EVIDENCE-BASED MANAGEMENT OF ACUTE PANCREATITIS

PhD Thesis

Doctoral School of Pharmacological and Pharmaceutical Sciences

Head of the doctoral school: Erika Pintér, MD, PhD, DSc

Szilárd Gódi, MD

First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary

Supervisors:

Áron Vincze, MD, PhD, Med. habil

First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary

Péter Hegyi, MD, PhD, DSc

Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary

Pécs, 2020

1. Table of contents

2. List of abbreviations

AB: antibiotic

ALI: acute lung injury

ANC: acute necrotizing collection

ANOVA: analysis of variance

ANP: acute necrotizing pancreatitis

AP: acute pancreatitis

APA: American Pancreatic Association

APACHE II: acute physiology and chronic health examination II

APFC: acute peripancreatic fluid collection

ARDS: acute respiratory distress syndrome

AUC: area under the curve

BISAP: bedside index of severity in acute pancreatitis

BMI: body mass index

CECT: contrast-enhanced computed tomography

CI: 95% confidence interval

CRA: clinical research administrator

CRF: case report form

CRP: C-reactive protein

CT: computed tomography

CTSI: computed tomography severity index

DAMP: damage-associated molecular pattern

ER: emergency unit

ERCP: endoscopic retrograde cholangiopancreatography

EUS: Endoscopic ultrasound

FNAB: fine-needle aspiration biopsy

GRADE: Grading of Recommendations Assessment, Development and Evaluation

HDL-C: high-density lipoprotein-cholesterol

HPSG: Hungarian Pancreatic Study Group

IAP: International Association of Pancreatology

ICU: intensive care unit

IL-1β: interleukine-1β

IL-1β-R: interleukine-1β receptor

IPN: infected pancreas necrosis

MAP: mild acute pancreatitis

MetS: metabolic syndrome

MODS: multi-organ dysfunction syndrome

MRI: magnetic resonance imaging

MSAP: moderately severe acute pancreatitis

Nuclear factor-κB: NFκB

OR: odds ratio

PC: pancreatic centre

PCT: procalcitonin

Pro-IL-1β: the ’pro’ form of interleukine-1β

PRSS1: human cationic trypsinogen

Q1-Q3: 25-75% quartiles

RCT: randomized controlled trials

ROC: receiver operation characteristic

SAP: severe acute pancreatitis

SD: standard deviation

SD: surgical department

SE: standard error of the mean

SIRS: inflammatory response syndrome

SPINK1: serine protease inhibitor Kazal type 1

TIMD: territorial internal medical department

TLRs: toll-like receptors

TNF-R1: tumour necrosis factor-receptor 1

TNF-α: tumour necrosis factor-α

TPC: tertiary pancreas centre

US: ultrasonography

WBC: white blood cell count

WON: walled-off necrosis

3. Introduction

Pancreatitis is the inflammation of the pancreas, which includes a continuum of disorders from acute pancreatitis (AP) through early chronic pancreatitis to chronic pancreatitis (1). AP, a potentially life-threatening condition, is one of the leading causes of emergency visits and hospital admissions among gastrointestinal disorders in developed countries (2). Disease-specific curative therapies are still lacking, which provides the ground for intensive research in various areas of pancreatology, including diagnostics, prognostics and therapeutic implications (3).

3.1 Incidence

The most extensive evidence on incidence of AP was provided by a thorough meta-analysis (2016) based on ten population-based cohort studies identified through systematic literature search (4). According to this report, crude incidence of AP proved to be 33.74 cases per 100,000 person-years (95% confidence interval [CI]: 23.33–48.81 cases). Incidence of AP ranged from 15.00 cases in Denmark to 83.70 cases in Sweden per 100,000 person-years across studies. If we consider the European studies, crude incidence of AP was 28.93 cases per 100,000 person-years (CI: 16.64–50.30 cases). Observations raised concerns about a rising trend in incidence of AP diagnosis (Figure 1), which might be explained by the better access to diagnostic tools and by the trend of acquired (mainly lifestyle-related) risk factors (5-7).

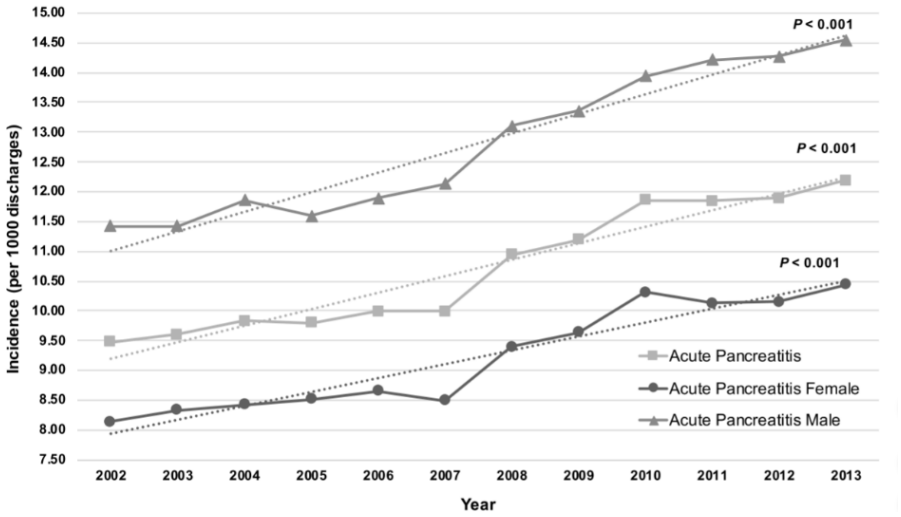


Figure 1. Incidence of acute pancreatitis between 2002 and 2013 in the US. P-values indicate a significant increase in incidence, shown by the dashed trend lines. The increment in incidence was observed in both males and females. Reprinted from *'Temporal Trends in Incidence and Outcomes of Acute Pancreatitis in Hospitalized Patients in the United States From 2002 to 2013'*, by Brindise et al., 2019, *Pancreas*.

Reliable data on incidence of AP in Hungary are still lacking. According to the unofficial report of the Hungarian Central Statistical Office, approximately 5,000–5,500 cases are diagnosed annually, which corresponds to an estimated crude incidence of 50–55 cases per 100,000 person-years.

3.2 Pathomechanism and aetiology

Mechanisms triggering and driving pancreatic inflammation are extensively studied, yet, some steps of initiation and progression have remained unexplored. In the process, we differentiate genetic susceptibility from acquired factors (mainly environmental risk factors). Nevertheless, according to the 'multiple hits on multiple targets' theory, the combination of potentially harmful factors ('hits') are required to impair different cellular/molecular structures ('targets') to initiate the development of AP (8).

Genetic susceptibility is driven by genes encoding pancreatic proteases or regulators of proteases. The gain-of-function or loss-of-function defects lead to premature activation of pancreatic digestive enzymes (the family of zymogens, from which trypsinogen should be highlighted), mediating pancreatic damage via autodigestion. One example is the loss-of-function mutation of a trypsin inhibitor, serine protease inhibitor Kazal type 1 (SPINK1). Another example could be the gain-of-function mutation of human cationic trypsinogen (PRSS1), becoming prone to early activation (9-11). Several types of mutations are characterized at http://www.pancreasgenetics.org/.

There are numerous environmental or acquired factors which are implicated in the pathomechanism of AP. Biliary pathologies, including but not limited to gallstone disease and microlithiasis, are thought to be responsible for 40–60% of AP cases via triggering reflux of bile to or retention of pancreatic juice in the pancreatic ducts, leading to early activation of digestive enzymes (12). Alcohol abuse is the second most common factor in the Western world accounting for 25–30% of AP cases where alcohol and its toxic metabolites lead to direct acinar and ductal cell damage as well as premature enzyme activation (13). Other aetiological factors include hypertriglyceridaemia (considered causative above 11 mmol/L, the third most common aetiology in the Western countries whereas the second most common aetiology in Japan), drugs (mainly chemotherapeutics and immunosuppressants), iatrogenic injury (endoscopic retrograde cholangiopancreatography [ERCP], surgery), trauma, infections, hypoxia and ischaemia, hypercalcaemia and pancreatic malformations. If none of the known aetiological factors

is identified in the background during a thorough investigation, idiopathic AP can be diagnosed (10–30% of the cases) (14).

