a mortality of 12.9% (13 patients). All patients were treated with prophylactic antibiotic; 24 of them (23.8%) develop infected necrosis and 20 out of 24 were operated on. So, four patients because of high anaesthesiological risk underwent medical treatment only, including three weeks of imipenem (two patients, 2 g/day i.v.) or meropenem (two patients, 1.5 g/day i.v.) treatment; favourable outcome was observed and morphological resolution registered in all patients at various interval time.

Conclusions

Many recent data indicates that patients with necrotizing AP may benefit from the application of a strict cardio-respiratory monitoring, sharp hydroelectrolytic and caloric supplementation and – last but not least – appropriate prophylactic antibiotic regimen. The usage of antibiotics able to reach the pancreatic necrosis and to cover the spectrum of bacteria most frequently involved is becoming a mandatory part of the treatments schedule all over the world. This represents a substantial step forward in the clinical practice as the overwhelming majority of clinical studies focused on the natural history and outcome of AP shows that bacterial infection of pancreatic necrosis is the leading cause of death in patients affected by this demanding disease.

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References

1. Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. Arch Surg, 1993; 128: 586-90.

2. Baron TH, Morgan DE. Acute necrotizing pancreatitis. N Engl J Med, 1999; 340; 1412-7.

3. Rau B, Pralle U, Uhl W, Schoenberg MH, Beger HG. Management of sterile necrosis in instances of severe acute pancreatitis. J Am Coll Surg, 1995; 181: 279-88.

4. Neoptolemos JP, Rarety M, Finch M, Sutton R. Acute pancreatitis: the substantial human and financial costs. Gut, 1998; 42: 886-91.

5. Gullo L, Migliori M, Olah A, Farkas G, Levy P, Arvanitakis C, Lankisch P, Beger HG. Acute pancreatitis in five European countries: etiology and mortality. Pancreas, 2002; 24: 223-7.

6. Bassi C. Infected pancreatic necrosis. Int J Pancreatol, 1994; 16: 1-10.

7. Buchler MW, Gloor B, Muller CA, Friess H, Seller ChA, Uhl W. Acute necrotizing pancreatitis: treatment strategy according to the status of infection. Ann Surg, 2000; 232: 619-26.

8. Uomo G, Cavallera A, Esposito P, Pacelli L, Visconti M, Rabitti PG. Extrapancreatic infections in acute pancreatitis – results of a prospective clinical study. Dig Liv Dis, 2002; 34: 824.

9. Uomo G, Visconti M, Manes G, Calise F, Laccetti M, Rabitti PG. Nonsurgical treatment of acute necrotizing pancreatitis. Pancreas, 1996; 12: 142-8.

10. Balthazar EJ, Ranson JH, Naidich DP, Megibow J, Caccavale R, Cooper MM. Acute pancreatitis: prognostic value of CT. Radiology, 1985; 156: 767-72.

11. Runkel N, Eibl G. Pathogenesis of pancreatic infection. In Buchler et al. (eds): Acute Pancreatitis: novel concepts in biology and therapy. Blackwell Science, Oxford, 1999: 255-61.

12. Manes G, Rabitti PG, Menchise A, Riccio E, Balzano A, Uomo G. Prophylaxis with meropenem of septic complications in acute pancreatitis: a randomized, controlled trial versus imipenem. Pancreas, 2003; 27: 79-83.

13. Craig RM, Dordal E, Myles L. The use of ampicillin in acute pancreatitis. Ann Intern Med, 1975; 83: 831-2.

14. Howes R, Zuidema GD, Cameron JL. Evaluation of prophylactic antibiotics in acute pancreatitis. J Surg Res, 1975; 18: 197-200.

15. Finch WT, Sawyers JL, Schenker S. A prospective study to determine the efficacy of antibiotics in acute pancreatitis. Ann Surg, 1976; 183: 667-71.

16. Bassi C, Pederzoli P, Vesentini S, Falconi M, Bonora A, Abbas H. Behavior of antibiotics during human necrotizing pancreatitis. Antimicrob. Agents Chemother, 1994; 38: 830-6.

17. Beger HG, Bittner R, Block S, Buchler MW. Bacterial contamination of pancreatic necrosis. A prospective clinical study. Gastroenterology, 1987; 91: 433-8.

18. Seiler CA, Uhl W, Friess H, Buchler MW. Strategies for antibiotic usage in acute pancreatitis. In: Buchler et al. (eds): Acute Pancreatitis: novel concepts in biology and therapy. Blackwell Science, Oxford, 1999; 283-90.

19. Sainio V, Kemppainen E, Puolakkainen P, Taavitsainen M, Kivisaari L, Valtonen V. Early antibiotic treatment in acute necrotising pancreatitis. Lancet, 1995; 346: 663-7.

20. Delcenserie R, Yzet T, Ducroix JP. Prophylactic antibiotics in treatment of severe acute alcoholic pancreatitis. Pancreas, 1996; 13: 198-201.

21. Schwarz M, Isenmann R, Meyer H, Beger HG. Antibiotic use in necrotizing pancreatitis. Results of a controlled study. Dtsch Med Wochenschr, 1997; 122: 356-61.

22. Nordback I, Sand J, Saaristo R, Paajanen H. Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis. A single-center randomized study. J Gastrointest Surg, 2001; 5: 113-8.

23. Pederzoli P, Bassi C, Vesentini S, Campedelli A. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. Surg Gynecol Obstet, 1993; 176: 480-3.

24. Luiten EJ, Hop WC, Lange JF, Bruining HA. Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis. Ann Surg, 1995; 222: 57-65.

