PERFECTION OF ANTIBACTERIAL THERAPY INFECTED FORMS OF PANCREATIC NECROSIS IN A VERSATILE SURGICAL HOSPITAL

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Introduction. The most significant directions of scientifically-practical researches in urgent pancreatology last decade there is a studying of an aetiology, various links pathogenic, perfection of methods of diagnostics and treatment of patients pancreatic necrosis (PN) [11]. Against as avalanche increasing disease of a acute pancreatitis there is practically invariable a relative density of patients with destructive forms of the disease making 20-30 % [1,7,8,11]. Thus, data are disturbing, what even in large specialised clinics it is not marked tendencies to decrease the in the general and postoperative lethality, especially at the infected forms PN, reaching 30-40 % and more than [2,3,6].

Now, a leading direction in complex treatment of infected forms PN and its complications, along with adequate surgical intervention is antibacterial therapy (ABT) [3,4,5,6,12]. The given circumstance is caused by high frequency infected pancreas gland (PG) and parietal peritoneum (PP) at PN, and also development various exstraabdominal is purulent-septic complications which get a dominating role among causes of death of patients [11,12,13,14,16,17,18]. In this connection the researches directed on optimisation ABT at PN have the important practical value.

Research materials. The presented work is based on the analysis of results of complex conservative and surgical treatment of 50 patients with the infected forms pancreatic necrosis (IPN), were on treatment in surgical branches of Republican hospital №2 - the Center of emergency Republics of Sakha (Yakutia) during the period with 2008 for 2011

Diagnosis PN and development of its complications is verified on the basis of the complex inspection including: clinical data, laboratory researches (including a level estimation endogenic intoxications (EI) under the maintenance of substances of low and average molecular weight (AMW) by M.J. Malahova technique [9] and oligopeptides (OP) on Loury [10] in plasma, erythrocytes to blood and urine with allocation of 5 phases EI: 1st phase – the latent; 2nd phase - accumulation of toxic products; 3rd phase – the time of decompensation systems and bodies detoxication; 4th phase - irreversible decompensation systems and bodies detoxication; 5th phase -

terminal, and also the control and the account of the important biochemical markers necrosis PG and parietal peritoneum, system inflammatory reaction (CBP) and infected PN (LDG, C-reactive protein, PCT)). Tool methods of diagnostics included ultrasonic and X-ray contrast computer scanning of bodies of a belly cavity, parietal peritoneum spaces, a video laparoscopy, medical-diagnostic punctures of liquid formations PG, a belly cavity and parietal peritoneum spaces under the control of ultrasound with the subsequent microbiological and cytologic analysis of the received material. The estimation of weight of the general condition and expressiveness organ insufficiency at patients PN was spent with use of integrated systems-scales, Ranson [19], APACHE II [15] and SOFA [13].

For carrying out of microbiological research crops of biomaterials, cultivation, allocation of pure culture of microorganisms spent by the standard techniques. Identification of the allocated is conditional-pathogenic microorganisms (CPM) spent classical methods with test system API use (bioMerieux, France).

Antibiotic sensibility defined a disco-diffuzion a method on Muller-Hinton agar with use of a set of standard disks with antibiotic preparations, according to the standard techniques and according to standards of National committee on clinical laboratory standards - NCCLS 2002, 2003, 2004 (National Committee for Clinical Laboratory Standarts, USA) and to methodical instructions Ministry of health the Russian Federation 4 from 04.03.2004). Revealing ß-laktamazy of the expanded spectrum (ESBL) at culture Enterobacteriaceae spent fenotopic methods (a method of "double disks»). For revealing producing metallo-ß-laktamaz (MBL) cultures used «HODGE-test», «a method of double disks with sodium salt ethylendiaminvyniger acids (ADTA)». At sensitivity definition used the standardised qualitative disks of firms Bio-Rad™ and BD™ (USA).

Internal quality assurance carried out with use international referens-culture Staphylococcus aureus ATCC 25923, Pseudomonas aeruginosa ATCC 27853, Enterococcus faecalis ATCC 29212, Escherichia coli ATCC 25922.

Input, statistical processing and the analysis of the given microbiological researches was made by means of software package Microsoft Excel for Windows 2000 and software WHONET 5.4.

Considering variants of development of the pathological process, all patients with IPN have been divided into three groups, depending on kliniko-patomorfology forms pancreatic infections, weights of the general condition, expressive organ insufficiency on integrated systems-scales Ranson, APACHE II, SOFA, and also to phases EI.

Group "A" patients with formation pancreatic abscess (PA) - 9 (have made 18%) patients.