Here, we introduce a model describing the development and course of AP. No matter what factors are in the background, activation of pancreatic digestive enzymes is an early step in which intracellular Ca^{2+} spike is a critical moment (this is the so-called calcium-dependent protease activation; another ancillary mechanism is the cathepsin B-dependent protease activation). Premature protease activation of any cause leads to injury of pancreatic acinar and ductal cells, by which the mechanisms of cell death are activated. The type of cell death can be necrosis, apoptosis, autophagy, necroptosis or pyroptosis. Protease activation and cell death form a vicious cycle by accelerating each other (some theories pose that cell death precedes protease activation, others scientists presume that protease activation comes first). Cell fragments and the released inflammatory mediators activate leukocytes, leading to inflammation in which Nuclear factor-κB (NFκB) pathway plays a key role. The process is illustrated in Figure 2. As a consequence, monocytes/macrophages and neutrophil granulocytes migrate to the pancreatic parenchyma, producing a large amount of various pro- and anti-inflammatory cytokines, chemokines and other mediators, which maintain and aggravate the vicious cycle of cell death and protease activation. In the meantime, amylase and lipase are released from the dying parenchymal cells to the circulation, serving as indicators of AP. The release of inflammatory mediators is responsible for the escalation of local immune response into systemic inflammatory response syndrome (SIRS), with an abrupt rise in C-reactive protein (CRP). Finally, since cytokines are vasoactive mediators, the cytokine storm causes distributive vasoplegic shock and multi-organ dysfunction syndrome (MODS) in severe cases (9, 15, 16).

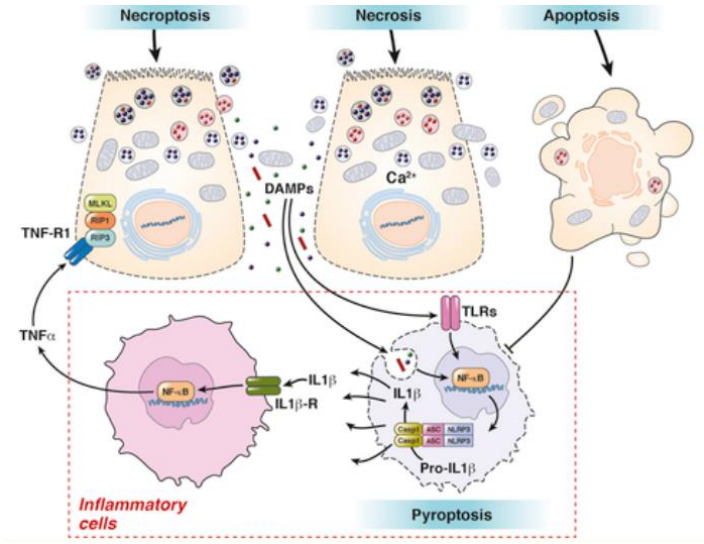


Figure 2. Relationship between cell death and immune response in acute pancreatitis. DAMP: damage-associated molecular pattern, IL-1β: interleukine-1β, IL-1β-R: interleukine-1β receptor, NFκB: Nuclear factor-κB, Pro-IL-1β: pro form of interleukine-1β, TLRs: toll-like receptors, TNF-R1: tumour necrosis factor-receptor 1, TNF-α: tumour necrosis factor-α. Reprinted and adapted from *'Genetics, Cell Biology, and Pathophysiology of Pancreatitis'* by Mayerle et al., 2019, *Gastroenterology*.

3.3 Diagnostic criteria

Although there were several international initiations to define AP and AP-related concepts in adults, the most widely accepted system is the 2012 revised Atlanta Classification (17). Based on the diagnostic criteria of this classification, the diagnosis of AP requires at least two of the followings ('two out of three criteria'):

1) abdominal pain consistent with AP (acute onset of a persistent, severe, epigastric pain often radiating to the back);
2) serum lipase activity or amylase activity at least three times greater than the upper limit of normal; and
3) characteristic findings of AP on contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI) or transabdominal ultrasonography (US).

3.4 Complications, severity and mortality

The disease course of AP varies: some cases are mild (almost asymptomatic) while the critically-ill patients require intensive care. Following the revised Atlanta Classification, we grade the severity of AP based on local and systemic complications (17).

3.4.1 Local complications

Local status can be assessed based on findings on CECT. Cases can be divided by the presence of pancreatic and/or peripancreatic necrosis into acute interstitial oedematous pancreatitis or acute necrotizing pancreatitis (ANP).

If fluid accumulates in the surrounding area of (but not in) the pancreas without necrosis, a definable wall and within four weeks after onset of AP, the condition is termed as acute peripancreatic fluid collection (APFC). If the (peri)pancreatic fluid contains liquid and solid components derived from pancreatic necrosis, the condition is termed as acute necrotizing collection (ANC).

If encapsulated fluid collection develops four weeks after the onset of interstitial oedematous AP (which is usually round or oval, locates mostly outside the pancreas and has no solid containment), the condition is termed as pancreatic pseudocyst. If the (peri)pancreatic necrosis develops a well-defined wall (usually four weeks after onset of ANP), the condition is termed as walled-off necrosis (WON).

If pancreas visualisation is permitted, US is sufficient to establish the diagnosis of AP. However, CECT outperforms US in detecting necrosis or other local complications

(18). The revised Atlanta Classification recommends CECT while the Appropriateness Criteria released by the American College of Radiology recommends CECT or MRI for the diagnosis of local complications. Documentation of local complications is not necessary in the early phase of AP, the ideal timing of imaging for this purpose is 5–7 days after onset (definitely later than 72 hours) (17, 19).

Considering the time frames in the definitions (>4 weeks after onset for pseudocyst and WON) and the fact that follow-up imaging is often missing, the true incidence of local complications is hard to be estimated. ANP might develop in 20–40% and WON in 1–9% of the cases (for details, see the review of Rana et al.) (20). However, a recent prospective observational study performing CECT at 5–7-day, 1-month and 3-month after onset detected a surprisingly high incidence of ANP (81%) and consequent WON (58.7%) (21). Another study recorded similarly high incidence of APFC (42.7%) and pseudocysts (6.3%) (22). Of note, these numbers should be treated with caution as a lot depends on the study population (e.g. the proportion of recurrent, acute-on-chronic or severe cases).

3.4.2 Systemic complications

Systemic complications are considered to be the consequence of cytokine storm. Newly developing organ failure (most commonly, acute respiratory failure, kidney failure or heart failure), as well as the deterioration of pre-existing chronic conditions (such as the decompensation of chronic heart failure), should be taken into account on assessment. The Modified Marshall Score is the recommended tool to determine organ failure (23). Transient (resolves within 48 hours) and persistent organ failure (lasts longer than 48 hours) should we distinguished (discussed under the heading ’3.4.4 Severity and mortality’). If organ failure affects more than one organ system, it is termed MODS (a synonym is multiple organ failure).

Lung injury (acute lung injury [ALI] or acute respiratory distress syndrome [ARDS]) with subsequent respiratory failure is the most common systemic complication of AP (probably due to the release of pancreatic phospholipase A2). Any organ failure develops up to 5–15% of patients: incidence of respiratory, renal and heart failure was 9, 7 and 4% in a study, respectively (24). Comparable incidences were calculated from data in our earlier cohort of 600 AP cases from Hungary (25).

3.4.3 Infectious complications

Site of infections can be extrapancreatic and pancreatic; both have the potential to evolve into sepsis. Common extrapancreatic infections include acute cholangitis, pneumonia, catheter-related and line infections, urinary tract infections. The most common form of pancreatic infections is the infected pancreas necrosis (IPN). 50% of IPN develops within seven days after onset, and its prognosis is poor with a mortality rate reaching 30% (vs the 13% with sterile necrosis) (26, 27). IPN can be diagnosed with computed tomography (CT)- or US-guided fine-needle aspiration biopsy (FNAB), followed by Gram stain/culture. However, strategies based on non-invasive diagnostics are becoming more popular: conservative treatment with empirical antibiotics (AB) (followed by 'rescue' FNAB in deteriorating cases) gains more and more attention (28).

