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FEATURES OF MICROBIOLOGICAL DIAGNOSIS AND CHOICE OF SELECTIVE ANTIBIOTIC THERAPY IN PATIENTS WITH ACUTE CHOLECYSTITIS

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Abstract

The objective: to improve the results of destructive forms of acute cholecystitis (AC) surgery by the development of antibiotic therapy algorithm and taking into account the severity of the disease according to Tokyo guidelines (2013). **Materials and methods:** 266 patients having been operated on for AC made up a treatment group and 203 patients - the control one. In 234 treatment group patients microflora's bacteriological study was carried out and its selective sensitivity to antibiotics was determined. **Results and discussion.** The AC treatment group patients (n=266) were arranged according to Tokyo guidelines (2013) into 3 grades. Mild course (grade I) consisted of 29 patients (11%), microbiological studies were not conducted. Antibiotic prophylaxis with beta-lactam antibiotics was used. At moderately severe AC (grade II, n = 200, 75%) escalation antibiotic therapy was carried out. At severe disease (grade III, n = 37, 14%) de-escalation antibiotic therapy was performed. Bacteriological studies were conducted in 237 patients with destructive forms of AC, at that 531 microflora isolates were cultured. Intestinal group microorganisms were the most frequently cultured. Beta-lactam antibiotics' sensitivity was prevailing and constituted 83.3%. The number of suppurations in the treatment group decreased from 9.8% to 4.3%, and mortality rate decreased from 1.48% to 0.75% ($p<0.05$) as contracted with control group where empirical antibiotic therapy was used. **Conclusions.** 1. Intestinal group microflora

prevailed in destructive forms of AC. 2. In mild course of cholecystitis antibiotic prophylaxis is consider to be method of choice, in moderately severe disease – escalating therapy, and in severe cases – de-escalating antibiotic therapy should be used, as that beta-lactam antibiotics had the highest selective sensitivity (83.3%). 3. AC is local intra-abdominal infection, where evidence-based antibiotic therapy has reduced postoperative complications to 4.3%, and mortality rate - to 0.75%.

Key words: acute cholecystitis, prophylactic, escalation, de-escalation selective antibiotic therapy, microbiological diagnostics.

The urgency of the problem.. Acute cholecystitis (AC) is an inflammation of the gallbladder (GB) with extra-and intrahepatic bile ducts (2000 m^2) of the liver frequent involvement in the pathological process, pancreas with the threat of the development of biliary peritonitis, perivascular ulcer and abscess, cholangitis, choledocholithiasis and holodolar and cholangitis. sepsis [4, 5, 11].

The frequency of surgical interventions in AC is close to that in appendectomies, and in the patients over 50 y. o. surpasses it with relatively high mortality rate [7].

AC is a local intra-abdominal infection, where adequate antibiotic therapy significantly affects purulent complications and mortality. A number of works [1, 2, 3, 6, 7, 8, 10, 12, 13] are devoted to the problems of choosing antibiotics in the treatment of AC, differentiation of tactics according to the severity of the course, determination of microflora sensitivity.

The objective: to improve the results of destructive AC surgery by the development of antibiotic therapy algorithm and taking into account the severity of the disease according to Tokyo guidelines (2013) and determine the selective sensitivity of the microflora cultured to antibacterial drugs.

Materials and methods. 266 AC patients were examined. They have been operated on in the surgical department of Kiev Regional Clinical Hospital in 2016 – 2018. The control group included 203 AC patients operated on in 2013–2015, similar in sex, age, comorbidities, treatment and surgical tactics to each other, but with an empirical choice of antibiotic therapy. On presentation the material into the bacteriological laboratory, smears were made, Gram's stained and micro scoped. After microflora's identification antibiotic was empirically administered.

To isolate aerobic bacteria pure cultures standardized nutrient media of industrial production namely 5% blood, gall-salt, Endo, enterococcus and chocolate agar were used. All of them are allowed for the use in Ukraine and have corresponding quality certificates.

Identification of isolates and determination of their sensitivity to antibacterial drugs was performed on a VITEK-2 Compact 15 microbiological analyzer (France).

Then the minimum inhibitory concentrations were determined and individually the treatment doses of drugs were calculated.

Results and discussion. The AC treatment group patients (n=266) were arranged according to Tokyo guidelines (2013) into 3 grades.

