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PANCREATOGENIC INFECTIONS: IMPORTANCE OF MICROBIOLOGICAL MONITORING AND PENETRATION OF ANTIMICROBIAL CHEMOTHERAPEUTIC AGENTS INTO THE PANCREAS WHEN DEFINING THERAPEUTIC APPROACH

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Abstract. The review provides the information on the spectrum of microorganisms initiating the development of clinical and morphological forms of pancreatogenic infections. It is shown that when analyzing pathological conditions, no features in the microbiological landscape of the secondary infection in the pancreas and the surrounding extraperitoneal cellular tissue are registered. It provides the information on the particular structure of the microorganisms spectrum in acute pancreatitis in the Italian, Mexican, Indian, Chinese and Russian patient populations. Special attention has been paid to the choice of antibacterial medications in acute pancreatitis; the choice is based on sensitivity of allocated microorganisms to these medications, and particularities of medication therapeutic concentrations formation in the pancreas tissues or its secret. Foreign researchers' experimental and clinical data regarding the penetration degree of various antibacterial agents into pancreatic tissue in the presence of pancreatic necrosis and efficiency of the agents in the process of drug correction of necrotizing pancreatitis. The analyzed information predetermines the need for a continuous microbiological pattern monitoring on the local level in association with assessment of its sensitivity and specificity to the prescribed antibacterial therapy of acute pancreatitis in the early stages of its infectious complications.
Keywords: pancreatic necrosis, pancreatogenic infection, antimicrobial agents, antibiotic resistance, penetration of antimicrobial agents into the pancreas

Infectious pancreatic necrosis and pancreatogenous abscess are the main clinical and morphological forms of pancreatogenic infections. Infectious pancreatic necrosis develops within about 2 weeks, pancreatic abscess – within 5 weeks since the disease starts. According to some reports, infection of the pancreas and the surrounding retroperitoneal fat is revealed by 3 to 4 days. Nowadays it is known that deaths occur less frequently in case of pancreatogenic infection development later than within 3 weeks rather than in case of secondary infection until 3 weeks [15].

The literature tells that a range of microorganisms is mostly presented by microorganisms of the Enterobacteriacae group - Escherihia coli, Klebsiella pneumonia and rarer by other representatives of the family; Pseudomonas aeruginosa by Gram-positive organisms – staphylococci, streptococci, and enterococci. In association with aerobic organisms, anaerobic organisms Bacteroides spp. and clostridia are registered [3, 4, 23, 28, 31]. The authors have not found out dependence of microorganism spectrum discharge on type of pancreatogenic infection. It should be noted that, according to Isenmann R. et al., patients with infected pancreatic necrosis have more Candida spp., with detection frequency 5 to 15%, compared to other intraabdominal infections [20].

When studying etiology of severe acute pancreatitis in Italy, a mixed flora has been detected among 68% patients. Pseudomonas aeruginosa (59%) associated with Candida albicans or C. glabrata has been the most frequent representative [17].

When studying a structure of the microorganism spectrum in case of acute pancreatitis in Mexico, staphylococci have been detected in most cases which is related by the researchers with alcohol ingestion [22].

418 (70.4%) strains of 594 ones which have been isolated by Chinese researchers in patients with acute destructive pancreatitis have been represented by gram-negative bacteria, 142 (23.9%) – by gram-positive ones and 34 (5.7%) – by fungi. Escherichia coli (19.8%) as well as Pseudomonas aeruginosa (13.0%) and Acinetobacter baumannii (11.8%) have been the most frequently detected gram-positive bacteria. Enterococcus faecium (10.1%), coagulase-negative staphylococci (5.4%) and Enterococcus faecalis (2.9%) have prevailed in the structure of the gram-positive flora [30].

When assessing the structure of causative agents and its dynamics in case of pancreatic necrosis among 51 patients, Indian researchers have found the agent in 37.3% patients; one agent has been found out in 27.5% patients and polymicrobial infection has been revealed in 9.8% patients. Within a first week of admission, colibacillus has been found out in 6 patients of 6 (100%), within a second week of treatment, it has been revealed in 5 of 8 patients (62.5%), and after week two – in 2 of 5 patients (40.0%). In total, 32 (62.7%) patients have had signs of extrapancreatic infection with 53 positive cultures. Staphylococcus has been mostly found in blood cultures. A study of sensitivity of the detected microorganisms has shown that most bacteria have been sensitive to beta-lactam antibiotics, aminoglycosides, and imipenem. The authors think that the after-treatment results in changing the microflora structure from gram-negative to gram-positive agents [24].

When studying a spectrum of agents discharged from bile, Romanian researchers have revealed that in case of antibiotic prophylaxis Escherichia coli has been found in 25 patients (42%) while it has been found in 14 patients (27%) of the control group; Klebsiella pneumoniae has been found in 6 patients (10%) and in 4 patients (8%); Enterococcus spp. has been found in 8 patients (13%) and in 11 patients (21%) respectively. Pseudomonas aeruginosa has been found only in the group of patients who had antibiotic prophylaxis – in 3 cases (5%) [32].

