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Antibiotic therapy in acute pancreatitis: From global overuse to evidence based recommendations

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ABSTRACT

Background: Unwarranted administration of antibiotics in acute pancreatitis presents a global challenge. The clinical reasoning behind the misuse is poorly understood. Our aim was to investigate current clinical practices and develop recommendations that guide clinicians in prescribing antibiotic treatment in acute pancreatitis.

Methods: Four methods were used. 1) Systematic data collection was performed to summarize current evidence; 2) a retrospective questionnaire was developed to understand the current global clinical practice; 3) five years of prospectively collected data were analysed to identify the clinical parameters used by medical teams in the decision making process, and finally; 4) the UpToDate Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system was applied to provide evidence based recommendations for healthcare professionals.

[1] The first three authors equally contributed.

Results: The systematic literature search revealed no consensus on the start of AB therapy in patients with no bacterial culture test. Retrospective data collection on 9728 patients from 22 countries indicated a wide range (31–82%) of antibiotic use frequency in AP. Analysis of 56 variables from 962 patients showed that clinicians initiate antibiotic therapy based on increased WBC and/or elevated CRP, lipase and amylase levels. The above mentioned four laboratory parameters showed no association with infection in the early phase of acute pancreatitis. Instead, procalcitonin levels proved to be a better biomarker of early infection. Patients with suspected infection because of fever had no benefit from antibiotic therapy.
Conclusions: The authors formulated four consensus statements to urge reduction of unjustified antibiotic treatment in acute pancreatitis and to use procalcitonin rather than WBC or CRP as biomarkers to guide decision-making.

Introduction

There is a general overuse of antibiotics (ABs) worldwide resulting in AB resistance, which is part of the most remarkable hazards to global health [1]. The misuse of AB has been associated with fungal infection, Clostridium difficile infection and increased costs [2,3]. In 2009, approximately $10.7 billion was spent on antibiotic therapy in the United States (US), including $6.5 billion in the outpatient, $3.6 billion in acute inpatient care, and $526.7 million in long-term care settings [4]. According to the latest report from Germany, the total amount of antimicrobials used in human medicine is estimated to range between 700 and 800 tonnes per year [5], 15% of its used by hospitals, while 85% in primary practice [6]. European Surveillance of Antimicrobial Consumption Networks report that antibiotic-resistant bacteria claim lives of approximately 700000 people each year globally [7]. The annual impact of resistant infections is estimated to be $20 billion in excess health care costs and 8 million additional hospital days in the US [8–10] and over 1.6€ billion and 2.5 million additional hospital days in the European Union (EU) [11]. Antimicrobials currently account for over 30% of hospital pharmacy budgets in the US [12].

The administration of ABs in acute pancreatitis (AP) has been widely and thoroughly investigated [13]. We must note that either direct pathologic insult of the pancreas i.e., alcohol, bile or fatty acids [14], or increased autoactivation of trypsinogen [15] without infection can activate inflammatory pathways, therefore AP itself is not an indication for AB therapy [16,17]. Notably, current guidelines do not recommend prophylactic AB therapy for the prevention of infectious complications in AP (IAP/APA guideline, Grade 1B) [18], (American College of Gastroenterology, strong recommendation, moderate quality of evidence) [19]. However, in cases of proven source of infection empiric administration of ABs is justified [20]. Based on the above mentioned suggestions we can calculate the rate of ABs should be used in AP: pancreatic infection is a rare event in AP (around 5%) [21], moreover there is only 14%–37.4% extrapancreatic indications (such as cholangitis or pneumonia) are reported [22–25], therefore, the justified rate of ABs use should be between 20 and 40% in AP.

However, the Hungarian Pancreatic Study Group (HPSG) found that 77.1% of the total study population (n = 600) received AB therapy and two thirds of this group had no signs of infection, meaning AB treatment was administered on a preventive basis [25]. In population-based studies, 14% of patients received unjustified (so called prophylactic) AB in Portugal [26], 25.5% in Canada [27], 27–58% in the USA [28], 30.7% in the UK [23], 81.4% in India [29], 44.6–69.3% [30] and 74.3% in Japan [31].

There could be several reasons behind AB overuse worldwide: 1) The guideline is insufficient regarding AP therapy. It only states that intravenous AB prophylaxis is not recommended for the prevention of infectious complications in AP (GRADE 1B, strong agreement), failing to offer indication for proper AB treatment [18]. 2) Misinterpretation of inflammatory biomarkers, such as C reactive protein (CRP) during AP [26]. It has been suggested that elevation of CRP can have major influence on prescribing prophylactic ABs in AP [26]. 3) Non-adherence to guidelines [13]. Several studies reported moderate or non-compliance to the recommendations for the management of AP [23,27,29,32–36]. 4) Defensive medical care in which healthcare providers try to protect themselves from malpractice claims [37–39].

These data clearly suggest the crucial importance of multicentre, multinational studies aiming to give proper recommendations for AB utilization in AP.

The specific aims of this study were to (1) summarize current evidence, (2) understand the current global practice, (3) understand the clinical parameters used by medical teams in the decision making process, (4) verify the usefulness of these parameters, (5) make more informed recommendations for healthcare professionals.

Methods

1. Systematic review

The systematic review aimed to summarize the recent evidence (1) on the guidance of AB therapy and (2) on the strategies how high-quality studies raised the suspicion of pancreatic infection in AP. We observed the rules of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guideline when reporting this work [40].

Eligibility

Eligible randomized controlled trials (RCTs) discussed (1) patients diagnosed with AP (2) who were given any ABs orally and/or intravenously (3) with available full-text of any languages. Studies applying continuous regional arterial infusion or other drugs (e.g., protease inhibitors) were excluded. We chose the inclusion of RCTs on the guidance of AB therapy or preventive AB therapy because high-quality studies centered around the suspicion of pancreatic infection are lacking. Our assumption that the best evidence on the topic might be present in these studies relies on two arguments. On one hand, definitive infection and infected pancreatic necrosis are high-priority hard outcomes of these studies focusing on infection control. On the other hand, suspicion of infection is a safety issue in these studies because of the required immediate intervention, such as a change in per protocol drug regime or a surgical/radiological approach.

Search and selection

We searched cited and citing articles, including previous meta-analysis and systematic reviews, of relevant reports for eligible studies. We did not contact the authors of original studies for information.

We conducted a comprehensive systematic search in MEDLINE (PubMed), EMBASE, and Cochrane Trials from inception up to 7 July 2018 for articles reporting on the use of antibiotics in AP. We applied the following query without any filters imposed on the search: pancreatitis AND (antibiotic OR antibiotics OR carbapenem OR imipenem OR meropenem OR ertapenem OR doripenem OR aminoglycoside OR amikacin OR gentamicin OR cephalosporin OR cefepime OR ceftriaxone OR ceftazidime OR cefoperazone OR cefixime OR cefuroxime OR cephalexin OR ceftobiprole OR cefazolin OR cefalotin OR glycopeptide OR vancomycin OR teicoplanin OR penicillin OR amoxicillin OR ampicillin OR oxacillin OR piperacillin OR mezlocillin OR ticarcillin OR sulbactam OR tazobactam OR clavulanate OR fluoroquinolone OR ciprofloxacin OR levofloxacin OR moxifloxacin OR ofloxacin OR pefloxacin OR metronidazole OR tigecycline OR linezolid OR daptomycin).