Grade I consisted of 29 patients (11%) with AC mild course. They had moderately promoted GB changes and none severe comorbidities. Microbiological studies were not conducted. Standard antibiotic prophylaxis (*Sulbactamum, Amoksiklav, Cephalosporins)* was used.

Grade II included 200 patients (75%) with moderately severe AC. GB was palpable and there was an infiltrate in the right hypochondrium. In this group before plated microflora sensitivity determination, the escalation antibiotic therapy was used (cepahalosporins of the IIIrd generation)

Grade III (n = 37, 14%) included patients with circumscribed, rarer generalized peritonitis. Patients with multisystem failure symptoms were not enrolled. De-escalation antibiotic therapy (carbapenems) was performed in this group.

All 266 patients were operated on under general endotracheal anesthesia using muscle relaxants. 253 patients (95%) were operated on with laparoscopic techniques with 6% conversions; 13 patients (5%) with laparotomy access.

Bacteriological studies were conducted in 237 (89%) of patients with phlegmonous and gangrenous AC forms and perivesical abscesses. Material for the study was taken from the abdominal cavity exudates, GB content, perivesical abscess. The investigation was conducted in dynamics, up to 3 times.

Both in monoculture and microbial associations 531 microflora isolate were excreted.

Table 1 presents the results of bacteriological studies in patients with destructive forms of AC.

Table 1

Bacteriological studies of 237 patients with destructive forms of acute cholecystitis

Microorganism	Number	%
Achromobacterxylosoxidansss. Xylosoxidans	1	0
Acinetobacterbaumannii	10	2
Actinomycesnaeslundii	1	0
Bacillus cereus	2	0
Bacillus sp.	1	0
Burkholderiacepacia	1	0
Candida albicans	5	1
Candida parapsilosis	1	0
Candida sp.	2	0
Chryseomonasluteola	1	0
Citrobacterfreundii	3	1
Citrobactersedlakii	2	0
Citrobacter sp.	2	0
Enterobacteraerogenes	26	5
Enterobacter cloacae	16	3
Enterococcus avium	1	0
Enterococcus casseliflavus	1	0
Enterococcus faecalis	17	3
Enterococcus faecium	29	5
Enterococcus gallinarum	1	0
Escherichia coli	66	12
Escherichia vulneris	1	0
Gemellahaemolysans	1	0
Gram positive bacteria	1	0
Gram positive cocci	1	0
Klebsiellaoxytoca	3	1
Klebsiellapneumoniae ss. Pneumoniae	50	9
Klebsiella sp.	1	0
Kocuriakristinae	3	1
Lactococcusgarvieae	2	0
Leuconostocmesenteroides ss. Mesenteroides	1	0
Morganellamorganii ss. Morganii	1	0
No growth	127	24
Normal flora	2	0
Peptostreptococcus sp.	1	0
Proteus mirabilis	5	1
Proteus rettgeri	4	1
Proteus vulgaris	5	1
Pseudomonas aeruginosa	17	3
Raoultellaplanticola	1	0
Serratiafonticola	3	1
Serratiamarcescens	1	0
Staphylococcus aureus ss. Aureus	38	7
Staphylococcus epidermidis	54	10
Staphylococcus haemolyticus	2	0
Staphylococcus hominis ss. Hominis	2	0
Staphylococcus saprophyticus ss. saprophyticus	1	0
Streptococcus pneumoniae	2	0
Streptococcus pyogenes	2	0
Streptococcus sp.	4	1
N = 531		

Escherichia coli (12%), *Staphylococcus epidermidis* (10%), *Klebsiella pneumonia* (9%), *Staphylococcus aureus* (7%), *Enterobacter aerogenes* and *Enterococcus faecium* (5% each) were cultured more frequently. In 127 AC patients (24%) there was no growth of aerobic microflora.

Table 2 presents the selective sensitivity of the microflora cultured in AC destructive forms patients to antibiotics.