25. Bassi C, Falconi M, Talamini G, Uomo G, Papaccio G, Dervenis C, Salvia R, Bertazzoni Minelli E, Pederzoli P. Controlled clinical trial of pefloxacin versus imipenem in severe acute pancreatitis. Gastroenterology, 1998; 115: 1513-7.

26. Takeda K, Matsuno S, Ogawa M, Watanabe S, Atomi Y. Continuous regional arterial infusion (CRAI) therapy reduces the mortality rate of acute necrotizing pancreatitis: results of a cooperative survey in Japan. J Hepatobiliary Pancreat Surg, 2001; 8: 216-20.

27. Maravi-Poma E, Gener J, Alvarez-Lerma F, Olaechea P, Blanco A, Dominguez-Munoz JE. Spanish Group for the Study of Septic Complications in Severe Acute Pancreatitis. Early antibiotic treatment (prophylaxis) of septic complications in severe acute necrotizing pancreatitis: a prospective, randomized, multicenter study comparing two regimens with imipenem-cilastatin. Intensive Care Med, 2003; 29: 1974-80.

28. Spicak J, Hejtmankova S, Cech P, Hoskovec D, Kostka R, Lefler J. Antibiotic prophylaxis in severe acute pancreatitis: Randomised multicenter prospective trial with meropenem. Pancreatology, 2003; 3: 220.

29. Isenmann R, Runzi M, Kron M, Kahl S, Kraus D, Jung N, Maier L, Malfertheiner P, Goebell H, Beger HG and the German Antibiotics in Severe Acute Pancreatitis Study Group. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. Gastroenterology, 2004; 126: 997-1004.

30. Golub R, Siddiqi F, Pohl D. Role of antibiotics in acute pancreatitis: a meta-analysis. J Gastrointest Surg, 1998; 2: 498-502.

31. Sharma VK, Howden CW. Prophylactic antibiotic administration reduces sepsis and mortality in acute necrotizing pancreatitis: a meta-analysis. Pancreas, 2001; 22: 28-31.

32. 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.

33. Banks PA. Practice guidelines in acute pancreatitis. Am J Gastroenterol, 1997; 92: 377-86.

34. Glazer G. Mann DW. United Kingdom Guidelines for the management of acute pancreatitis. Gut, 1998; 42 (suppl. 2): 1S-13S.

35. Dervenis C, Johnson CD, Bassi C, Bradley EL, Imrie CW, McMahon MJ, Modlin I. Diagnosis, objective assessment of severity, and management of acute pancreatitis: Santorini consensus conference. Int J Pancreatol, 1999; 25: 195-210.

36. Uomo G, Pezzilli R, Cavallini G. Management of acute pancreatitis in clinical practice. ProInf-AISP study. Ital J Gastroenterol Hepatol, 1999; 31: 635-42.

37. Runzi M, Layer P, Buchler MW, Beger HG, Ell Ch, Folsch UR, Goebell H, Hopt UT, Lankisch PG, Schmidt WE, Schniegel W, Scholmerich J. Therapie der akuten pankreatitis. Gemeinsame leitiinen. Z Gastroenterol, 2000; 38: 571-81.

38. Toouli J, Brooke-Smith M, Bassi C, Carr-Locke D, Telford J, Freeny P, Imrie C, Tandon R. Guidelines for the management of acute pancreatitis. J Gastroenterol Hepatol, 2002; 17(Suppl): S15-S39.

39. Mayumi T, Ura H, Arata S, Kitamura N, Kiriyama I, Shibuya K, Sekimoto M, Nago N, Hirota M, Yoshida M, Ito Y, Hirata K, Takada T. Evidence-based clinical practice guidelines for acute pancreatitis proposal. J Hepatobiliary Panc Surg, 2002; 9: 413-22.

40. Uhl W, Warshaw A, Imrie C, Bassi C, McKay CJ, Lankisch PG, Carter R, DiMagno E, Banks PA, Withcomb DC, Dervenis C, Ulrich CD, Stake K, Ghaneh P, Hartwig W, Werner J, McEntee G, Neoptolemos JP, Buchler MW. IAP guidelines for the surgical management of acute pancreatitis. Pancreatology, 2002; 2: 565-73.

41. Bradley EL. Guiding the reluctant. A primer on guidelines in general and pancreatitis in particular. Pancreatology, 2003; 3: 139-43.

42. Pezzilli R. Antibiotic prophylaxis in acute necrotizing pancreatitis: yes or no? JOP. J Pancreas, 2004; 5: 161-4.

43. De Waele JJ, Vogelaers D, Hoste E, Blot S, Colardyn F. Emergence of antibiotic resistance in infected pancreatic necrosis. Arch Surg, 2004; 139: 1371-5.

44. Gotzinger P, Wamser P, Barlan M, Sautner T, Jakesz R, Fugger R. Candida infection of local necrosis in severe acute pancreatitis is associated with increased mortality. Shock, 2000; 14: 320-3.

45. 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: 208-13.

46. 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: 592-6.

47. Olah A, Pardavi G, Belagyi T, Nagy A, Issekutz A, Mohamed GE. Early nasojejunal feeding in acute pancreatitis is associated with a lower complication rate. Nutrition, 2002; 18: 259-62.

48. Dervenis C. Enteral nutrition in severe acute pancreatitis: future development. JOP. J Pancreas, 2004; 5: 60-3.

49. Uomo G, Talamini G, Rabitti PG, Cataldi F, Cavallera A, Rengo F. Influence of advanced age and related comorbidity on the corse and outcome of acute pancreatitis. Ital J Gastroenterol Hepatol, 1998; 30: 616-21.

50. Uomo G. Inflammatory pancreatic diseases in older patients – recognition and management. Drugs Aging 2003; 20: 59-70.