Yield of search was combined in reference manager software (EndNote X7.4, Clarivate Analytics, Philadelphia, PA, US) to remove overlaps between databases and duplicates, then, two independent investigators screened the records by title, abstract, and full-texts against our eligibility criteria in duplicate. Discrepancies were resolved by third party arbitration.

Data collection

A pre-constructed data collection table was designed by our research team. After this step, training was organized to increase the consistency of data collection. Data were extracted by two independent review authors in duplicate. Discrepancies were resolved by a consensus meeting of our research team.

The following data were extracted: publication data (authors, year), setting (country, centres, setting), definition and etiology of AP, eligibility criteria of the study, the total number of patients (in intention to treat and per protocol analyses), and interventions (drug regimens and/or guidance of therapy). In addition, definitions of suspected and definitive pancreatic and extrapancreatic infections, and the consequent clinical management were collected.

2. Retrospective data analysis

To assess the worldwide trends in administration of AB we sent a letter of invitation and a questionnaire to the member of the International Association of Pancreatology in November 2017. Colleagues have provided data from their past-year inpatients' practice accordingly to gender, etiology, mortality and severity of AP, and AB therapy irrespectively from its indication. Percentage of AB treatments was calculated, and it has been illustrated on a colour scaled map.

3. Prospectively collected data analysis

The Hungarian Pancreatic Study Group (HPSG) (https://tm-centre.org/en/study-groups/hungarian-pancreatic-study-group/) was established in 2011 with the aim to improve patients' care in pancreatic disease. We have developed an international, uniform and prospective electronic data registry to collect high quality data from patients suffering from AP. From January 1, 2013 to November 30, 2016, 1070 episodes of AP have been enrolled. Centre distribution is indicated in Supplementary Fig. 1. Diagnosis of AP was based on the A1 recommendation of the IAP/APA guideline. Two of the following alterations were confirmed in each patient: abdominal pain (clinical symptom), pancreatic enzyme elevation at least three times above upper limit and morphological changes (imaging techniques).

Four quality control points were established in our registry. First, the local clinical research assistant electronically uploads the data and confirms equivalency with the hard copy. Second, the local institutional principal investigator (who holds a medical doctoral degree) double-checks the uploaded data and confirms the validity and accuracy. Third, the central data administrator, who is based at the headquarters of HPSG, controls the accuracy and finally (in house monitor), the registry leader reviews the presented data and verifies them. Patients with inadequate or insufficient data are excluded.

To answer our post hoc defined research question, data from HPSG pancreatic registry were analysed. We selected 56 parameters relating to our research question (Supplementary Fig. 2.). Those patients' data were used for further analysis where the following information were available in its entirety: age, gender, length of hospitalization, severity, based on revised Atlanta classification, mortality, complications and details about AB therapy (starting date, type of antibiotics, etc.) [17]. Data of 962 patients met the criteria mentioned above, so this cohort was used for further analysis.

The following groups have been designated. Patients in Group1 and 2 did not receive AB therapy. Patients in Group 1 did not receive AB therapy and their no symptoms or evidence of infection. Patients in Group 2 did not receive AB treatment either, however, there were symptoms which may associated with infection (ie. fever) or the followings were declared: positive bacterial culture, cholangitis, upper or lower respiratory tract infection, urogenital infection, and infection of any other organ system.

Members of Group 3, 4 and 5 all received AB treatment. In Group 3, patients had no features characteristic of infection, therefore received AB as prevention. In these patients there were no signs of infection or negative bacterial culture. Patients in Group 4 received empirical AB therapy since they had features characteristic of infection (with no (a) or negative bacterial culture (b)). Group 5 patients took AB as a targeted therapy following positive bacterial culture, specifying the exact cause of infection and/or gas in and/or around the pancreas on CECT or MRI.

Statistical analysis

For descriptive statistics, the number of patients, mean, standard deviation (SD), standard error of mean (SEM), minimum, median and maximum values were calculated for continuous variables, and the case number and percentage were computed for categorical values.

For inferential statistics, the following tests were applied to determine statistical significance of differences between groups. To compare two groups of independent samples, the *t*-test was used for normally distributed data and the Mann-Whitney *U* test for non-normally distributed data. To compare more than two groups, one-way ANOVA followed by the Tukey post hoc test was employed for normally distributed data with homogenous group-wise standard deviation; Brown-Forsythe Levene-type test was applied to test of variance homogeneity; the Welch test followed by the Games-Howell post hoc test for normally distributed data with heterogeneous group-wise standard deviation; and the Kruskal-Wallis test followed by the Holm p-value adjustment method for non-normally distributed data.

The association between categorical variables was inspected by the Chi-square test and Fisher's exact test. To compare proportions for more than two groups, the pairwise proportion test followed by

the Holm p-value adjustment was used. The level of statistical differences were defined in all cases.

The relevant statistical tests are also described in the legends to the figures. Statistical analyses were performed using SPSS (Version 23, IBM, New York, NY, USA) and R Studio (Version 1.1.453, fmsb package).

The authors have read the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement—checklist of items, and the manuscript was prepared and revised accordingly [41].

4) Development of evidence based recommendations

Grading

Strength of recommendation and quality of evidence were based on the guideline of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, an internationally accepted system established in 2011 (https://www.uptodate.com/home/grading-tutorial#). Strength of any recommendation depends on the establishment between benefits and risks and burden. Three-category has been imitated for quality of evidence regarding treatment effect. All authors determined the strength of the consensus by voting yes or no: 95% or more 'yes' votes = 'full agreement'; at least 70% 'yes' votes = 'strong agreement', and more than 50% 'yes' votes = 'weak agreement'.

5) Ethics

The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council (22254–1/2012/EKU). All participants provided written consent of participation to this study. The ethics committee carefully checked and approved the consent procedure.

Results

There is no consensus on the start of AB therapy in patients with no bacterial culture test

Supplementary Figure 3 shows the flowchart of this systematic review. After careful selection, only 1 RCT reporting on the guidance of AB therapy was eligible for inclusion [42]. In this study, procalcitonin (PCT)-guided (>0.5 ng/ml) AB regime proved to be superior over 2-week prophylactic AB treatment in severe AP (Supplementary Fig. 4). We identified 22 studies [42–63] reporting on prophylactic antibiotic treatment in AP. Severe AP/acute necrotizing pancreatitis were analysed in 18 of 22 studies, however, these entities were defined in many forms: 9 and 11 studies incorporated CRP (ranging from >100 to >200 mg/l) and pancreatic necrosis (confirmed by CT or FNA) into the definitions Supplementary Fig. 5. Despite the inclusion of RCTs, the way how the studies defined the suspicion of an infection was vague. Factors taken into consideration were, as follows: CRP (5 studies), fever (generally in 5 studies, 2 of them considered persistent fever only), criteria of SIRS/organ failure/sepsis (3 studies), air bubbles in necrosis on CT (2 studies), and leukocytosis (2 studies). Only 2 studies suspected an infection when a rise in inflammatory markers occurred following an initial decrease. Interestingly, neither of the studies testing prophylactic ABs mentioned PCT, as a marker of infection in the included studies. The general approach proved a suspected infection was FNA and culturing in most cases followed by surgery as a treatment. A change in drug regime was managed either empirically and/or by culturing.