Value of indicators of weight of the general condition at them has made on scales Ranson <3 points, APACHE II <9 points and SOFA less than 4 points. Level EI, as a rule, corresponded I-II to phases. Group - "B" - patients with infected pancreatic necrosis (IP) - 17 (34%) patients. Values of indicators on integrated scales Ranson> 3, APACHE II> 9 and SOFA more than 4 points. Level EI corresponded III-IV-V to phases. Group - "C" - 24 (48%) patients with infected pancreatic necrosis in a combination with pancreatic abscess and infected pancreatic necrosis (IP+PA). Value of indicators of weight of the general condition at them has made on integrated scales Ranson> 3, APACHE II> 9 and SOFA more than 4 points. Level EI corresponded III-IV-V to phases.

Statistical processing of a clinical material is made with use of software package Stat Plus 2007 for Windows XP. At an estimation of all set average values (μ) and a standard deviation (σ) were calculated; the factor of reliability of differences was defined under test Mana-Uitni.

Results and discussions. By results of our researches PA development is noted at 9 (18%) patients of group "A", thus 5 (55,6%) are executed by the patient traditional external drainage abscess cavities, 4 (44,4%) patients have been operated by the technique improved by us consisting in opening of a cavity of an abscess and imposing of drainage-washing system using minilaporotomy with elements of an "open" laparoscopy by means of the complete set of tools "miniassistant". Lethal outcomes and complications in this group it is noted.

Such form pancreatogenic infections as IP (group "B"), is revealed during research at 17 (34%) patients. This patients needed performance stage endoscopic sanitation or transition on wide laparotomy with subsequent use of modes of operative intervention "on demand" or «under the program», that depended on a concrete clinical situation. Has thus died 2 (11,7 %) patients.

Combination IP to the PA is revealed by us in 24 (48%) cases (group "C"). As a rule, occurrence of such form pancreatogenic infections was marked on the expiration of the second week from the moment of the beginning of disease, and corresponded to evolution widespread sterile pancreatic necrosis, that also has demanded use in surgical treatment of operative modes "on demand" or «under the program» depending on displays of pathological process. Has thus died 5 (20,8%) patients.

For a substantiation and the control spent antibiotic therapies at 50 patients with pancreatogenic infection are spent 126 microbiological researches. The microflora is found out in 110 (87,3%) tests. It is allocated and identified 196 cultures CPM. In 75 (59,5%) researches the monoculture, in 51 (40,5%) - microbic associations is allocated. Two-componental microbic associations are allocated in 29 (23,1%), three-componental - in 17 (13,5%), four-componental - in 5 (3,9%) tests. Results of bacteriological researches are presented to tab. 1.

Table 1

Sources of allocation of microorganisms at patients IPN

Biological material	Quantity the investigated tests		Quantity of tests with growth	
	Absolute value	%	Absolute value	%*
Wound the separated	39	31,0	38	97,4
Exudates belly cavity	50	39,7	48	96,0
Bile	18	14,2	14	77,7
Blood	11	8,8	7	63,6
Urea	5	3,9	2	40,0
Phlegm	3	2,4	1	33,3
Total	126	100	110	87,3

The note: * - it is presented sow in separate biomaterials

Apparently from tab. 1, the greatest sow microorganisms was observed in wound separated - 97,4% and exudates a belly cavity - 96,0% of positive results of researches. In bile and blood of patients microorganisms are revealed in 77,7 and 63,6% of tests, in urine, phlegm - in 40,0 and 33,3% of tests accordingly.

Studying of specific structure of the allocated microorganisms has shown, that at pancreatogenic infections the flora which has made 69,3% from all allocated cultures prevails gramnegative. Among gramnegative bacteria prevailed not fermenting gramnegative bacteria (GNB): Pseudomonas aeruginosa - 31,1%, Acinetobacter spp. - 7,1%, family Enterobacteriaceae: Klebsiella pneumoniae - 13,8% and Escherichia coli - 10,2%.

Grampositive the flora is revealed in 27,0% of researches. Prevailing agents among grampositive bacteria were sort activators enterococcus, in particular, E. faecalis - 11,2 %, E. faecium - 8,2% and coagulasonegative culture (CNS): S. epidermidis - 3,6% and S. saprophyticus - 1,5%. The fungoid infection basically has been presented Candida spp. Also (tab. 2) is found out in 3,0 %.

