Infectious complications of acute pancreatitis: spectrum of causative agents and approaches to antibacterial therapy

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Abstract
The aim of this study was to determine optimal regimes of antibacterial therapy on different stages of acute pancreatitis (AP) clinical course and susceptibility of causative agents, which cause AP infectious complications (IC), to antibiotics.
119 patients with severe and moderate AP were enrolled to the study. The I group was formed from 57 patients (treated during 2015-2016 years). The II group included 62 patient (treated during 2017-2018 years). Antibiotics from reserve group were used for infectious complications' prophylaxis in the I group. Broad-spectrum antibiotics were administrated in the II group. There were no statistically significant difference in the arise of IC (I group – 24,5%; II group – 25,8%; p=1,0). Associations of microorganisms were found in 18,5% samples in the I group and 47,4% in the II. There were 23,8% antibiotics with sensitivity more then 50% in the I group and 19,2% in the II. 10,0% of IC causative agents produced extended spectrum beta lactamases (ESBL) in the I group. In the II group there were 29,6% ESBL-producing microorganisms.
Causative agents of IC in patients with AP are in majority microorganisms, which are resistant to several antibiotics. This characteristic of microorganisms does not depend on type of drug, which is used for prophylactic antibiotic administration during early stages of AP clinical course. The increase of ESBL producing bacteria, Gram-negative bacteria and microorganisms' associations among IC causative agents is observed. Administration of antibiotics from reserve group in case of IC occurrence is recommended.

Key words: acute pancreatitis, infectious complications, causative agents.

Introduction

Acute pancreatitis (AP) is a widespread disease with significant social and economical burden. For example, in United States AP stands on the third place as a reason for hospitalization of patients with digestive tract diseases. Number of people who are treated with this diagnosis annually exceeds 275 000 persons with financial burden of approximately 2,6 billion dollars. Morbidity for AP in US ranges from 5 to 30 incidents per 100 000 people and has a trend to increase[1,2]. Mortality from AP fluctuates in range from 4% to 5% reaching 17-35,2% in case of severe AP with infected necrosis and organ failure[3,4].

According to current clinical approaches patients with mild AP should not be treated with antibiotics. Prescription of antibiotics seems reasonable in case of pancreatic and/or retroperitoneal tissues necrosis presence to prevent purulent complications[5,6]. Nevertheless, it not recommended by majority of existing guidelines in the beginning of mild or moderate AP[7,8]. Lots of experts think, that admission of antibiotic therapy and surgical intervention are indicated when the infection of necrotic tissues is proven[9]. Furthermore, there is an opinion that non-surgical approach can be used in clinically stable patients with infected pancreatic necrosis[10]. In any of abovementioned situations rational antibacterial therapy plays an important role in treatment of patients with AP.

The aim of our study was to determine optimal regimes of antibacterial therapy on different stages of AP clinical course and susceptibility of causative agents, which cause AP infectious complications (IC), to antibiotics.

Material and Methods

119 patients with severe and moderate AP were enrolled to the study. All of them were treated in surgical department of Poltava Regional Clinical Hospital named after M.V. Sklifosovskiy of Poltava Regional Council during 2013-2018 years. The group of our patients consisted of 71 men and 48 women. Mean age of patients was 48,0±14,84 years. Formation of groups was made basing of patients` treatment time. The I group was formed from 57 patients, who were treated during 2013-2014 years. The II group included 62 patient, who were treated during 2017-2018 years. Athlanta classification (2012 revised) was used for severity grading of AP[11].

We analyzed 65 samples (27 in the I group and 38 in the II) obtained from patients with IC of AP. In each specimen causative agent (or agents) was identified and its antibiotic susceptibility was investigated. Considering bacterial associations, general data array consisted of 106 distinct microbiological isolates (34 in the I group and 72 in the second).

Statistic analysis of obtained data was made using STATISTICA 6.0 software system. In particular, two by two contingency tables with calculation of Fisher's exact two-tailed test and Mann-Whitney U test were used to compute the probability of statistically significant difference between groups. Probability values were rounded to three decimal places.

Results

Drugs from reserve group (ertapenem, doripenem, meropenem) were prescribed to patients from the I group for IC prophylaxis as was established by local treatment protocols. Later on suppuration of necrotic tissues or/and acute fluid collections was observed in 14 cases (24,5%). Approaches to antibiotic prescription were changed in 2016 and all the patient from the II group were treated with wide spectrum drugs (ceftriaxone, ciprofloxacin) for prevention of necrotic tissues/acute fluid collections suppuration. IC were diagnosed in 16 patients (25,8%) in the II group. There were no statistically significant difference between groups (p=1,0).