Antibiotics are overused worldwide

9869 patients' data were collected from 23 countries and it showed a global overuse of ABs. The highest rates of AB therapy could be seen in Asia (China 81.4%, Taiwan 80.6%) and Eastern Europe (Albania 78.6%, Bulgaria 78%), whereas the lowest rates are observed in Western Europe (Spain 31.8%, United Kingdom 31.2%) (Fig. 1). There is no association between the rate of AB therapy and the outcome (mortality, severity) of the disease between the countries. The details of centres and countries can be found in Supplementary Fig. 6.

There is a large detection bias in the initiation of AB therapy and bacterial culture test

In these series of data analysis we aimed to understand the decision making process of physicians concerning the initiation of AB therapy in AP. 962 of 1070 prospectively collected patients in the HPSG AP registry had details concerning AB therapy. Firstly, we confirmed that the registry represents a normal distribution of AP concerning age, gender, etiology, length of hospitalization (LOH), severity and mortality (Supplementary Fig. 7). Secondly, we performed the analysis on the major outcome parameters (LOH, severity and mortality) and found that (i) worse LOH, severity and mortality parameters are associated with AB treatment, (ii) holding off the AB therapy among patients with suspected infection (Group 2) is not associated with poor outcome, (iii) patients having bacterial culture (Group 4b) test had significantly worse outcome than patients having no bacterial test (Group 4a) among AB treated groups, (iv) confirmed infection had the worst outcome in AP (Group 5) (Fig. 2A and B) (v) the willingness of the initiation of AB therapy elevates parallel with the severity and finally (vi) the highest level of AB therapy is in biliary AP (Fig. 2C).

90% of AB therapy started in the first 3 days of AP

74% of AB are started on Day 1, 10.5% on Day 2, whereas 6.0% on Day 3 (Supplementary Fig. 8A). Early AB treatment had no association either with shorter AB administration (Supplementary Fig. 8D), or with the outcome of AP (Supplementary Figs. 8E and J). Administration of three different ABs (Supplementary Figs. 8B, F, G, K) or higher number of changes in the AB regime (Supplementary Figs. 8C, H, I, L) are associated with longer AB therapy and worse outcome of the disease suggesting that if patients' condition do not improve during AB therapy or bacterial resistance occurs doctors initiate AB therapy changes. Detailed statistics can be found in Supplementary Fig. 9. In 52% of the cases single AB, in 43.7% double AB, whereas in 4.3% three or more AB were administered. In the single AB group cephalosporin 29.5%, whereas in the double AB group ciprofloxacin and metronidazole were the most commonly chosen therapies (Supplementary Fig. 10). Of course a cohort analysis is not enable to differentiate between the drugs, but not surprisingly imipenem or not conventional AB therapies were associated with more severe pancreatitis and higher mortality (Supplementary Fig. 10). Detailed statistics can be found in Supplementary Fig. 11.

Elevated CRP level, white blood cell (WBC) count, lipase and amylase levels are the biomarkers used for the initiation of AB therapy

We investigated the four most commonly monitored laboratory markers (amylase, lipase, C-reactive protein, WBC count) during the course of AP. Mean levels of these parameters on the starting day of AB therapy were compared. The amylase and lipase levels showed association with the AB treatment, but as we expected, not

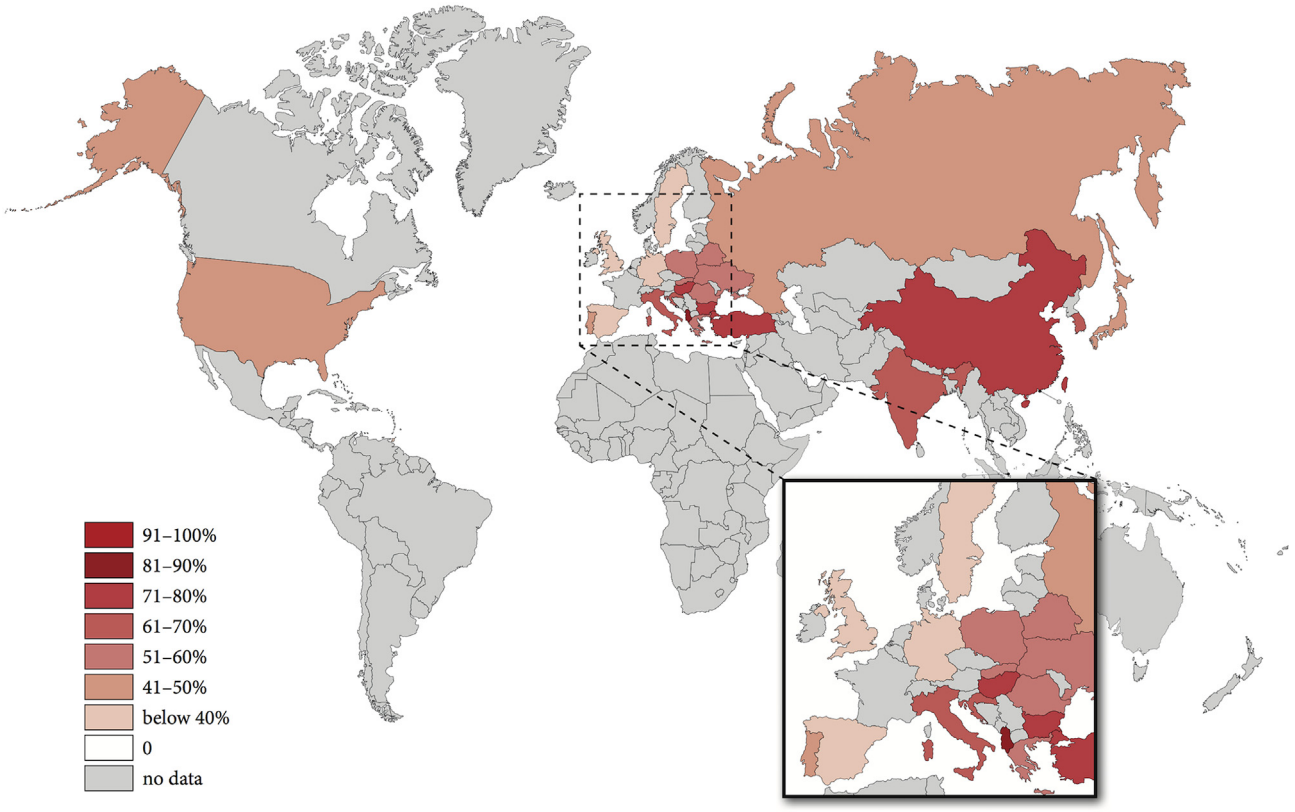


Fig. 1. Map of antibiotic use worldwide. There is a general overuse of AB worldwide (57.2%). The highest rates of AB therapy are in Asia (China 81.4%, Taiwan 80.6%) and Eastern Europe (Albania 78.6%, Bulgaria 78%), whereas the lowest rates are observed in Western Europe (Spain 31.8%, United Kingdom 31.2%).