Table 2

Microflora selective sensitivity in AC patients

Антибіотик	Кількість	%R	%I	%S
1	2	3	4	5
Beta-lactamase	18	16.7		83.3
ESBL	16	50.0		50.0
PEN.ND10 Penicillin G	31	67.7	0.0	32.3
PEN_NM Penicillin G	12	75.0	0.0	25.0
AMP_ND10 Ampicillin	84	83.3	1.2	14.3
AMP_NM Ampicillin	33	81.8	0.0	18.2
AMX_NM Amoxicillin	1	100.0	0.0	0.0
AMX_ND25 Amoxicillin	66	47.0	12.1	40.9
AZL_ND75 Azlocillin	35	77.1	0.0	22.9
PIP_ND100 Piperacillin	66	60.6	7.6	31.8
PIP_NM Piperacillin	21	57.1	4.8	33.3
TIC_ED75 Ticarcillin	27	81.5	0.0	18.5
OXA_ED1 Oxacillin	3	100.0	0.0	0.0
OXA_NM Oxacillin	12	50.0	0.0	50.0
AMC_ED25 Amoxicillin/Clavulanic acid	24	50.0	8.3	41.7
CCV_ND30 Ceftazidime/Clavulanic acid	7	28.6	0.0	71.4
CSL_ND30 Cefoperszcne/Sulbactam	63	41.3	19.0	39.7
SAM_ND10 Ampicillin/SulDactam	43	32.6	14.0	53.5
SAM_NM Ampicillin/Sulbactam	23	43.5	4.3	52.5
TCC_ND75 Ticarcillin/Clavulanic acid	8	50.0	0.0	50.0
TZP_NDiOOPineracil'in/T azobactam	89	31.5	14.6	53.9
TZP_NM Piperacillin,Tazobactam	33	45.5	21.2	30.3
CZO_NM Cefazolin	21	47.6	0.0	52.4
CZO_ND30 Cefazolin	88	58.0	3.4	38.6
CFPJMD75 Cefoperazone	36	47.2	11.1	41.7
CXM_ND30 Cefuroxime	114	66.7	3.5	29.8
CXM_NM Cefuroxime	15	73.3	0.0	26.7
MAN_ND30 Cefamandole	29	44.8	6.9	48.3
CAZ_ND30 Ceftazidime	133	60.2	12.0	27.8
CRO_ND30 Ceftriaxone	61	59.0	4.9	36.1
CRO_NM Ceftriaxone	32	56.2	0.0	43.8
CTX_ND30 Cefotaxime	71	62.0	12.7	25.4
FEP_NM Cefepime	52	57.7	5.8	36.5
FEP_ND30 Cefepime	111	65.8	9.0	19.8
FOX_ND30 Cefoxitin	98	45.9	3.1	51.0
FOX_NM Cefoxitin	7	28.6	0.0	71.4
CFM_NM Cefixime	12	75.0	0.0	25.0
CFM_ND5 Cefixime	26	61.5 ’	11.5	26.9
CPD_ND10 Cefpodoxime	1	0.0	100.0	0.0

1	2	3	4	5
CXA_NM Cefuroxime axetil	15	73.3	0.0	26.7
ATM_ND30 Aztreonam	48	64.6	20.8	14.6
ATM_NM Aztreonam	20	60.0	0.0	40.0
DORJMD10 Doripenem	17	58.8	5.9	35.3
ETP_ND10 Ertapenem	2	0.0	50.0	50.0
IPM_ND10 Imipenem	74	35.1	6.8	58.1
IPMJMM Imipenem	21	33.3	28.6	38.1
MEM_NM Meropenem	41	31.7	17.1	51.2
MEM_ND10 Meropenem	96	41.7	13.5	44.8
AMK_ND30 Amikacin	103	46.6	7.8	45,6
AMK_NM Amikacin	29	20,7	3,4	72,4
GEN_NM Gentamicin	48	43,8	4,2	52,1
GEN_ND10 Gentamicin	77	39,0	5,2	55,8
KAN_ND30 Kanamycin	76	63,2	15,8	21,1
NET.ND30 Netilmicin	146	21,2	2,1	76,7
TOB_ND10 Tobramycin	190	31,1	4,7	64,2
TOB_NM Tobramycin	21	28,6	9,5	57,1
RIFJMD5 Rifampin	12	16,7	8,3	75,0
CIP_ED10 Ciprofloxacin	58	50,0	1,7	48,3
CIP_NM Ciprofloxacin	46	65,2	0,0	34,8
GAT_ND5 Gatifloxacin	64	43,8	3,1	51,6
LOM_ND10 Lomefloxacin	1	100,0	0,0	0,0
LVX_ND5 Levofloxacin	103	54,4	2,9	42,7
LVX_NM Levofloxacin	51	56,9	0,0	43,1
MFX_NM Moxifloxacin	35	57,1	2,9	40,0
MFX_\'D5 Moxifloxacin	66	51,5	6,1	42,4
NOR_ND10 Norfloxacin	71	64,8	4,2	31,0
NOR_MM Norfloxacin	11	90,9	0,0	9,1
OFX_ND5 Ofloxacin	123	47,2	6,5	46,3
PEF_ED5 Pefloxacin	2	100,0	0,0	0,0
SXT_NM Trimethoprim/Sulfamethoxazole	46	37,0	0,0	21,7
TMP_ND5 Trimethoprim	36	66,7	0,0	J3,3
TMP_NM Trimethoprim	14	50,0	0,0	50,0
FO3_N320 Fosfomycin	14	50,0	7,1	42,9
FOS_ED20 Fosfomycin	5	80,0	0,0	20,0
FOS_NM Fosfomycin	11	45,5	0,0	45,5
CLI_NM Clindamycin	21	61,9	0,0	38,1
CLI_ND2 Clindamycin	96	44,8	8,3	46,9
LIN_ED15 Lincomycin	6	50,0	33,3	16,7
COL_ND10 Colistin	52	5,8	1,9	92,3
COL_NM Colistin	18	11,1	5,6	83,3
AZM_ND15 Azithromycin	68	70,6	7,4	22,1
ERY_NM Erythromycin	21	66,7	0,0	33,3
ERY_ND15 Erythromycin	68	48,5	26,5	25,0
LNZ_NM Linezolid	15	0,0	0,0	100,0