3.4.4 Severity and mortality

Unlike the original 1992 Atlanta Classification, the revised 2012 Atlanta Classification re-defines disease severity of AP based on the development and duration of organ failure and the development of local complications (17, 29). The classification differentiates mild, moderately severe and severe AP (MAP, MSAP and SAP, respectively), the three-grade severity is detailed in Table 1. MAP and MSAP are associated with low mortality (<1%) whereas SAP has high mortality approximating 30% (Figure 3) (25). Although these criteria are more exact than other classification systems, the revised Atlanta Classification was not designed to grade severity on-admission so that it conveys little meaning to practitioners. This problem derives from the duration-based definition of organ failure (transient vs persistent) and the (un)reliability of early assessment of local complications (discussed under the heading '3.4.1 Local complications'). The severity of AP should be re-assessed multiple times during hospitalization, at discharge and follow-up visit.

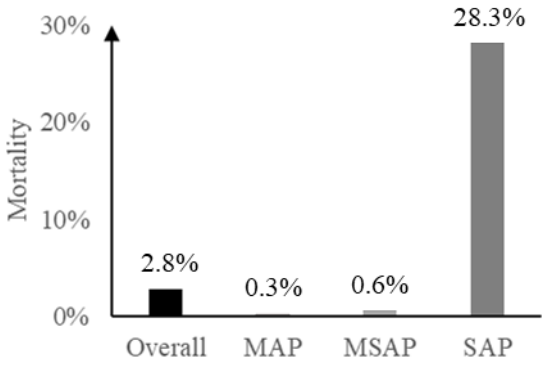


Figure 3. Mortality of acute pancreatitis by severity. MAP: mild acute pancreatitis, MSAP: moderately severe acute pancreatitis, SAP: severe acute pancreatitis. Reprinted and adapted from *'Prospective, Multicentre, Nationwide Clinical Data from 600 Cases of Acute Pancreatitis'* by Párniczky et al., 2016, *PloS One*.

SAP, MSAP and MAP account for approximately 5–15, 15–30 and 60–75% of the cases, respectively (30-32). If we consider Hungarian data, these proportions were 8.8, 30.0 and 61.2% in our previous study, respectively (25).

Table 1. The revised Atlanta Classification for disease severity

Grade of severity	Criteria
MAP	No organ failure No local complications
MSAP	Transient organ failure (resolves within 48 hours) and/or Local or systemic complications without persistent organ failure
SAP	Persistent organ failure (lasts longer than 48 hours)

MAP: mild acute pancreatitis, MSAP: moderately severe acute pancreatitis. SAP: severe acute pancreatitis

Although tremendous efforts were made to reduce mortality of AP, yet, the disease has remained potentially life-threatening with a fatality rate of 1–5% (32-34): AP is responsible for 1.6 deaths (CI 0.85–1.58) per 100,000 person-years (4). Hungarian data showed an overall mortality of 2.8% in our previous study (25). Nevertheless, the tendency is promising: mortality was reduced from 1.8 to 1.1% in the US between 2003 and 2012 (shown in Figure 4) (6, 34). Although specific therapies are still not available, early recognition of deteriorating cases and more effective intensive care substantially contributed to this improvement.

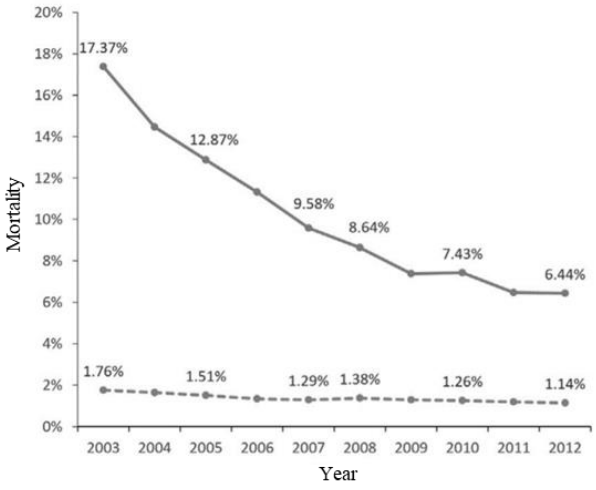


Figure 4. Mortality of acute pancreatitis in the US. The solid line represents overall mortality, the dashed line represents the mortality of those who developed acute kidney failure as systemic complication. Reprinted from '*Acute pancreatitis: Trends in outcomes and the role of acute kidney injury in mortality – A propensity-matched analysis'* by Devani et al., 2018, *Pancreatology*.

There are many classification systems designed to predict mortality or severity of AP. The most commonly used include but are not limited to the bedside index of severity in acute pancreatitis (BISAP) (33), the computed tomography severity index (CTSI) (35), the modified CTSI (36), Ranson (37) and the acute physiology and chronic health examination II (APACHE II) (38). All of these scoring systems are moderate to good predictors of severity as well as mortality (39).

3.5 Management

3.5.1 Evidence-based guidelines

The Working Group International Association of Pancreatology/American Pancreatic Association (IAP/APA) Acute Pancreatitis Guidelines released an evidence-

based guideline on the management of AP in 2013 (40), which, after update and adaptation, was translated to and published in Hungarian language by the Hungarian Pancreatic Study Group (HPSG) in 2015 (41). The guideline panel of IAP/APA consisted of multidisciplinary experts from many fields involved in the care of AP. The panel formulated pre-defined questions, then performed a systematic literature search to collect all question-related evidence. Based on the data, recommendations were made adhering to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system quantifying the quality of evidence (as very low, low, moderate or high) and the strength of recommendation (as weak or strong) (42).

In addition to the IAP/APA guideline (40), evidence-based guidelines were released by the American College of Gastroenterology (2013) (43) and the Japanese Society of Hepato-Biliary-Pancreatic Surgery (2015) (44), while other organizations including but not restricted to the American Gastroenterological Association (2018) (45), the World Society of Emergency Surgery (2019) (46), the Canadian Medical Association (2016) (47) and the Italian Association for the Study of the Pancreas (2015) (48) released their guidelines as well.

3.5.2 Cornerstones of clinical management

1. The diagnosis should be established based on the ’two out of three criteria’ (as discussed above).
2. Patients should be admitted to centres specialized for care in gastroenterology or pancreatology.
3. Aetiology should be thoroughly investigated.
4. Early fluid resuscitation is an essential part of management.
5. Close monitoring in the initial phase and admission to intensive care in time can save lives.
6. Preventive ABs or probiotics should not be given.
7. Changes in electrolytes and inflammatory markers should be monitored in the early phase.
8. Endoscopic ultrasound (EUS) / magnetic retrograde cholangiopancreatography / ERCP and same-admission cholecystectomy should be considered in the case of biliary aetiology or plasmapheresis in the case of hypertriglyceridemic aetiology.
9. Enteral feeding should be initiated in SAP.

10. If invasive intervention is required due to local complications, the step-up approach is recommended.
11. Patients should be screened for local complications at discharge and follow-up visit.
12. AP is often recurrent so that lifestyle changes are required.

3.5.3 Centralized care

Medicine evolves rapidly, which process is well-reflected by the exponential slope of the curve describing the propagation of data on certain conditions. Being up-to-date about many fields of science has become a demanding challenge (49). Besides, to provide state-of-the-art care, accumulating extensive theoretical knowledge alone is not enough: active management of cases is required, allowing to put theories into practice. To sum up, the key to success depends on the knowledge and the number of cases treated (these together may be called expertise). These encouraged the establishment of units specialized in providing care for a narrow spectrum of conditions, giving birth to the concept of centralization of care. The efficacy of centralization is plausible to be generalizable to all treatable diseases with a potential risk of severe complications in the fields of both conservative and operative medicine.

Centre volume (that is, the number of cases admitted to or procedures performed in a unit) and physician volume (that is, the number of cases treated or procedures performed by a physician) are important determinants of quality of care. Research implicated that the latter may be more important than the former, at least in the field of operative medicine (50). Adjusted mortality of pancreatic resection was 12% lower in very high-volume vs very low-volume hospitals, and similar tendencies were observed regarding other operations (51). In another study, 30-day survival of patients with oesophageal, gastric and pancreatic cancer significantly improved with the higher number of cases operated (3.4, 7.2 and 4.1% reduction of mortality with each case added, respectively) (52). The efficacy of centralization in operative care can be illustrated through several other examples in- and outside the scope of gastrointestinal surgery (53-60).