A

	GROUPS		n	%	LOH	p	MILD	MOD	SEV	p	MORT	p
1	noAB		122	12.7%	8.3 ± 0.4		81.9%	18.0%	0.8%		0.8%	
2	noAB-susplNF		122	12.7%	8.2 ± 0.4	[1] = 0.887	78.7%	19.7%	1.6%	[1] = 1.000	0.8%	[1] = 1.000
	noAB		**244**	**25.4%**	**8.3 ± 0.3**		**79.9%**	**18.9%**	**1.2%**		**0.8%**	
3	prevAB		120	12.5%	12.3 ± 1.1	[3] < 0.001	67.5%	26.7%	5.8%	[1] = 0.244	0.8%	[1] = 1.000
4a	AB-noBACT	no bact culture	420	43.7%	10.7 ± 0.3		74.0%	23.6%	2.4%		1.4%	
4b	AB-noBACT	neg bact culture	102	10.6%	18.6 ± 1.5	[4a] < 0.001	32.3%	56.9%	10.8%	[4a] = 0.007	3.9%	[4a] = 0.559
5	AB-pozBACT		76	7.9%	22.9 ± 1.6	[4b] = 0.063	30.3%	40.8%	28.9%	[4b] = 0.028	6.6%	[4b] = 1.000
	AB		**718**	**74.6%**	**13.4 ± 0.5**	**[noAB] < 0.001**	**62.4%**	**30.6%**	**7.0%**	**[noAB] < 0.001**	**2.2%**	**[noAB] < 0.271**
			962	100%								

B

	n		1	2	noAB	3	4a	4b	AB[3-4 only]	p
MILD	620	100%	16.0%	15.5%	31.5%	13.1%	50.2%	5.3%	68.5%	
MOD	235	100%	9.4%	10.2%	19.6%	13.6%	42.1%	24.7%	80.4%	[MILD] < 0.001
SEV	31	100%	3.2%	6.5%	9.7%	22.6%	32.3%	35.5%	90.3%	[MILD+MOD] = 0.023
MORT	13	100%	7.7%	7.7%	15.4%	7.7%	46.2%	30.8%	84.6%	
	886									

C

	n	%		noAB	AB
Biliary	405	42.1%	100%	18.0%	82.0%
Alcohol	181	18.8%	100%	34.8%	65.2%
Hyperlipidaemia	23	2.4%	100%	21.7%	78.3%
Post ERCP	28	2.9%	100%	28.6%	71.4%
Idiopathic	207	21.5%	100%	30.4%	69.6%
Other	87	9.0%	100%	31.0%	69.0%
Combined	31	3.2%	100%	16.1%	83.9%
	962	100%			

Fig. 2. Grouping of patients based on sign of infection, antibiotic (AB) treatments and microbiology examination. General characterisation of AB administration, length of hospitalization (LOH) and mortality. Based on the AB treatment patients were divided into two main groups (non-AB and AB) and six subgroups. **Group 1:** Patients had no sign of inflammation and did not received ABs. **Group 2:** Patients had sign of inflammation (fever, imaging alterations, etc.) but did not received ABs. **Group 3:** Patients had no sign of inflammation but received preventive ABs. **Group 4a:** Patients had sign of inflammation (fever, imaging alterations, etc.) and received antibiotics, however no microbiology culture was requested. **Group 4b:** Patients had sign of inflammation (fever, imaging alterations, etc.) and received antibiotics. Microbiology culture was done but no pathogen bacteria were found. **Group 5:** Patients had sign of inflammation (fever, imaging alterations, etc.), microbiology culture was performed with positive results and received AB treatment. **A.** LOH was significantly longer in AB therapy groups then in non-AB groups. (13.4 ± 0.5 days vs 8.3 ± 0.3 days, $p < 0.001$) In presence of suspected infection (Group 2) LOH (8.3 ± 0.4 days vs 8.2 ± 0.4 days), severity and mortality were the same as in Group 1. Preventive AB therapy (Group 3) resulted significantly longer hospitalization compare to Group 1 (12.3 ± 1.1 days vs 8.3 ± 0.4 days, $p < 0.001$). Significantly more patients with moderate (220/718 vs 46/244, $p < 0.001$) and severe disease (50/718 vs 3/244, $p < 0.001$) course received AB therapy. There was no significant difference in mortality between the groups. **B.** If we retracted Group 5 (patients with proven infection), the rate of AB therapy still remained significantly high in moderate and severe AP ($p < 0.001$, $p = 0.023$). **C.** AB treatment in context of etiology of AP.

with the severity of the disease (Fig. 3A–B, E-F). In addition, significantly higher inflammatory markers (CRP and WBC) were associated with the AB treatment and more severe AP (Fig. 3C–D, G-H).

Elevation of PCT level but not CRP, WBC, lipase or amylase levels are associated with infection in the early phase of AP

CRP levels progressively increase, whereas WBC values decrease during the first 3 days of AP irrespectively of AB therapy in either suspected (Group 4a and b) or in confirmed (Group 5) infection (Fig 4A, F). Suspected infection (Group 2) did not show difference in CRP and WBC levels compared to Group 1 among the non-AB groups (Fig. 4B, G). Preventive AB therapy (Group 3) was administered in patients with significantly higher CRP and WBC levels ($p < 0.001$, $p = 0.046$), however, both CRP and WBC level decreased nearly the same level as Group 1 by day 5 (Fig. 4C, H). Bacterial culture test (Group 4b) was performed in patients with significantly higher CRP ($p = 0.008$) (Fig. 4D). These data are in accordance with the results at the start of AB therapy in AP (Fig. 3.). Very importantly, neither CRP nor WBC showed differences between patients having positive blood culture (Group 5) vs. patients having negative blood culture tests (group 4b), suggesting that CRP and WBC have no association with infection at the early phase of AP (Fig. 4E, J, L, M). However, PCT level, as confirmed in earlier studies showed correlation with infection (Fig. 4K, N) with acceptable sensitivity and specificity (AUC:0.73). Fig. 5 shows the changes of amylase and lipase during AP. It is very clear that neither infection (Group 2) nor AB treatment (Group 3, 4 and 5) change the pattern of enzyme levels during AP.