Table 2

Specific structure of microorganisms allocated at patients IPN

Species of microorganism	Quantity cultures	
	Absolute value	%
Gramnegative microorganisms	**136**	**69,3**
Including GNB	**77**	**39,3**
Acinetobacter spp.	14	7,1

Pseudomonas aeruginosa	61	31,1
Flavobacterium spp.	2	1,0
Including Enterobacteriaceae	**59**	**30,1**
Enterobacter spp.	9	4,6
Escherichia coli	20	10,2
Klebsiella pneumoniae	27	13,8
Citrobacter spp.	3	1,5
Grampositive microorganisms	**53**	**27,0**
Including Enterococcus	**38**	**19,4**
Enterococcus faecalis	22	11,2
Enterococcus faecium	16	8,2
Including Staphylococcus	**2**	**1,0**
S. aureus	2	1,0
Including (CNS)	**10**	**5,1**
S. saprophyticus	3	1,5
S. epidermidis	7	3,6
Including Streptococcus	**2**	**1,0**
Str. pneumoniae	1	0,5
Str. viridans	1	0,5
Grampositive coccus	**1**	**0,5**
Corynebacterium spp.	1	0,5
Anaerobics	**1**	**0,5**
Clostridium perfringens	1	0,5
Fungis	**6**	**3,0**
Candida spp.	6	3,0
Total:	**196**	

The presented spectrum of microorganisms gives representation about the basic activators, characteristic for IPN. Thus, analyzing data of bacteriological researches in dynamics, it is noticed, that with increase in terms of treatment in branch of resuscitation and intensive therapy (ITS) (basically it is patients at which was available widespread character of defeat PG and PP it was necessary for them to use modes of operative intervention "on demand" or «under the program»), against spent ABT the microflora structure varied. In the treatment beginning in exudates a belly cavity prevailed E. coli (6,1%), in the subsequent it was possible to notice increase in a share of

hospital, "problem" microorganisms. It was most often found out P. aeruginosa - at 26 (56,0%) patients. Eventually (7-10 days) essential value got CPM: Acinetobacter spp., Klebsiella spp. Are allocated in 4,0 and 8,1% of researches, accordingly, possessing high resistance to the majority of modern antibiotics. Besides, at a long finding of the patient in ITS occurrence of the mixed microflora - 2, 3 and more componential, and also contamination organism CPM (positive results of crops are revealed at research phlegm, urine, bile) was marked. Bacteriaemia it is revealed in 64,3% of researches of blood at patients with clinical signs of generalisation pancreatogenic infections. Most often in blood found out E. coli (69,5%). Thus, as a rule, the specific parity of activators in blood not always corresponded to microflora peritoneal exudate.

The analysis antibioticsensibility has shown, that high activity concerning E.coli (it is tested 20 cultures), Kl. pneumonia (27 cultures) it is marked at meropenem, sensitivity has made 100%. Production ESBL has been established for cultures E.coli, Kl.pneumonia with frequency of 65% (13 cultures) and 66,6% (18 cultures), accordingly. Cefoperazon/sulbaktam was active concerning 84,6% (11 cultures) ESBL-producing cultures E.coli and 83,3 % (15 cultures) ESBL-producing cultures Kl.pneumonia.

From allocated 61 cultures P.aeruginosa it is revealed 24 carbopenemresistens cultures (39,3 from all allocated P.aeruginosa). Fenotipic (the test with ADTA and «HODGE-test») production MBL is revealed at 9 cultures (37,5% from carbopenemresistens cultures P.aeruginosa). Production MBL of a part isoletion is confirmed by means of multiplex polymiraz by the chain reaction, spent in scientific research institute of antimicrobic therapy (Smolensk). MBL-positive cultures concerned to VIM - to type (gene presence blaVIM). 30 cultures (49,1 %) P.aeruginosa were resistance to ciproflozacinum and cefoperasonum, to amycacinum - 36 %.

Thus, the characteristic of a microbic spectrum, data on dynamics of its structure during treatment confirm complexity of problem ABT. Considering possible lacks of empirical stage ABT: incorrect selection of antibacterial preparations during treatment in other treatment-and-prophylactic establishments of Yakutsk and Republics Sakha (Yakutia), uncontrollable the doctor reception of antibacterial preparations by the patient at a pre-hospital stage, an economic component of concrete treatment-and-prophylactic establishment and being based on results of continuous bacteriological monitoring at pancreatogenic infections, in treatment by us were used following advanced schemes ABT in which basis schemes ABT the chairs of faculty surgery of the Russian state medical university offered by employees of N.I.Pirogova [3] (tab. 3) are put. Defining factors at a choice of starting antibacterial preparations were: Weight of the general condition of the patient and expressiveness polyorgans insufficiency estimated on integrated systems-scales Ranson, APACHE II, SOFA, phase EI, specific structure of microorganisms by

results of bacteriological research, volume, type of an antibacterial preparation and duration previous ABT, duration of a finding of the patient in a hospital and-or ОРиИТ, and also presence of the fact developed exstraabdominal infectious complication.