The role of centralization in non-surgical fields of gastroenterology, such as in gastrointestinal endoscopy, was recognized by the European Society of Gastrointestinal Endoscopy as well. The physician volume is particularly important in the learning phase of one’s carrier. Higher centre and physician volume were found to favourably impact quality indicators of ERCP (including the rate of post-ERCP pancreatitis) (61-65) or

colonoscopy in cancer screening (66), recurrence after ablation of Barrett's dysplasia (67) or the success rate of transjugular intrahepatic portosystemic shunt insertion (68). Interestingly, the volume-mortality relationship may not apply to variceal bleeding (69-71).

Although we have evidence for the beneficial effect of centralization in AP as well, evidence-based guidelines make heterogenous recommendations that are of low quality of evidence (indicated with 'C'). This means that further research is very likely to have a substantial impact on our confidence in the estimate, either proving or disproving it (42). The American guideline recommends referral to a specialist unit for cases with idiopathic AP (conditional recommendation, low quality of evidence) (43) while the Japanese guideline (1C) and IAP/APA guideline (GRADE 1C, strong agreement) recommend referral for SAP (40, 44). Besides, the latter expands the indication of referrals for those patients requiring interventional radiologic, endoscopic or surgical intervention (GRADE 1C, strong agreement) (40). Only the IAP/APA guideline attempts to define specialist units (GRADE 2C, weak agreement) (40):

'A specialist center in the management of acute pancreatitis is defined as a high volume center with up-to-date intensive care facilities including options for organ replacement therapy, and with daily (i.e. 7 days per week) access to interventional radiology, interventional endoscopy with EUS and ERCP assistance as well as surgical expertise in managing necrotizing pancreatitis' (Section E, Statements 14).

Current evidence warrants further investigation about the role of centralized care in AP.

3.5.4 Antibiotic use

The three leading evidence-based guidelines make recommendations about the use of ABs in AP cases without confirmed pancreatic/extrapancreatic infections (termed as preventive or prophylactic use of ABs), as follows:

- *'Intravenous antibiotic prophylaxis is not recommended for the prevention of infectious complications in acute pancreatitis. (GRADE 1B, strong agreement)'* by the IAP/APA Evidence-Based Guidelines for the Management of Acute Pancreatitis (Section F, Statement 17) (40).
- *'Routine use of prophylactic antibiotics in patients with severe acute pancreatitis is not recommended (strong recommendation, moderate quality of evidence)'* and *'The use of antibiotics in patients with sterile necrosis to prevent the development*

of infected necrosis is not recommended (strong recommendation, moderate quality of evidence)' by the American College of Gastroenterology Guideline: Management of Acute Pancreatitis (Statements 21, 22) (43).

- *'The prophylactic administration of antibiotics is not necessary in mild acute pancreatitis, since the incidence and mortality rates of infectious complications from mild acute pancreatitis are low. (1A)* and *'The prophylactic administration of antibiotics in severe acute pancreatitis and necrotizing pancreatitis may improve the prognosis, if carried out in the early phases of pancreatitis (within 72 h of onset). (2B)'* by the Japanese Guidelines for the Management of Acute Pancreatitis: Japanese Guidelines 2015 (Section I, Statement 17) (44).

Based on these recommendations, prophylactic use of ABs is not recommended generally in AP (moderate quality of evidence), MAP (high quality of evidence) or SAP (moderate quality of evidence). The Japanese and the US guidelines disagree on the prophylactic use of ABs in ANP: the former may attribute some benefit for early prophylactic AB treatment, whereas the latter does not recommend prophylactic use of ABs.

The question as to whether prophylactic ABs should be given has been debated for decades: several randomized controlled trials (RCT) were conducted in the past 50 years. According to a recent (2017) meta-analysis performed by the Cochrane Collaboration, prophylactic ABs did not yield statistically significant benefit regarding short-term (<3 months) mortality (odds ratio [OR]: 0.81, CI: 0.57–1.15), rate of organ failure (OR: 0.78, CI: 0.44–1.38), rate of IAP (OR: 0.82, CI: 0.53–1.25) or rate of sepsis (OR: 0.42, CI: 0.11–1.60) based on the data of 17 RCTs in AP. Findings were consistent in ANP and SAP as well based on the data of ten and nine RCTs, respectively. It must be noted, however, that the grade of evidence was rated as very low for all outcomes due to the limitations of the studies, which means that future studies carry the potential to change these associations (72). Although the leading guidelines were released earlier than this meta-analysis, their recommendations are in line with its findings (except for that in the Japanese guideline attributing potential benefit to early prophylactic use of ABs in SAP).

According to our previous research, 77.1% of patients received ABs during hospital stay. Considering the estimated incidence of pancreatic and extrapancreatic infections (30–35%), this number is twice as high as expected. However, the majority of the patients received ABs for prophylaxis, indicating a significant AB overuse. Interestingly, there was no difference in the outcomes of patients receiving prophylactic ABs and those

receiving therapeutic ABs to control confirmed pancreatic or extrapancreatic infections (SAP accounted for 7.2 vs 7.8% in the groups with prophylactic vs therapeutic AB use, respectively) (25).

Choosing the population which may benefit from AB treatment is a hard choice. Many biomarkers used as pervasive indicators of an ongoing infection (white blood cell count [WBC] and acute-phase proteins, e.g. cytokines, CRP and even procalcitonin [PCT]) can change during the natural course of AP, posing difficulty in distinguishing inflammation of sterile and infective origins (73-75). Currently, reliable non-invasive biomarkers are still lacking.

3.6 Determinants of disease course

There are many on-admission variables which were implicated to be associated with a more severe disease course in AP. The associations of age, comorbidities, aetiology of AP, smoking and obesity with severity and mortality of AP were extensively studied.

In a meta-analysis from 33 studies, our research team concluded that ageing is associated with a higher proportion of SAP (each year increase between 20 and 70 years of age was associated with an increment of 0.193% in incidence of SAP). In contrast, we observed a biphasic linear association between age and mortality (the inclination of the slope increased above 57.5 years of age) (76). When we analysed the joint effect of ageing and comorbidities with multivariate analysis in our cohort of AP cases, we found that comorbidities are responsible for the increment in mortality in elderly, but both ageing and comorbidities are essential regarding severity (Figure 5). A Charlson Comorbidity Score >2 was independently associated with two times increased frequency of SAP (OR: 2.10, CI: 1.08–4.09) and with four times higher mortality (OR: 4.48, CI: 1.57–12.80). Out of the comorbidities investigated, mortality was significantly positively associated with pre-existing congestive heart failure, peripheral vascular disease, cerebrovascular disease, moderate/severe renal disease, moderate/severe liver disease and metastatic tumour. Interestingly, diabetes mellitus was not associated with worse prognosis (77).

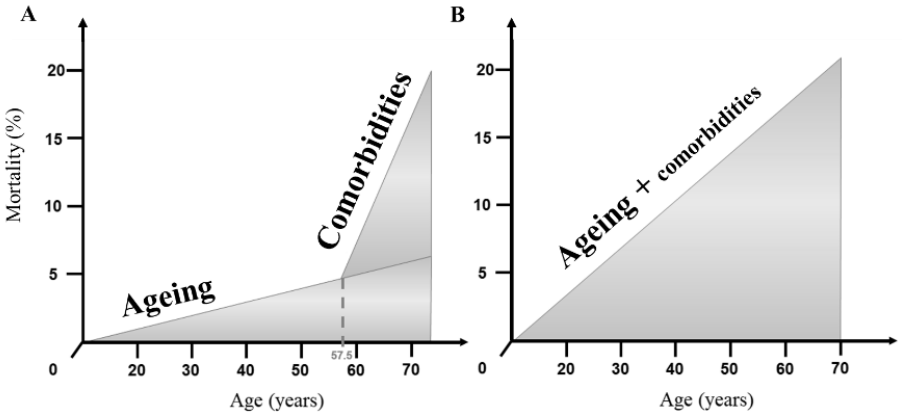


Figure 5. A model describing the joint effect of ageing and comorbidities on mortality (A) and severity (B) of acute pancreatitis. Comorbidities seem to be responsible for the prominent excess in mortality with ageing (with a cut-off point at 57.5 years, indicated by the dashed line), whereas ageing and, to a lesser extent, comorbidities are both important regarding severity. Adapted and reprinted from *'Aging and Comorbidities in Acute Pancreatitis II.: A Cohort-Analysis of 1203 Prospectively Collected Cases'* by Szakács et al., 2018, *Frontiers in Physiology*.