Pancreatic infection causes the worst outcome in AP

Here we correlated the disease outcome with the infected organs. Biliary, respiratory, urogenital infection or elevated PCT or fever alone with no identified organ infection resulted in a moderate severity range (8.3%–14.3%) without mortality, however pancreatic infection caused 25% severe AP with extremely high mortality rate (25%), (Fig. 6). Detailed statistics can be found in Supplementary Fig. 12.

Increase in the pathogen numbers is associated with the worse outcome of AP

The most common pathogens were Staphylococci (34.2%), Enterococci (27.4%), Clostridium difficile (22.4%), Escherichia coli (18.4%) and Pseudomonas (13.2%). Due to the relatively low event rates, we could not analyse the differences among pathogens, however, it was obvious that increased numbers of detected pathogens strongly correlates with worse outcomes in AP (Supplementary Fig. 13).

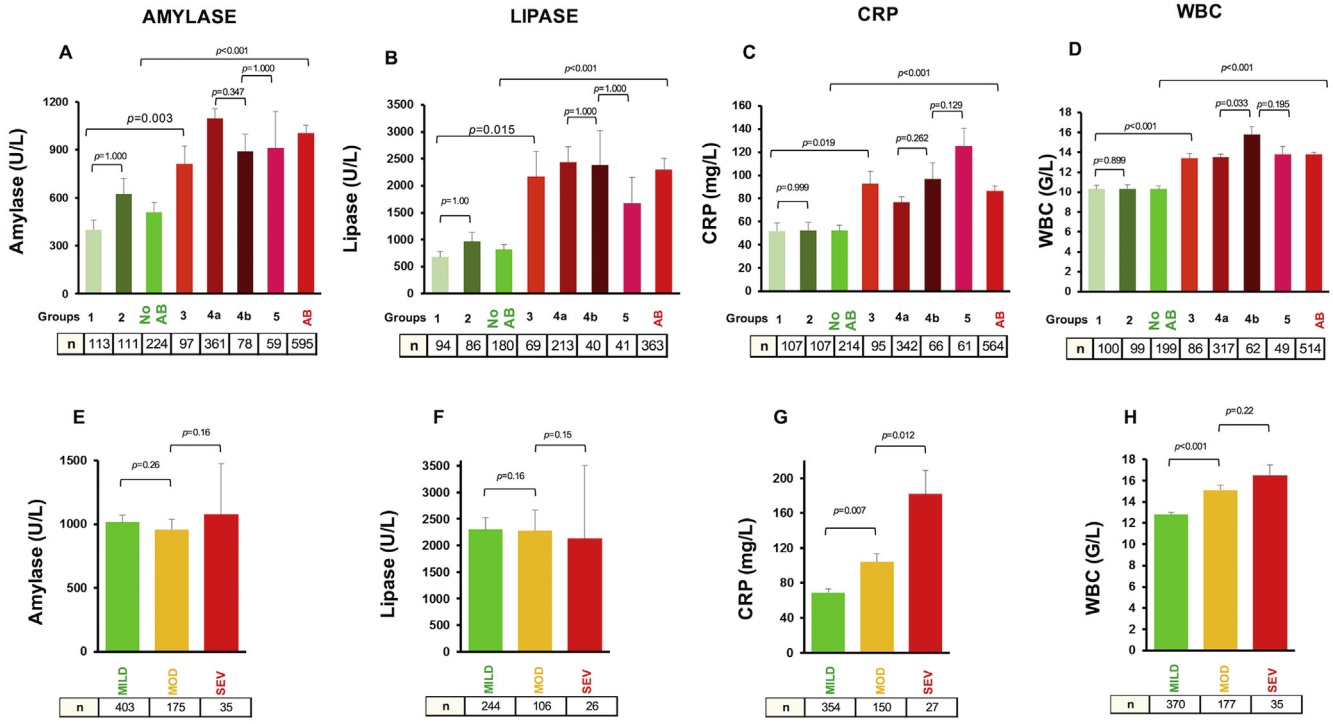


Fig. 3. Most commonly monitored laboratory markers on starting day of AB therapy. Average amylase, lipase, C-reactive protein (CRP) and white blood cells (WBC) were calculated on starting day of AB therapy. In non-AB groups day-matched controls were selected. **A.** Average amylase in non-AB group (510.01 ± 57.91 U/L) compare to AB group (1004.15 ± 50.22 U/L) has been significantly differed ($p < 0.001$). **B.** There has been a significant difference ($p < 0.001$) between average lipase in non-AB (815.83 ± 96.73 U/L) and AB (2298.72 ± 207.82 U/L) groups. **C.** CRP showed a significant difference between non-AB and AB groups (52.16 ± 4.91 mg/L vs 86.4 ± 4.2 mg/L, $p < 0.001$) similar trends have been detected with regards to WBC levels (10.32 ± 0.28 G/L vs 13.8 ± 0.2 G/L, $p < 0.001$ **(D)**. **E.** Average amylase (1015.25 ± 55.10 U/L, 957.41 ± 83.33 U/L, 1077.48 ± 397.02 U/l and lipase **(F)** (2303.05 ± 219.19 U/L, 2286.82 ± 378.21 U/L, 2131.42 ± 1377.75 U/L) did not differ between severity groups (mild-moderate: $p = 0.26$, $p = 0.16$; moderate-severe: $p = 0.16$, $p = 0.15$). **G.** Average CRP (68.77 ± 4.32 mg/L, 104.56 ± 8.71 mg/L, 181.7 ± 27.26 mg/L) and WBC **(H)** (12.83 ± 0.21 G/L, 15.11 ± 0.49 G/L, 16.5 ± 0.98 G/L) levels showed correlation with severity of AP (mild-moderate: $p = 0.007$ and $p < 0.001$, moderate-severe: $p = 0.012$ and $p = 0.22$).