Table 3

Schemes ABT recommended to the patient with IPN

Schemes ABT	Indications to application
1 scheme ABT **Monotherapy** Cefoperazone	1) Ranson < 3, APACHE II < 9, SOFA<4 points 2) I-II phases EI 3) Negation of reception of antibiotics at the moment of hospitalisation and-or duration of treatment in a surgical hospital (ITS) less than 5 days 4) Absence of septic complications
2 scheme ABT **The combined therapy** CS III + Metronidazole Pefloxacin/Levofloxacin+Metronidazole	1) Ranson <3, APACHE II <9, SOFA <4 points 2) I-II phases EI 3) Negation of reception of antibiotics at the moment of hospitalisation and-or duration of treatment in a surgical hospital (ITS) less than 5 days 4) Absence of septic complications
3 scheme ABT **Monotherapy** Imipenem cilastin Aertapenem Meropenem	1) Ranson> 3, APACHE II> 9, SOFA> 4 points 2) III-IV-V phases EI 3) ABT in the anamnesis and-or duration of treatment in a surgical hospital (ITS) more than 5 days 4) Presence of septic complications 5) Repeated receipts in ITS
4 scheme ABT **The combined therapy** Cefepim/Metronidazole	1) Ranson> 3, APACHE II> 9, SOFA> 4 points 2) III-IV-V phases EI 3) ABT in the anamnesis and-or duration of treatment in a surgical hospital (ITS) more than 5 days 4) Presence of septic complications 5) Repeated receipts in ITS
Modes ABT at an infection caused by "problem" microorganisms (Without dependence from weight of a condition and phase EI)	
P. aeruginosa	Meronem>Ceftazidim> Imipenem cilastin>Ciprofloxacin
MRSA	+Vancomicin or linezolid
E. coli, Klebsiella spp. (ESBL) Indirect sign of production ESBL - intermediate sensitivity to any of CS III	CS I-IV not to appoint/cancel The most reliable mode - Meronem, Imipenem/cilastin

Candida spp.	+Fluconazole, at resistance-amfoterecin either Kaspofungin or Varoconazole

The indication to appointment of 1st and 2nd schemes ABT were: weight of the general condition and expressiveness polyorgans insufficiency on integrated scales Ranson <3, APACHE II <9 points, SOFA <4; I-II phases EI; negation of reception of antibiotics at the moment of hospitalisation and-or duration of treatment in a surgical hospital (ITS) less than 5 days; absence of septic complications.

The indication to appointment of 3rd and 4th schemes ABT were: weight of the general condition and expressiveness polyorgans insufficiency on integrated scales Ranson> 3, APACHE II> 9, SOFA> 4 points; III-IV-V phases EI; ABT in the anamnesis and-or duration of stay in a surgical hospital (ITS) more than 5 days; presence of septic complications; repeated receipts in ITS.

Apparently from tab. 3, as the basic starting preparations for ABT the preparations possessing the greatest efficiency concerning the majority of activators, both abdominal joined, and nosocomialy infections, the microbiological situation in a concrete versatile surgical hospital thus was necessarily considered. So 1st scheme is applied at 4 (8%), 2nd at 5 (10%), 3rd scheme at 29 (58%) and 4th scheme at 12 (24%) patients. Thus the basic way of introduction of antibacterial preparations was intravenous, at 11 (22%) patients applied intraarterial introduction.

The positive clinical effect is received at application of all 4 presented schemes ABT at patients with IPN. Efficiency spent ABT, before reception of bacteriological data, was estimated on clinical data, major of which were: dynamics of development of the infectious centre and intensity of inflammatory reaction of an organism (regress of symptoms of system inflammatory reaction (on integrated scales Ranson, APACHE II, SOFA), temperature reaction, indicators of efficiency of functioning of bodies of blood circulation and breath, indicators an intoxication index. Result correctly picked up ABT was decrease in the basic indicators of system inflammatory reaction within 3-5 days of treatment. Objective acknowledgement of validity ABT were data of bacteriological researches. After allocation of the activator and definition of its resistance, main principle ABT was transition to chemotherapy the most effective preparation.

Thus, by results of research it is possible to draw following **conclusions**: 1. At a certain stage of development pancreatogenic infections, pancreatogenic a sepsis there comes, inherently, struggle with nosocomial and the is conditional-pathogenic infection, differing high resistance to antibiotics. 2. Efficiency ABT and accordingly increase of probability of a favorable outcome of disease in many respects depends on correct use of the information on a microbiological situation in a concrete surgical hospital. 3. Monitoring data nosocomial florae and its resistance to

antibacterial preparations will allow to provide, first of all, the proved and adequate mode empirical ABT. 4. Researches have shown, that the most effective antibacterial means in treatment pancreatogenic infections (on an example of a concrete surgical hospital) are group preparations carbopenems and cefalosporinum III generations (ingibitorprotections). 5. Certainly, resistance of microbic agents to antibiotics raises eventually, therefore indispensable condition ABT is timely replenishment of the hospital data card by effective antibacterial preparations.

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