Although the disease course becomes similar after initiation of the cascade of cytokine storm, hypertriglyceridaemic aetiology seems to be associated with a more severe disease course (25, 78-80). Unlike alcoholic and biliary aetiologies which have limited influence on severity and mortality (25, 81-84).

Among lifestyle factors, alcohol intake is considered to be a causative factor of AP (8). Smoking (alone or with regular alcohol intake) aggravates the disease course, increases the risk of recurrent AP and facilitates the transition from AP to chronic pancreatitis (8, 25, 85, 86). Considering that obesity has become increasingly common in developed countries, its potential modifying effect on disease course has come to light. An individual patient data-level meta-analysis aggregated the population of four cohorts of AP cases and found that obesity proved to be an independent predictor of multiple organ failure (Figure 6) (87). Findings from a study-level meta-analysis (19 studies, 9,997 cases) indicated that patients with a body mass index (BMI)>25 kg/m^2 (i.e. overweight and obesity) tend to be almost three times more likely to develop SAP compared to those with normal BMI (OR: 2.87, CI: 1.90–4.35). Moreover, BMI>30 kg/m^2 (i.e. obesity) was a significant risk factor of mortality compared to normal BMI (OR: 2.89, CI: 1.10–7.36) (88). However, we should take into account that obesity is mostly part of metabolic

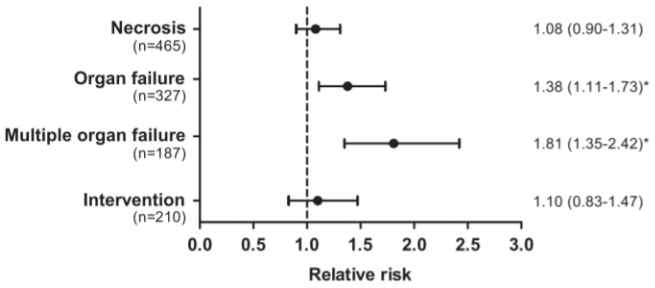


Figure 6. Effects of obesity on the outcomes of acute pancreatitis. The analysis was adjusted for age, sex, comorbidities and aetiology. *indicates p<0.05. Reprinted from *'The association between obesity and outcomes in acute pancreatitis: an individual patient data meta-analysis'* by Smeets et al., 2019, *Eur J Gastroenterol Hepatol*.

syndrome (MetS). In 2006, a harmonized definition of MetS was released, nominating waist circumference, hypertriglyceridaemia, high-density lipoprotein-cholesterol, hypertension and diabetes mellitus as its components (two out of the five criteria should be met, see Table 2) (89). MetS is a common comorbid condition in AP; its prevalence varies from 18 to 62.8% across studies (30, 90, 91). Besides, it was implicated to be a potential prognostic factor of the disease course.

Table 2. The components of metabolic syndrome

Measure	Categorical cut points
Elevated waist circumference	Region-specific, ≥94 cm for males and ≥80 cm for females in Caucasians
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)	>1.7 mmol/L
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator)	<1.0 mmol/L for males, <1.3 mmol/L for females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	≥130 mm Hg for systolic and/or ≥85 mm Hg for diastolic
Elevated fasting glucose (drug treatment of elevated glucose is an alternate indicator)	>5.6 mmol/L

HDL-C: high-density lipoprotein-cholesterol.

4. Objectives and hypotheses

1. We aimed to **compare the efficacy and cost-effectiveness of centralized care vs non-centralized** care in AP through the example of two tertiary hospitals from two Hungarian cities. Based on the pre-existing data, we hypothesize that the outcomes of centralized care will outperform that of non-centralized care.
2. We aimed to **assess guideline adherence and identify the indicators of right AB use** in AP. Based on the data from our previous cohort study, we assume that there is a significant AB overuse across Hungary. Based on prior international data, CRP is unlikely to be a reliable indicator of infections. In contrast, PCT is assumed to have a better diagnostic performance.
3. We aimed to **investigate the effects of MetS on the disease course** of AP with a particular focus on the effects of the components alone and in combination. Since many comorbidities, including obesity, are known to affect disease course, we hypothesize that components will be independent risk factors of adverse outcomes of AP while their joint effect will be more pronounced than their effect alone.

5. Methods

5.1 Study design and data sources

We performed three retrospective cohort studies (92-94), where the primary source of data was the Hungarian Registry for Pancreatic Patients (in the followings, AP Registry) (discussed under the heading ’5.2 AP Registry’). Ancillary data were collected from an international survey to assess worldwide guideline adherence regarding AB use in AP (discussed under the heading ’5.3 International survey’). We performed a systematic review of papers in medical databases to assess strategies how high-quality studies defined/suspected pancreatic infection and to review if we have high-quality evidence supporting the efficacy of biomarker-guided AB therapy (discussed under the heading ’5.4 Systematic review’).

5.2 AP Registry

5.2.1 Background and objectives

HPSG is dedicated to improving the care of pancreatic diseases in Hungary by surveillance of patient care as per the principles of evidence-based medicine. Following these objectives, HPSG established multiple patient registries of pancreatic diseases including AP, chronic pancreatitis, pancreatic cancer and autoimmune pancreatitis (for more information, visit https://tm-centre.org/hu/). The AP Registry was established in 2011 and had been operating consecutively since then. The registry should be considered as a multicentre observational study with detailed, systematic prospective data collection but without pre-defined clinical questions.

5.2.2 Sites of recruitment

The registry is free to join for all centres providing care for AP patients after claiming local ethical permission for operation. Centres should dedicate a local principal investigator who is liable for patient recruitment, consenting, data collection, upload and quality. In most centres, clinical research administrators (CRA) facilitate the work.

5.2.3 Eligibility and data collection

After establishing the diagnosis of AP as per the 2012 Atlanta Classification, patients are offered to participate in the registry. When the written informed consent is signed in duplicate, the patient is considered eligible for inclusion. Patients are allowed to withdraw consent to participate any time; in this case, all data shall be removed from the database, and all biological samples shall be destroyed.

Data are recorded by the treating physician, the nursing staff and CRAs onto regular hospital files or directly onto paper-based case report forms (CRF), depending on the data type. All paper-based files are then converted to electronic CRFs and uploaded to the secured server of the Centre for Translational Medicine (Hungary) via an online registry platform.

Data are collected on admission (A form) and during hospitalization daily (B forms, one/day). The A form contains relevant data about medical history (including but not limited to previous pancreatic diseases, comorbidities, regular medications, history of smoking and alcohol consumption), AP-related complaints, findings on physical examination, vital parameters, laboratory studies, imaging, on-site medications, endoscopic, surgical and radiological interventions, fluid resuscitation and nutrition. B forms contain all fields of the A form except for those related to medical history and aetiology of AP. Besides, disease outcomes including mortality, severity and complications are recorded.

5.2.4 Data validation

To ensure data quality, a four-level quality control system was developed. The first revision of the forms is performed by the CRA of the recruiting site, followed by the revision of the medical doctor in charge. The third revision is made by the principal CRA of the registry, and, finally, the principal investigator closes the case. Amendments and acquisition of missing data can be requested on revisions.

5.2.5 Data extraction

Centres uploading data in the registry are encouraged to raise research questions and form the corresponding hypotheses. If these questions are judged to merit further investigation, the list of data required to perform statistical analysis is claimed and downloaded from the server in a tabularized format where all information is numerically coded. Data extraction is followed by problem-tailored analysis.

5.2.6 Statistical considerations

In our studies, we investigated data quality by counting missing data for each variable of interest first. For outcome variables and baseline demographic factors (age and sex), data quality reached or approached 100%.

After choosing the variables for analysis, descriptive statistics are performed. For categorical variables, we calculated frequencies (%). For continuous variables, we

investigated distribution with Q-Q plots and calculated mean with standard deviation (SD) or standard error of the mean (SE) for normally distributed variables and median with 25–75% quartiles (Q1–Q3) and/or range for non-normally distributed variables. Based on descriptive statistics, the included population was compared to the whole population of the registry to test the representativity of the sample.

In univariate comparative analyses of categorical variables, we calculated ORs with CIs and/or compared the groups with the chi^2-, the Z- or the Fisher's exact tests with Bonferroni correction of the p-values (if needed). For continuous variables, we used the independent sample t-test, the Welch test or the Mann-Whitney test, depending on the distribution and the variance of the sample. If multiple groups were compared, we used the one-way analysis of variance (ANOVA) with posthoc Tukey test or the Kruskal-Wallis test followed by the Holm p-value adjustment, depending on the distribution of the data.