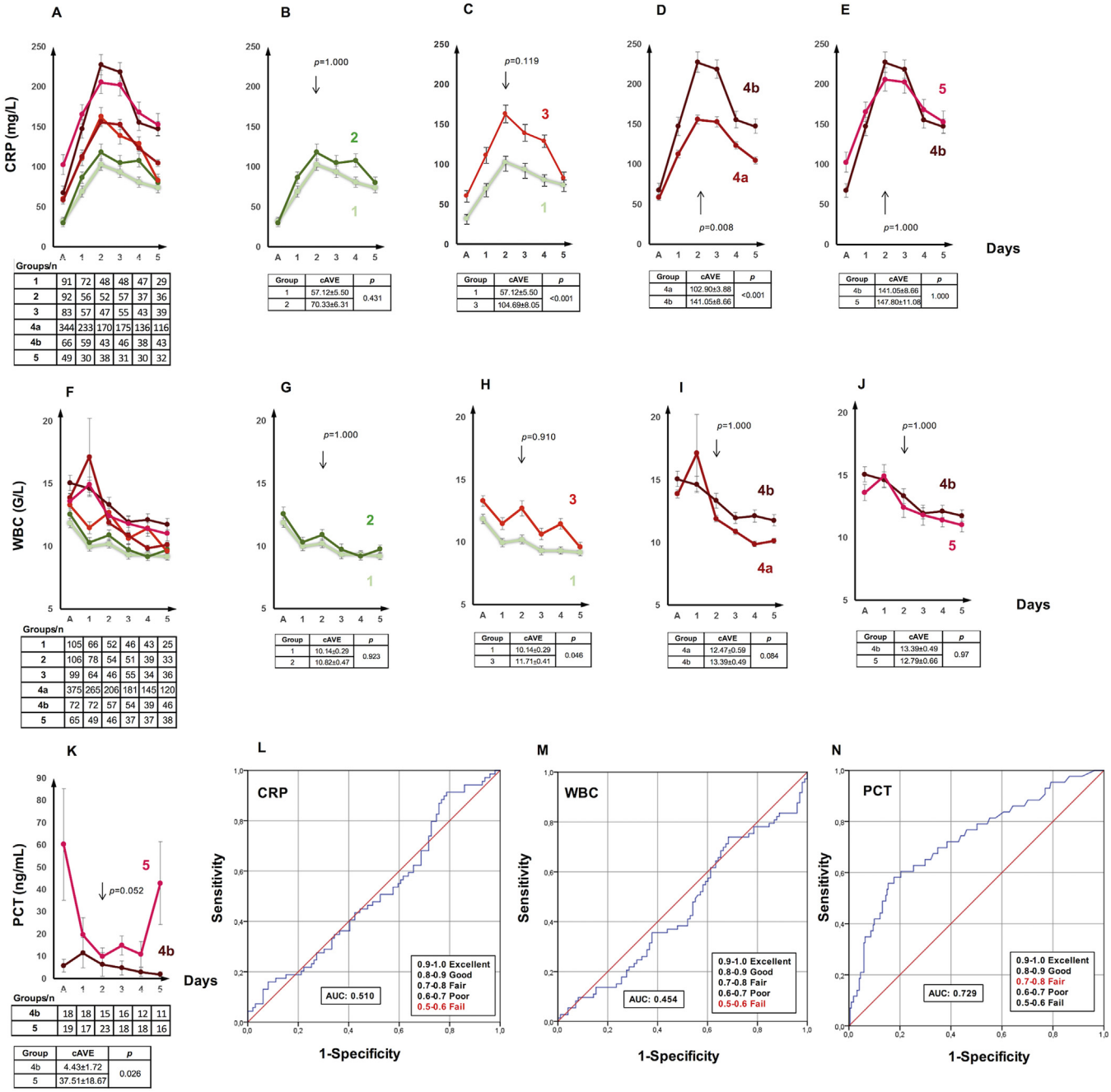


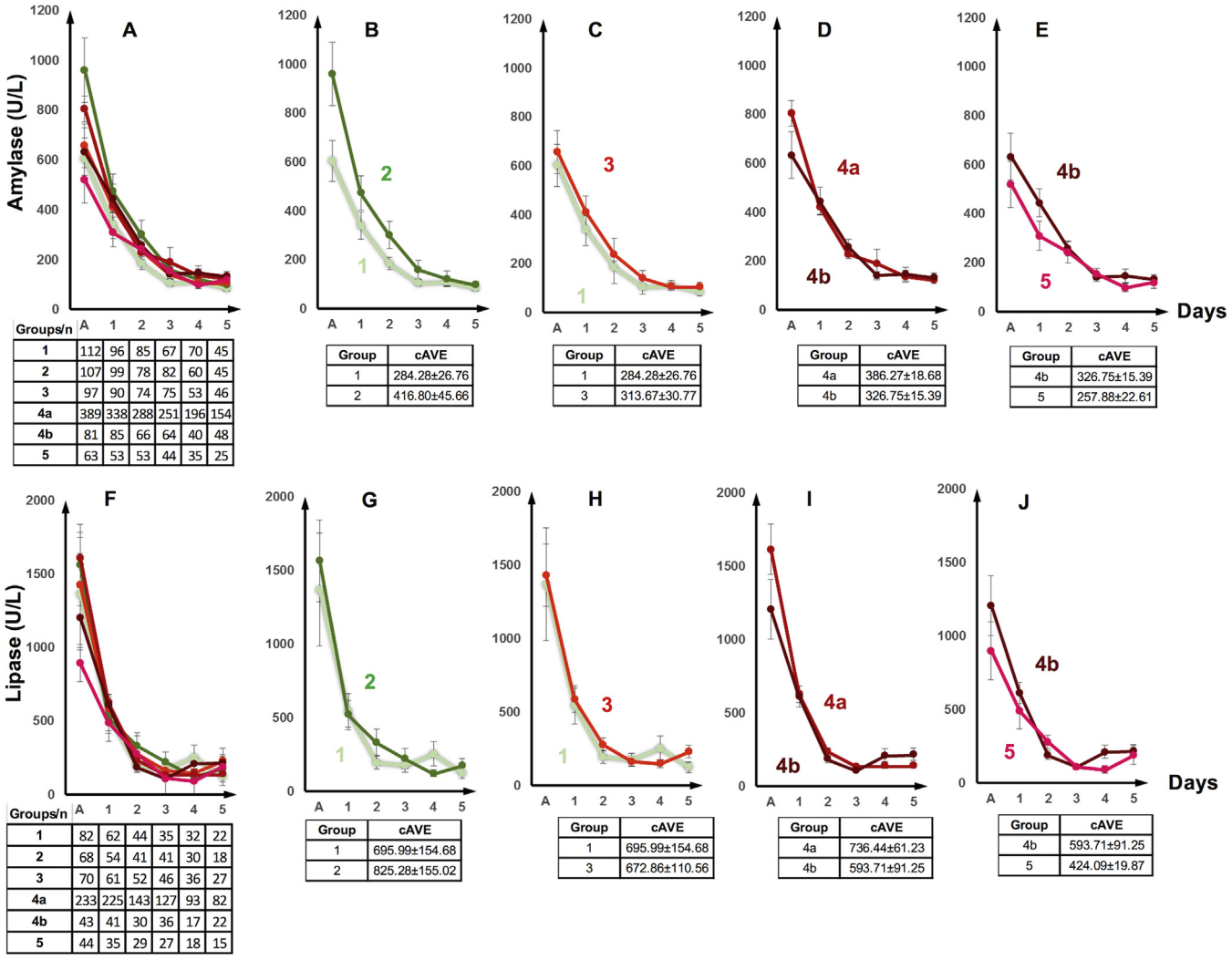
Fig. 4. Trends in the changes of CRP and WBC during the early phase of AP. A. Due to the inflammation of the pancreas, irrespectively from the infection CRP levels rose during the first 3 days. **F.** Non-similar trend can be seen in WBC levels. **B and G.** Suspected infection (Group 2) in AP did not show difference ($p = 0.431$, $p = 0.923$) in cumulative average (cAVE) of CRP (70.33 ± 6.31 mg/L) and cAVE of WBC levels (10.82 ± 0.47 G/L) compare to Group 1 (57.12 ± 5.50 U/L, 10.14 ± 0.29 G/L). **C and H.** Preventive AB therapy (Group 3) was administered in patients with significantly higher CRP (104.69 ± 8.05 mg/L) and WBC levels (11.71 ± 0.40 G/L) ($p = <0.001$ and $p = 0.046$, respectively), however we observed the CRP increase, then drop at day 3 and decreased nearly the same level as Group 1 by the day 5. **D and I.** Bacterial culture (Group 4b) was performed in patients with significantly higher CRP (102.90 ± 3.88 mg/L vs 141.05 ± 8.66, $p < 0.001$). **E. and J.** Proven infection (Group 5) did not result in significant difference in CRP and WBC levels in the first five days. K: cAVE of PCT differ significantly between Group 4b and Group 5 ($p = 0.026$). **L, M and N.** CRP (AUC: 0.51) and WBC (AUC: 0.45) failed, however PCT (AUC: 0.73) fairly can predict infection in AP.