Belgian researchers have found out that bloodstream infections have occurred in 15% of 45 examined patients with severe acute pancreatitis. When analyzing a structure of agents, microorganisms of gram-positive flora have prevailed – 57% isolated strains. Gram-negative microorganisms have been found in 35% cases, fungi have been found in 8% cases. Relation of the bloodstream infection with the pancreas necrotic discharge has been shown [33].

Data on etiology of main pancreotogenic peritonitis agents differ a bit by home authors. In the Russian Federation, main agents of infectious complications in destructive pancreatic necrosis are Enterobacteriaceae bacteria – 24 to 58% (in particular, Escherichia coli – 17 to 35%, and Klebsiella pneumonia – 5 to 24%, other Enterobacteriacae bacteria – 15 to 30%), Pseudomonas aeruginosa – 11 to 16%, streptococci – 8 to 11%, staphylococci – 5 to 15%, enterococci – 3 to 40%, Bacteroides spp. and anaerobic bacteria – 17 to 48%, Candida fungi – in 5 to 37% cases [2, 4].

According to the results of researches in some regions of the Russin Federation, the predominant microorganisms are gram-negative Enterobacteriacae microorganisms: Escherichia coli (16%), Klebsiella pneumoniae (16%), Proteus mirabilis (5%), Enterobacter aerogenes (2%), Serratia marcescens (2%). Pseudomonas aeruginosa has been found in 7 cases (19%), Acinetobacter baumannii – in 2 cases (4%) [5].

The results of studying sensitivity of isolated strains have shown that Enterobacteriacae microorganisms have kept sensitivity to carbapenems [2, 4, 5, 8]. However, according to the data of the multicenter epidemiological study of antibiotic resistance of nosocomial infection agents (MARATHON), resistance to meropenem, imipenem, and ertapenem in 2.8, 8.4 and 14.0% isolates respectively, mostly it has been K. pneumonia. The carbapenemase products of groups OXA-48 (3.3%) and NDM-1 (0.4%) have been found in 3.7% isolates [10].

Rate of extended spectrum beta lactamases (ESBL)-producing and cephalosporin-resistant strains which have been isolated from the patients with complicated intraabdominal infections and pancreatic necrosis has been up to 59% isolated strains of enterobacteria [1]. Level of enterobacteria resistance to amikacin has differed according to the data of various authors: 50 to 100% sensitive strains have been shown [1, 5]. Fluoroquinolones have shown low activity. Ciprofloxacin- and levofloxacin-resistant strains have been found in 55 to 67% cases among Escherihia coli and Klebsiella pneumoniae [1, 5, 8].

The multicenter epidemiological study MARATHON has revealed a rise of Enterobacteriacae strains producing extended spectrum beta lactamases (ESBL) up to 78.2%, 90.6% – among Klebsiella pneumoniae, 82.1% –

among Escherihia coli. Level of resistance to gentamicin has reached 60.4%, to ciprofloxacin – 70.5% and to trimethoprim/sulfamethoxazole – 63.7%. Among non-beta lactam antibiotics,the most efficient ones have been amikacin, fosfomicin and tigecycline, resistance to which has been shown in 36.1%, 14.1% and 15.9% isolates respectively [10].

A prevalence study of gram-negative bacteria producing metallo-beta-lactamase (MBL) has shown increase of the rate of MBL-positive Pseudomonas aeruginosa isolates (4.5 to 20.3% within 2002-2004 and 2006-2007) in Russia (in 1998 to 2010), Belorussia and Kazakhstan (in 2005 to 2010) [11].

When studying Pseudomonas aeruginosa sensitivity in patients with pancreatic necrosis in some regions of the Russian Federation, 57% isolated strains of Pseudomonas aeruginosa have shown resistance to ceftazidime, cefoperazone and cefepime. Carbapenems have shown a bit higher activity: 57% strains have proved to be resistant to meropenem, 42% strains – to imipenem/cilastatin. When analyzing data on associated resistance of carbapenem-resistant strains, it has been revealed that 3 strains (42%) have proved to be sensitive to cefepime and ceftazidime (28%). Pseudomonas aeruginosa has shown high sensitivity to aminoglycosides. Resistance to amikacin has been found in 14% cases only, and to gentamicin – in 27% cases. Pseudomonas aeruginosa isolated strains have shown high level of resistance to fluoroquinolones: it has been isolated 72% strains resistant to ciprofloxacin, 82% strains resistant to levofloxacin [5]. Lack of absolute meropenem-imipenem cross-resistance could be related to particularities of resistance acquisition by P. aeruginosa [9].

Detection frequency and sensitivity of gram-positive microorganisms in Russia have been much lower compared to other regions in the world: Staphylococcus aureus has been found in 11.5% cases. Level of methicillin-resistant Staphylococcus aureus has been 7.1%; Staphylococcus epidermidis – 4.8%, Enterococcus spp. – 4.8%. [7].