In multivariate analyses, we used logistic regression and calculated adjusted ORs. Available-case analysis was used for missing data.

To investigate the diagnostic accuracy of biomarkers, we constructed receiver operation characteristic (ROC) curves and calculated area under the curves (AUC).

The analyses were carried out with the SPSS (Versions 23, 24 and 25, IBM, New York, NY, USA) and the R Studio (Version 1.1.453, fmsb package).

5.2.7 Ethical considerations

The operation of the AP Registry was approved by the Scientific and Research Ethics Committee of the Medical Research Council (Hungary) under registration number 22254-1/2012/EKU. All investigations were carried out adhering to the Declaration of Helsinki ethical guidelines (updated in October 2013, Fortaleza, Brazil).

5.3 International survey

5.3.1 Background and objectives

The IAP includes the worlds' leading pancreatologists from top pancreas centres. With this survey, we aimed to assess international trends of AB use in AP.

5.3.2 Data collection

In November 2017, an invitation for data collection was sent to the members of the IAP. The following data were collected: gender, aetiology, mortality and severity of AP, and details of AB therapy irrespectively of its indication.

5.4 Systematic review

5.4.1 Background and objectives

Systematic reviews are the mainstays of evidence-based medicine. The number of publications exceeds one million yearly. Even if someone narrows the focus on a specific topic, it is almost impossible to keep pace with the release of the most recent papers. Summary publications, especially guidelines and systematic review (with or without meta-analysis) aim to overcome this issue by delivering reliable information, the essentials of knowledge in a quickly and easily digestible format (49). The key to their success relies on full reproducibility by using the standard and transparent methodology proposed by the flagship of evidence-based medicine, the Cochrane Collaboration (available at https://www.cochrane.org/). With this systematic review, we aimed to gather all information about the guidance on and strategies of AB use in AP.

5.4.2 Data sources and eligibility

We searched three medical databases (MEDLINE via PubMed, Embase and CENTRAL) systematically up to July 2018 with the following query: *'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'*. We did not impose any restrictions (e.g. to language or publication date) on the search.

The query was designed to identify all papers which discuss guidance on and strategies of AB use in AP. To obtain the highest level of evidence, we included only RCTs.

5.4.3 Selection, data collection and risk of bias assessment

First, yields of the search from all databases were combined in a reference manager software, EndNote (version X7.4, Clarivate Analytics, Philadelphia, PA, USA). The software is capable of removing the duplicate references automatically. Then, we

screened the remaining records for eligibility following a standard three-step selection by title, abstract and full-text.

Eligible papers were subjected to thorough data collection along with our pre-defined data collection sheet. The following data were extracted: characteristics of the study population (definition of AP, demography, aetiology), definitions of suspected and definitive pancreatic and extrapancreatic infections, interventions (drug regimens and/or guidance of therapy) and study setting.

Selection and data collection were carried out by two investigators independently in duplicate, discrepancies were resolved by involving a third party.

Since our question of interest did not concern the primary objective of the RCTs (typically, the efficacy of AB 'A' vs AB 'B' on the course of AP, mainly on infection control), risk of bias assessment could not be carried out with the tool dedicated to assessing RCTs (i.e. the Cochrane Risk of Bias Tool).

6. Results

6.1 Centralized care

6.1.1 Characteristics of the study population

Between 1 January 2016 and 31 December 2016, 195 and 160 patients were treated in Healthcare Model A (providing centralized care) and Healthcare Model B (providing non-centralized care), respectively. Logistics of patient referral is illustrated in Figure 7. In Healthcare Model A, nine emergency units (ER) referred patients directly to the pancreatic centre (PC). In Healthcare Model B, one ER referred patients to territorial internal medicine departments (TIMD), a tertiary pancreatic centre (TPC), a surgical department (SD) or directly to the intensive care unit (ICU).

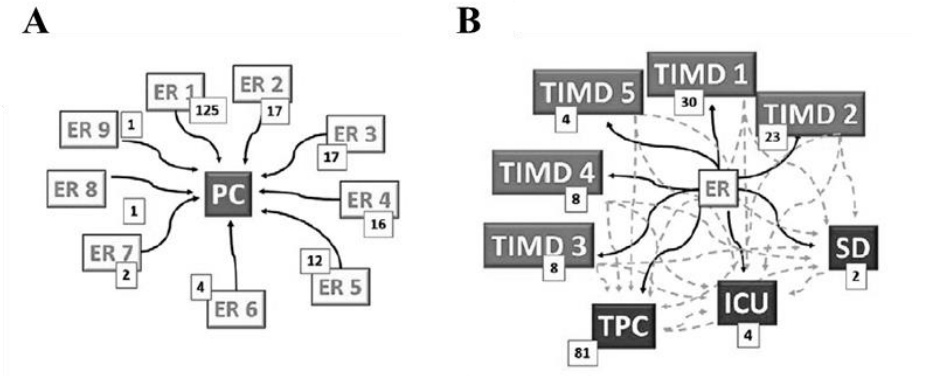


Figure 7. The models of centralized (A) and non-centralized care (B) of acute pancreatitis. The arrows with solid line represent the direction of regular patient referral; those with dash line occasionally represent referrals. The number of patients in each unit is shown in squares. ER: emergency unit, ICU: intensive care unit, PC: pancreatic centre, SD: surgical department, TIMD: territorial internal medical department, TPC: tertiary pancreas centre. The figure is the author's own work.

Baseline characteristics of the study population are summarized in Table 3. Of note, there was no statistically significant difference in age and sex between the groups. The leading aetiology was the biliary origin in both centres.

6.1.2 Severity, mortality, complications and length of hospital stay

Mortality was significantly lower in Healthcare Model A vs Healthcare Model B (1.0 vs 6.3%, respectively; p=0.007). SAP developed in 7.1 vs 11.9% in Healthcare Model A vs Healthcare Model B, the difference did not attain the level of statistical significance (p=0.310) (Figure 8). We observed no difference regarding local and systemic complications between the groups (Table 4).

Length of hospital stay was significantly shorter in Healthcare Model A vs Healthcare Model B (median 6 days [Q_1–Q_3: 5–9] vs 8 days [Q_1–Q_3: 6–11], respectively; p=0.020).

Table 3. Characteristics of the study population

	Healthcare Model A (centralized, n=195)	Healthcare Model B (non-centralized, n=160)
Age (mean±SD in years)	57.0±17.2	57.3±16.5
Sex (male%)	56	57
Aetiology (%)		
Biliary	42.1	33.3
Alcoholic	15.4	8.3
Hypertriglyceridaemic	2.1	6.4
Alcoholic + Hypertriglyceridaemic	4.1	7.7
Other combined	8.2	5.8
Post-ERCP	3.1	3.2
Other	7.2	15.4
Idiopathic	17.9	19.9

ERCP: endoscopic retrograde cholangiopancreatography; SD: standard deviation.

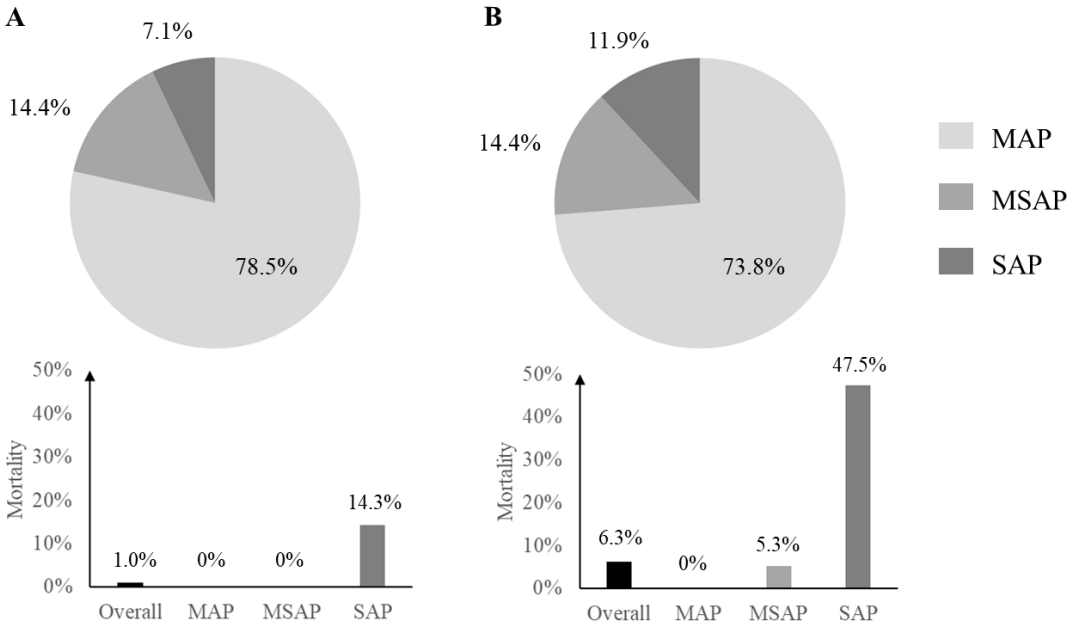


Figure 8. Severity and mortality in Healthcare Model A (providing centralized care) and Healthcare Model B (providing non-centralized care). Pie charts show the distribution of severity, and bar charts show overall and severity-stratified mortality. Severity was graded by the 2012 Atlanta Classification. MAP: mild acute pancreatitis, MSAP: moderately severe acute pancreatitis, SAP: severe acute pancreatitis. The figure is the author's own work.