Consensus statements

Based on the systematic review and retrospective and prospective data analysis, the authors from 62 centres/23 countries accepted the following statements and recommendations as amendments to the current guidelines (Table 1.)

Statement 1: There is a general overuse of ABs in AP, therefore, centres should make a strong effort to reduce it to a justifiable level (GRADE 1C: strong suggestion, low quality evidence, full agreement)

Statement 2: CRP and WBC values are not associated with infection in the early phase of AP, therefore CRP and WBC should not be used as biomarkers for decision making concerning AB



Groups/n	A	1	2	3	4	5
1	112	96	85	67	70	45
2	107	99	78	82	60	45
3	97	90	74	75	53	46
4a	389	338	288	251	196	154
4b	81	85	66	64	40	48
5	63	53	53	44	35	25

Group	cAVE
1	284.28±26.76
2	416.80±45.66

Group	cAVE
1	284.28±26.76
3	313.67±30.77

Group	cAVE
4a	386.27±18.68
4b	326.75±15.39

Group	cAVE
4b	326.75±15.39
5	257.88±22.61

Groups/n	A	1	2	3	4	5
1	82	62	44	35	32	22
2	68	54	41	41	30	18
3	70	61	52	46	36	27
4a	233	225	143	127	93	82
4b	43	41	30	36	17	22
5	44	35	29	27	18	15

Group	cAVE
1	695.99±154.68
2	825.28±155.02

Group	cAVE
1	695.99±154.68
3	672.86±110.56

Group	cAVE
4a	736.44±61.23
4b	593.71±91.25

Group	cAVE
4b	593.71±91.25
5	424.09±19.87

Fig. 5. Trends in the changes of amylase and lipase during the early phase of AP. There are no significant differences between the groups.

therapy in the early phase of AP (GRADE 1C: strong suggestion, low quality evidence, full agreement).

Statement 3: Progressive elevation of CRP is part of the inflammatory response in AP, therefore, an upward trend of CRP levels should not be an indicator for AB treatment in the early phase of AP (GRADE 1C: strong suggestion, low quality evidence, full agreement).

Statement 4: Elevation of PCT levels during the early phase of AP is associated with infection, therefore, it can guide the choice to start AB treatment in the absence of proven infection (GRADE 2C: weak suggestion, low quality evidence, full agreement).

Discussion

At the beginning of our study, we performed a systematic review in which we showed that (i) PCT can be a good marker for suspected infection (ii), there is no consensus concerning the compulsory start of AB therapy in patients with no positive bacterial culture test, (iii) patients having necrosis have no benefits from AB therapy. These data have predicted the results of our international retrospective data analysis, which showed that administration of ABs widely differs between countries.

Generally, in Western European countries less AB is administered, whereas Eastern European and Asian countries are the most frequent users of AB. Our data are in accordance with several national surveys performed in the past two decades. In Germany, 47% of respondents use AB prophylaxis [32] and 44% of the doctors always administer AB in cases of severe AP [33]. In the UK and Ireland, 24% use prophylaxis in AP regardless of the severity [64]. Prophylactic AB treatment is utilized by 73% of the European members of the International Hepato-Pancreato-Biliary Association [65]. 40.9% of the interviewed American clinicians give AB in more than 75% of patients with severe AP [35]. In Japan, before the publication of the Japanese evidence-based guidelines in 2003, 82.5% of the physicians used AB prophylaxis after the publication 76.1% [34], which is still a frequent practice pattern, considering that the Japanese guidelines also endorse routine use of AB prophylaxis in mild to moderate AP [66,67]. These data show without proper guideline, the physicians' willingness of AB therapy is very high. The high rate of AB treatment can also be explicable with the fact that the death rate can increase from 2 to 35% due to bacterial infection of the necrotic pancreatic tissue [25,68] Organ failure alone was associated with a mortality of 19.8% [68,69], whereas, infected necrosis without organ failure has low mortality [70]. Based on these observations, it is not surprising that several trials