Only one causative agent was identified in the majority of cases (81,5%) in the specimens collected from the patients in the I group. The situation with number of causative agent in the single sample was different in the II group: only 52,6% of obtained specimens showed monoculture growth and the difference between groups was statistically significant for this parameter (p=0,020). Microbial associations were detected only in 18,5% from all samples in the I group. There also were samples with 4 and 5 causative agents in the same specimen in the II group, albeit such phenomenon wasn't seen in the I group. Percentage of samples with three microorganisms in the II group was three times higher than in the I one(Table 1).

Table 1: Samples with different number of causative agents obtained from patients with IC,%

Number of microorganisms in the sample	I group	II group	p
1	81,5	52,6	0,020
2	11,1	15,8	0,724
3	7,4	23,7	0,105
4	0,0	2,6	1,0
5	0,0	5,3	0,507
Total	100,0	100,0	-

The most common causative agent in the I group was Pseudomonas aeruginosae (32,4%), though its prevalence decreased down to 13,9% in the II group (difference statistically significant, p=0,037). Klebsiella pneumoniae was the most frequent microorganism in the II group (25,0%), but in the I group it was rather more uncommon – 2,9% only (difference statistically significant, p=0,006). This bacteria with Staphylococcus aureus and Enterobacter spp. were the most rare microorganisms in the I group. In the II group the less common causative agents were Stenotrophomonas maltophilia, Serratia marcescens and Alcaligenes spp. (1,4% for each), meanwhile in the I group none of them was detected. Fungi (Candida spp.) were found only in the II group in small amount (2,8%). There was no strains of Staphylococcus aureus isolated in the II group, though it was present in the I group (Table.2).

Table 2: Prevalence of IC causative agents in patients with AP,%

Causative agent	I group	II group	p
Staphylococcus aureus	2,9	0,0	0,321
Staphylococcus spp.	14,7	6,9	0,285
Streptococcus spp.	5,9	5,6	1,0
Enterococcus spp.	17,6	9,7	0,341
Pseudomonas aeruginosae	32,4	13,9	0,037
Stenotrophomonas maltophilia	0,0	1,4	1,0
Acinetobacter spp.	5,9	15,3	0,217
Alcaligenes spp.	0,0	1,4	1,0
Nonfermenting Gram-negative bacilli*	2,9	0,0	0,321
Escherichia coli	11,8	8,3	0,723
Klebsiella pneumoniae	2,9	25,0	0,006
Serratia marcescens	0,0	1,4	1,0
Citrobacter spp.	0,0	2,8	1,0
Enterobacter spp.	2,9	5,6	1,0
Candida spp.	0,0	2,8	1,0
Total	100,0	100,0	-

*Note: *- only group affiliation was identified without further differentiation*

The majority of causative agents was represented by Gram-negative bacteria in both groups. Nonetheless their prevalence raised from 58,8% in the I group to 77,1% in the II with trend to statistically significant difference between groups (Table 3).

Table 3: Some characteristics of IC's causative agents isolated from patients with AP,%

Characteristic	I group	II group	p
Gram-positive bacteria	41,2	22,9	0,066
Gram-negative bacteria	58,8	77,1	
Nonfermenting Gram-negative bacilli	41,2	31,9	0,388
ESBL producers	10,0	29,6	0,126

In the same time the incidence of nonfermenting Gram-negative bacilli decreased (31,9% in the II group and 41,2% in the I). Prevalence of ESBL producing bacteria raised in the II group in 3 times comparing with the I, though the difference was not statistically significant (p=0,126).Evaluation of IC causative agents' susceptibility was made for 21 antibiotics in the I group and for 26 in the II group(Table 4).