Table 4. Complications

	Healthcare Model A (N^0, % of total)	Healthcare Model B (N^0, % of total)	p-value
No complication	150 (76.8)	118 (73.8)	0.337
Local complications	43 (22.1)	35 (21.8)	0.872
Systemic complications	21 (10.5)	27 (16.9)	0.177

6.1.3 Therapeutic approach and interventions

The proportion of ERCPs, necrosectomy or guided drainage did not differ between groups (Table 5). However, enteral feeding was more frequently used in Healthcare Model A, whereas AB use was less frequent in this group ($p<0.001$ for both comparisons). Patients with MAP, MSAP and SAP received ABs in 35.3% (n=54), 64.3% (n=18) and 92.9% (n=13) in Healthcare Model A and in 70.3% (n=83), 91.3% (n=21) and 100.0% (n=19) in Healthcare Model B, respectively; AB use was significantly lower in Healthcare Model A regarding MAP and MSAP ($p<0.05$ for both) but not significantly different regarding SAP ($p=0.424$)

Table 5. Therapeutic approach and interventions.

	Healthcare Model A (N^0, % of total)	Healthcare Model B (N^0, % of total)	p-value
ERCP	85 (43.6)	59 (36.9)	0.143
Necrosectomy	1 (0.5)	2 (1.3)	0.793
Radiology or EUS-guided drainage	8 (4.1)	2 (1.2)	0.118
Enteral feeding	179 (91.8)	36 (22.5)	<0.001
Antibiotic use	85 (43.6)	123 (76.9)	<0.001

EUS: endoscopic ultrasonography, ERCP: endoscopic retrograde cholangiopancreatography

6.1.4 Cost of care

The average cost of care per capita was 964 Euro in Healthcare Model A, whereas it was 1,285 Euro is Healthcare Model B with a difference of 25% between groups. This calculation is limited to medication use, disposables, procedures and investigations but does not include the costs of staff and hospital stay.

6.2 Antibiotic use

6.2.1 Systematic review

We conducted a systematic review to assess if any RCT investigated biomarker-guided AB treatment in AP and how RCTs defined suspected or definitive pancreatic infections. After careful search and selection, 23 studies proved to be eligible, one of which reported on PCT-guided ABs treatment, the other 22 tested prophylactic AB use. The flowchart of the selection process is shown in Figure 9.

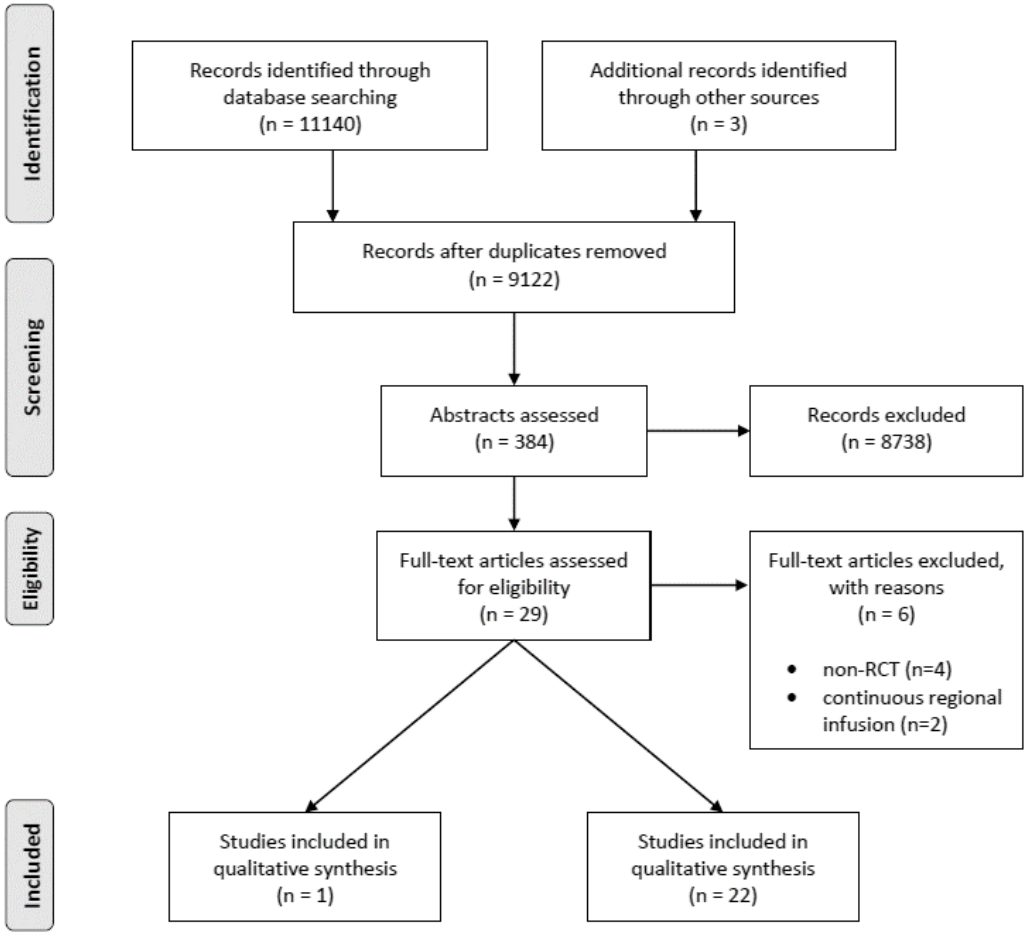


Figure 9. The flowchart of the selection process. RCT: randomized controlled trial. Reprinted from *'Antibiotic Therapy in Acute Pancreatitis: From Global Overuse to Evidence Based Recommendations'* by Párniczky et al., 2019, *Pancreatology*.

Supplementary Table 1 summarizes the baseline characteristics of the studies included. The only RCT investigating the guidance of AB therapy was a two-arm study in SAP. On the intervention arm, the administration of ABs was driven if PCT level exceeded 0.5 ng/ml, and the AB treatment was stopped if the level fell below 0.5 ng/ml. On the control arm, ABs were given for two weeks for all patients, then continued if any infection was confirmed. While the clinical efficacy of the strategies was found to be equal, the PCT-guided treatment proved to be more cost-effective (24,401±2,631 vs 27,813±2,529 US dollars for the PCT-guided vs control groups, respectively; $p<0.001$) (95).

In the remaining 22 studies testing the efficacy of AB treatment vs various control groups, the definitions for pancreatic infection was substantially heterogeneous (96-117). Generally, the definitions were based on laboratory and clinical factors (alone or in combination). These factors included CRP (in five studies), elevated WBC (in two

studies), fever (in two studies), SIRS/organ failure/sepsis (in three studies) and air bubbles within the pancreatic necrosis on CECT (in two studies). Surprisingly, none of the studies used PCT to define suspected or definitive infection. A change in inflammatory biomarkers (i.e. a rise following an initial decrease) was taken into consideration only in two studies.

Taken together, there is no evidence-based consensus on how to define pancreatic infection and how to guide AB therapy in AP.