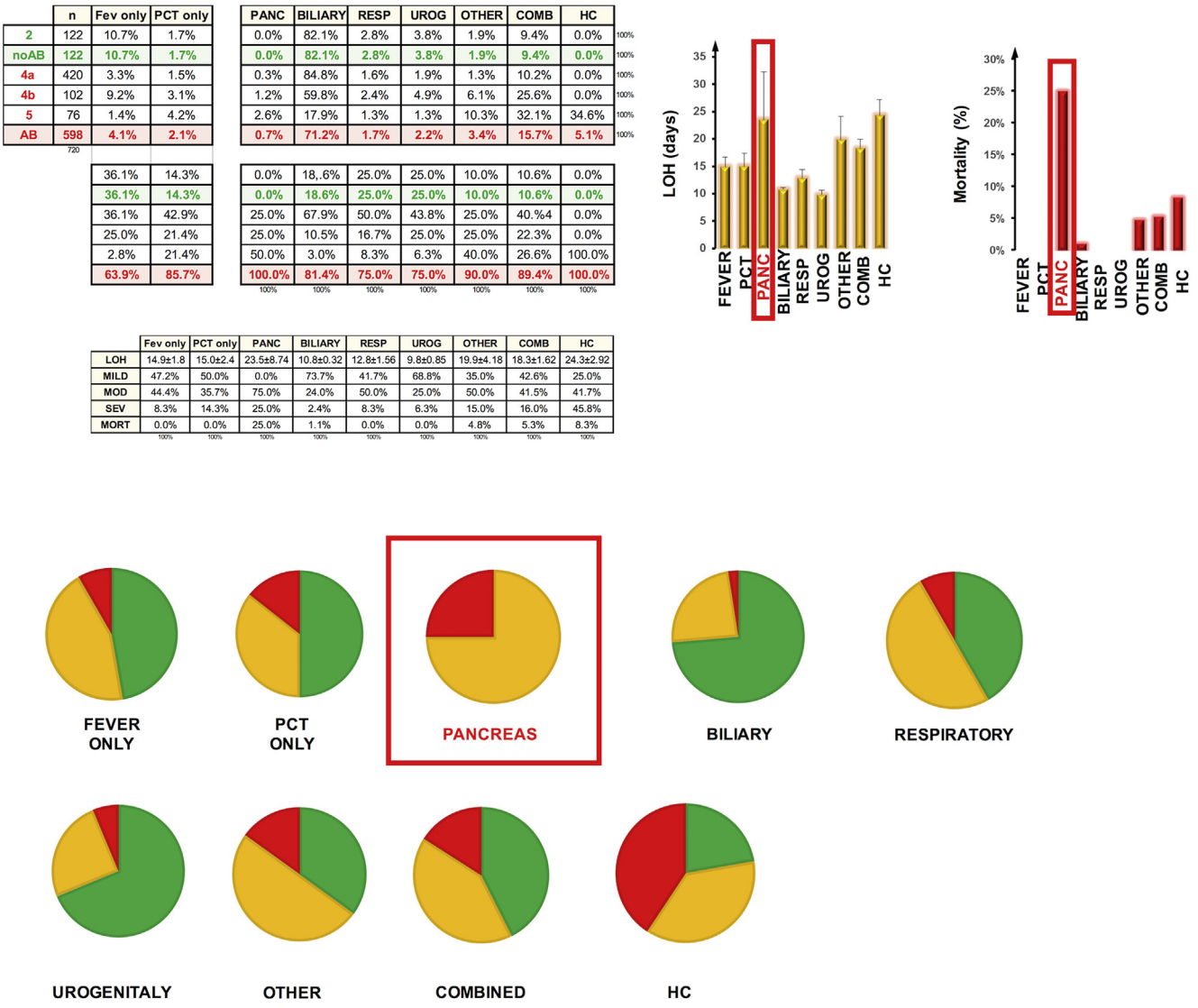


Fig. 6. Source of infection in AP. Infection of the pancreas extended the length of hospitalization (LOH) to 25.55 ± 4.76 days, deteriorated the course of the disease (moderate 25%, severe 75%) and elevated the mortality to 25%. Ple charts represent the distribution of mild (green), moderate (yellow) and severe (red) cases in each group of AP patients.

Table 1
Summary of the consensus statements.

	Statements	Grade of evidence	Level of agreement
1	There is a general overuse of antibiotics in AP, therefore, centres should make a strong effort to reduce it to a justifiable level.	1C	full (99%)
2	CRP and WBC values are not associated with infection in the early phase of AP, therefore CRP and WBC should not be used as biomarkers for decision making concerning AB therapy in the early phase of AP.	1C	full (97%)
3	Progressive elevation of CRP is part of the inflammatory response in AP, therefore, an upward trend of CRP levels should not be an indicator for AB treatment in the early phase of AP.	1C	full (97%)
4	Elevation of PCT levels during the early phase of AP is associated with infection, therefore, it can guide the choice to start antibiotic treatment in the absence of proven infection.	2C	full (96%)

and meta-analysis were performed to understand the usefulness of preventive AB in AP [44,49,53,54,56,57,59,61,71]. A recently published Cochrane review showed that neither of the preventive AB treatments decreased short-term mortality in AP [72].

The most important goals of our study were (i) to find out what parameters mislead physicians during the initiation of AB therapy (ii) to find a biomarker(s), which can predict infection without bacterial culture test. In this investigation we showed with several analysis that elevation of amylase, lipase levels, CRP and WBC mislead the doctors decision making on the initiation of AB therapy.

CRP and WBC have been confirmed to be strongly associated with the severity of AP [73–75] however, data on lipase and amylase are contradictory [76–79]. In our study, the initiation of AB therapy was based on the severity and most probably on a predicted infection diagnosed by the elevation of inflammatory biomarkers namely the CRP and WBC. Here we confirmed that these laboratory parameters have no association with infection, but PCT, which showed correlation with infection with acceptable sensitivity and specificity.

Finally, based on the systematic review and the retrospective and prospective cohort analyses, the participants of this trial accepted important statements and recommendations as amendments to the current guidelines. The authors strongly believe that the evidence and consensus statements presented in this article will significantly decrease unnecessary AB therapy in AP worldwide.

Authors contribution

P. Hegyi and A. Párniczky formulated the research questions and designed the study. F. Izbéki, L. Gajdán, A. Halász, Á. Vincze, I. Szabó, G. Pár, J. Bajor, P. Sarlós, J. Czimmer, J. Hamvas, T. Takács, Z. Szepes, L. Czakó, M. Varga, J. Novák, B. Bod, A. Szepes, J. Sümegi, M. Papp, Cs. Góg provided patients' data to the Hungarian Pancreatic Registry. They have also controlled the quality of the data.

Zs. Szakács and A. Párniczky performed the systematic review.

W. Huang, Q. Xia, P. Xue, W. Li, W. Chen, N. V. Shirinskaya, V. L. Poluektov, A. V. Shirinskaya, P. Hegyi Jr., M. Bátovský, J. A. Rodriguez-Oballe, I. M. Salas, J. Lopez-Diaz, J. E. Dominguez-Munoz, X. Molero, E. Pando, M. L. Ruiz-Rebollo, B. Burgueño-Gómez, Y. Chang, M. Chang, A. Sud, D. Moore, R. Sutton, A. Gougol, G. I. Papachristou, Y. Mykhailovych Susak, I. Olehovych Tiuliukin, A. P. Gomes, M. J. Oliveira, D. J. Aparício, M. Tantau, F. Kurti, M. Kovacheva-Slavova, S. Stecher, J. Mayerle, G. Poropat, K. Das, M. V. Marino, G. Capurso, E. Małecka-Panas, H. Zatorski, A. Gasiorowska, N. Fabisiak, P. Ceranowicz, B. Kuśnierz-Cabala, J. R. Carvalho, S. R. Fernandes, J. H. Chang, E. Kwang Choi, J. Han, S. Bertilsson, H. Jumaa, G. Sandblom, S. Kacar, M. Baltatzis, A. V. Varabei, V. Yeshy, S. Chooklin, A. Kozachenko, N. Veligotsky provided retrospective data about the antibiotic therapy in acute pancreatitis in their centre. E.M Tóth, Zs. Szakács, Sz. Gódi, R. Hágendorn, D. Illés, B. Koncz, K. Márta, A. Mikó, D. Mosztbacher, B.Cs Németh, D. Pécsi, A. Szabó, Á. Szücs, P. Varjú, A. Szentesi, E. Darvasi, B. Erőss contributed to the study implementation, data acquisition and quality control of the prospectively collected data, A. Párniczky, E.M Tóth, P. Hegyi interpreted the data, T. Lantos performed the statistical analysis, A. Párniczky, E.M Tóth, T. Lantos with the technical help of K. Márta constricted the figures.

A. Párniczky and P. Hegyi wrote the article, all authors have read, approved the final manuscript and have been involved in the consensus voting.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.04.003.

Financial or ethical conflict of interest

Authors disclose any financial or ethical conflict of interest.

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