Table 4: IC causative agents' susceptibility to antibiotics,%

Antibiotic	I group		II group		p
	n	Susceptibility	n	Susceptibility	
Penicillin	6	16,7	11	45,5	0,350
Ampicillin	13	30,8	37	20,3	0,600
Ampicillin/sulbactam	n/d	n/d	19	10,5	-
Amoxicillin/clavulanic	n/d	n/d	25	0,0	-
Piperacillin	n/d	n/d	12	12,5	-
Piperacillin/tazobactam	3	0,0	24	20,8	0,583
Ticarcillin/clavulanic	n/d	n/d	19	21,1	-
Cefuroxime	4	0,0	17	0,0	1,0
Cefotaxime	2	50,0	9	0,0	0,327
Ceftriaxone	3	0,0	27	14,8	0,695
Cefoperazone	6	25,0	n/d	n/d	-
Cefoperazone/sulbacta	4	25,0	24	81,3	0,015
Ceftazidime	20	10,0	50	9,0	0,995
Cefepime	16	0,0	49	5,1	0,635
Imipenem	8	0,0	38	5,3	0,831
Meropenem	17	35,3	50	31,0	0,814
Ciprofloxacin	11	22,7	46	8,7	0,373
Levofloxacin	16	0,0	34	16,2	0,327
Amikacin	18	11,1	47	36,2	0,096
Gentamicin	33	34,8	58	21,6	0,276
Tobramycin	18	27,8	41	56,1	0,085
Vancomycin	8	100,0	16	100,0	1,0
Tigecycline	13	84,6	8	100,0	0,595
Aztreonam	n/d	n/d	9	27,8	-
Clindamycin	n/d	n/d	8	37,5	-
Linezolid	8	100,0	7	100,0	1,0

Chloramphenicol	10	65,0	19	36,8	0,211

Note: «n/d» - susceptibility to antibiotic was not tested in this group; n – number of bacterial samples tested for susceptibility

Microorganisms in the I group showed 100% susceptibility to vancomycin and linezolid. The majority of causative agents also was susceptible to tigecycline (84,6%). Bacteria's resistance in 50% and less percent was detected for 5 drugs from 21 (23,8%). Cefotaxime was the only broad spectrum antibiotic in abovementioned list (susceptibility of 50,0%). Total resistance was detected for 6 drugs (28,6%) including imipenem**,** cefepime**,** and piperacillin/tazobactam. For 10 (47,6%) antibiotics bacterial susceptibility varied from 10,0-35,3% (including meropenem – 35,3%).

Zero resistance to vancomycin, linezolid and tigecycline was detected in the II group. Susceptibility of 50% and more was registered to five antibiotics (19,2%). Total resistance was detected to cefuroxime**,** cefotaxime and amoxicillin/clavulanic acid. Susceptibility in range of 5,1-45,5% was registered for 18 (69,23%) drugs, including cefepime – 5,1%, imipenem – 5,3%, meropenem – 31,0%.

In the II group susceptibility to 5 antibiotics decreased comparing with the I one. Relatively stable level of resistance (variations in range of 6%) was registered for 8 drugs in both groups. In case of 7 antibiotics there was increase of susceptibility, including statistically significant difference for cefoperazone/sulbactam (p=0,015; susceptibility raised to 81,3%) and trend to it for amikacin and tobramycin (p<0,1).

Discussion

According to obtained results, we observe significant number of microbial associations in samples from patients with IC. This data corresponds with information from other institutions [12,13]. Presence of Gram positive bacteria among causative agents can be explained by coinfection with skin microorganisms[14]. Some authors advocate, that a shift from Gram-negative to Gram-positive flora is connected with prophylactic antibiotic prescription[12]. Still Gram-negative bacteria dominate as causative agents in this study, though all included patients received antibiotics prophylactically. There were no strains of MRSA or VRE in bacterial isolates from our study despite wide and poorly controlled prescription of antibiotics in our country. P. aeruginosae and other nonfermenting Gram-negative bacilli played important role as IC causative agents, but there is also essentially big prevalence of ESBL producers in samples obtained from patients with IC. Similar situation is described by other authors both for severe AP IC and in case of other intraabdominal infections [15,16].

General tendency leads to increase of antibiotic resistance worldwide, and the same can be observed in our study. There is also constant resistance to some antibiotics of reserve group, such as imipenem and cefepime. Despite that, raise of susceptibility to some drugs was observed in this study. In our opinion, it can be a result of proper antibiotic stewardship according to local hospital protocols, which use "cycling" strategy with one year period of antibiotic rotation, though the final outcome of this strategy is still questionable [17-19].

Causative agents of IC in patients with AP are in majority microorganisms, which are resistant to several antibiotics. This characteristic of microorganisms does not depend on type of drug, which is used for prophylactic antibiotic administration during early stages of AP clinical course.

The increase of ESBL producing bacteria, Gram-negative bacteria and microorganisms' associations among IC causative agents is observed.

Administration of antibiotics from reserve group in case of IC occurrence is recommended.

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