The gram-positive flora has been represented by strains of Staphylococcus aureus and coagulase-negative staphylococcus and has differed, according to the data of various authors, in 15 to 27% isolated strains while 63% strains have been methicillin-resistant [3, 5, 30].

In case of acute necrotizing pancreatitis, it is widely accepted to choose antimicrobial drugs resting on results of discharged microorganisms' sensitivity assessment and particularities of forming a curative concentration of antibacterial medications in tissues or secretion of the pancreas.

To simulate acute pancreatitis, several models have been used: with induction of bile acid intraductal injections [13], with standardized intraductal infusion of glycodeoxycholic acid and intravenous infusion of caerulein [27], by pancreatic duct ligation followed by injection of proserin [6].

The experimental study of antimicrobial drug penetration in the pancreas tissue in rats without signs of affected pancreas has shown that a tissue/plasma ratio for amikacin has been 16%, for amoxicillin/clavulanic acid – 24%, for piperacillin – 27%, for ofloxacin – 59%, and for cefoperazone – 108%. The tissue/plasma ratio in rats in the presence of pancreatitis simulation has been 7%, 23%, 26%, 52% and 70% respectively [29].

High penetration of cefepime and meropenem in the pancreas tissue has been shown in rats with acute pancreatitis. Meropenem has had precedence over cefepime in penetrability into pancreas necrotic tissue, however both medications have made curative concentration in pancreas tissues [26].

The study of imipenem and cefotaxime penetration in 6 and 48 hours after simulating acute pancreatitis in rats has shown that imipenem has been accumulated at the initial stage of acute necrotic pancreatitis, has been marked by prominent edema and pancreatic capillary bloodstream depression, and has tended to reduce acinar cells in the course of the disease while solving the edema and necrosis progressing. Low concentration of cefotaxime has been found in the pancreas edematous tissue early after induction of acute necrotic pancreatitis and increase of the concentration has been revealed upon edema solution and pancreatic capillary bloodstream resetting [21].

The study conducted by Italian researches has shown a high penetration of imipenem, pefloxacin and metronidazole into the pancreas tissues in patients with pancreatic necrosis, while in case of prescribing aminoglycosides the penetration has been insufficient, which should be considered when prescribing antimicrobial therapy of pancreatic necrosis [14].

The study of ciprofloxacin concentration in pancreas necroses, peripancreatic necroses of fatty tissues and lesser sac fluid in patients with pancreatic necrosis has suggested ciprofloxacin efficiency when developing a preferable curative organ concentration of the drug in the course of medication correction of necrotic pancreatitis. The mean ratio of ciprofloxacin penetration has been 137.5% into lesser sac fluid, 59.6% (3 to 214%) in pancreas necroses, and 67.1% (1 to 250%) in peripancreatic necroses [12].

When comparing penetration of ciprofloxacin and ofloxacin into pancreatic juice after their single oral administration at a dose of 500 mg and 400 mg respectively in patients who had pancreas transplantation, it was shown that ofloxacin concentration has exceeded values of the minimal inhibitory concentration within several hours. Ciprofloxacin concentration has exceeded the minimal inhibitory concentration for a short time [16].

According to the data of German researches, after intravenous administration of ceftazidime at a dose of 35 mg/kg in patients with pancreatitis, ceftazidime concentration in pancreas tissues has varied 9 to 79% in the blood plasma. In five days after antibiotic administration at a dose of 2 grams three times per day, ceftazidime concentration has been 1.8 to 6.9 mg/kg including pancreas necrosis areas. The analysis of ceftazidime penetration into the pancreas has shown its potential efficiency in patients with acute necrotic pancreatitis which is related to development of the drug curative concentration in the pancreas tissues [18].

The study of meropenem penetration into pancreatic juice of the patients who underwent hepatobiliary and pancreatic surgery has shown that after 0.5-hour infusion of 500 mg meropenem its concentration in the pancreatic juice has been higher than the minimal inhibitory concentration for the most agents [19].

Tigecycline administration has shown a positive therapeutic and microbiological efficiency in 6 patients with acute pancreatitis when curing pancreatic abscess and in case of extra-pancreatic infectious complications [25].

According to the results of numerous studies of preventive antimicrobial use efficiency, quite contradictory data have been obtained. The meta-analysis made in Germany has revealed no proof of death reduction and infectious pancreatic necrosis rate decrease in case of preventive antimicrobial administration [34].

Another meta-analysis made in China has shown the advantage of preventive antimicrobial administration associated with true reduction of pancreatic infection, peripancreatic infectious complications and extra-pancreatic infections as well as with the length of hospital stay while it has shown no influence on death cases and surgery necessity in case of acute necrotic pancreatitis [35].

Thus, regarding pancreatic infection clinic in case of pancreatic necrosis, population and geographic microbiological particularities of the diseases under research have importance both in etiology and choise of efficient antimicrobial treatment.

The mentioned studies have predetermined the necessity of continuous local monitoring of the microbiological flora in association with assessment of the flora sensitivity to the prescribed treatment of acute pancreatitis with early infectious complications considering the level of antimicrobial chemotherapeutic drug penetration into the pancreas.

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