The highest sensitivity of microflora isolated in destructive forms of AC patients (83.3%) is marked for beta-lactam antibiotics - penicillins, cephalosporins, monobactams, and carbapenems.

In the group of patients with AC mild forms antibiotic prophylaxis was used. Escalation antibacterial therapy was used in 200 mean heavy variant of AC patients (75%) and then a follow-up transition to selective antibiotics according to the results of microbiological sensitivity. In 37 AC severe form patients (14%) de-escalation antibiotic therapy (carbapenems) was used immediately

Before the results of selective sensitivity were obtained imipenem 0.5 gr i.v. 4 times per day or meropenem 0.5 gr i.v. 4 times per day or ertapenem 1 gr once per day were considered to be therapy of choice for the patients with severe course of AC.

Alternative therapy included: cefoperazon / sulbactam 2-4 gr i.v. twice per day or cefoperazon 2-4 gr i.v. twice-thrice per day or cefotaxim 1-2 gr i.m. thrice per day or levofloxacin 0. 5 gr i. v. once –twice per day or ciprofloxacin 0.5 gr i.v. twice per day with metronidazole 0.5 gr i.v. thrice per day.

If microflora cultured was antibiotics-resistant (lack of growth) their change was carried out according to clinical signs.

The duration of antibiotic therapy was determined clinically. Decrease in body temperature below 37.5° C, normalization of leukocytes number in peripheral blood and the number of immature forms in the leukocyte formula, good condition of the postoperative wound was taking into account.

The duration of antibiotic therapy in AC destructive forms patients averaged 13.4 ± 0.5 (minimum 6, maximum 24 days of continuous therapy).

Compared with the control group of 203 AC patients, 266 treatment group patients had decreased number of suppurations (from 9.8% to 4.3%; $p<0.01$), and decreased mortality rate (from 1.48% to 0.75%; $p<0.05$).

Conclusions:

1. Severity of illness was determined according to Tokyo Agreement (Tokyo guidelines, 2013). For the patients of the first grade (light course), we recommend the use of antibiotic prophylaxis. Under moderate course escalation antibiotic therapy and under severe course of the AC de-escalation antibiotic therapy, followed by the use of selective antibacterial agents should be administered.

2. The highest selective sensitivity of microflora cultured in the patients operated on for AC destructive forms was revealed to beta-lactam antibiotics (83.3%).

3. The use of differentiated antibiotic regimens based on the severity of the disease according to Tokyo guidelines (2013) and the identification of the selective sensitivity of microflora with the optimal therapeutic and surgical tactics were able to reduce the number of purulent complications in the control group from 9.8% to 4.3% ($p<0.01$) and mortality rate from 1.48% to 0.75% ($p<0.05$).

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