6.2.2 International survey

Figure 10. shows the findings of our international survey on the frequency of AB use in AP. Data were collected across 23 countries from 9,869 patient. The global tendency showed significant overuse of ABs. It exceeded 80% in Asia (based on Chinese and Taiwanese data), approached 80% in Eastern Europe whereas it was only approximately 30% in Western Europe. In Hungary, the AB use was 74.7%.

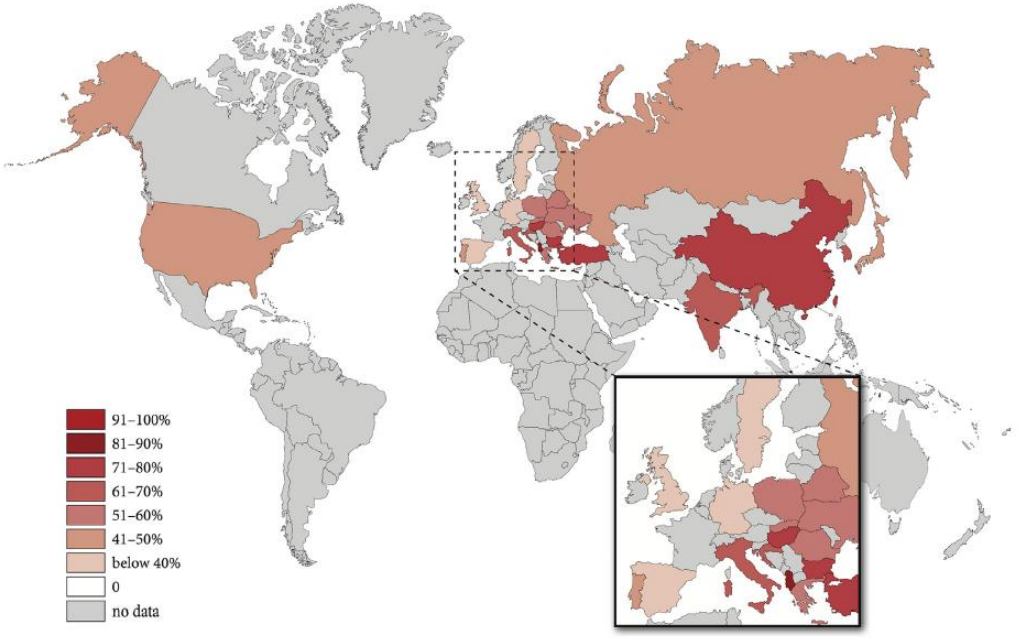


Figure 10. Map of antibiotic use worldwide. In average, 57.2% of patients with acute pancreatitis received antibiotics. Reprinted from *'Antibiotic Therapy in Acute Pancreatitis: From Global Overuse to Evidence Based Recommendations'* by Párniczky et al., 2019, *Pancreatology.*

6.2.3 Registry analysis

6.2.3.1 Characteristics of the study population

Altogether, 962 of 1,070 patients from the AP Registry were eligible for inclusion. We set up groups based on AB treatment and status of infection, as shown by Figure 11.

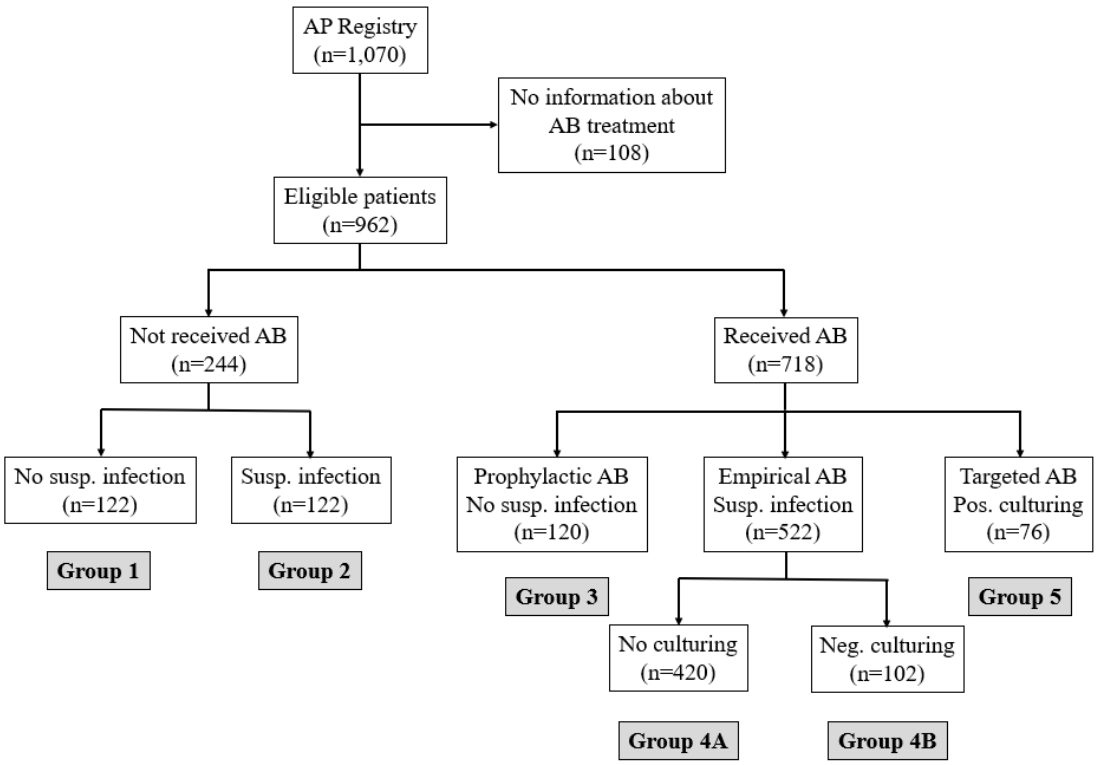


Figure 11. Study subgroups. Groups 1 and 2 did not, whereas Groups 3–5 did receive antibiotics. Infection was suspected based on clinical signs and symptoms. Prophylactic (Group 3), empirical (Group 4) and targeted (Group 5) antibiotic treatment were defined if no infection was suspected, infection was suspected without positive culturing and infection was verified with culturing, respectively. Group 4 was divided into 4A (suspected infection without culturing performed) and 4B (suspected infection with negative culturing). AB: antibiotic, Neg.: negative, Pos.: Positive, Susp.: Suspected. The figure is the author's own work.

Mortality and SAP accounted for 1.8 and 5.5% in the study population, respectively. The leading aetiology was the biliary origin (42.1%), followed by idiopathic AP (21.5%) and alcoholic AP (18.8%). Distribution of AB use by aetiology is summarized in Table 6. Most of the patients received ABs irrespective of aetiology.

Table 6. Antibiotic use by aetiology.

Aetiology	N^0 of patients (% of total)	Antibiotic use (%)
Biliary	405 (42.1)	82
Alcoholic	181 (18.8)	65
Hypertriglyceridaemic	23 (2.4)	78
Post-ERCP	28 (2.9)	71
Idiopathic	207 (21.5)	70
Other	87 (9.0)	69
Combined	31 (3.2)	84

ERCP: endoscopic retrograde cholangiopancreatography.

6.2.3.2 Mortality, severity and length of hospital stay

Mortality of AP was 2.2 and 0.8% in patients who received (Groups 3–5) or did not receive ABs (Groups 1, 2), respectively; without significant difference between the groups. MAP, MSAP and SAP accounted for 79.9, 18.9 and 1.2% (Groups 1, 2) vs 62.4,

30.6 and 7.0% (Groups 3–5), respectively ($p<0.001$). Length of hospital stay was significantly longer for those receiving ABs (13.4±0.5 vs 8.3±0.3 days for Groups 3–5 and Groups 1, 2, respectively; $p<0.001$).

Table 7 summarizes mortality, severity and length of hospital stay across groups. The rate of SAP and mortality were the highest while the length of hospital stay was the longest in Group 5. SAP was more common in Group 5 (positive culturing) compared to Group 4B (negative culturing) ($p=0.028$), but the difference in mortality did not attain the level of statistical significance. Also, SAP was more common in Group 4B (negative culturing) compared to Group 4A (no culturing) ($p=0.007$). Group 1 and Group 2 (neither received ABs) did not differ in outcomes significantly.

Table 7. Mortality, severity and length of hospital stay across groups.

Group	Mortality (%)	Severe course (%)	Length of hospital stay (days)
No antibiotic use			
Group 1	0.8	0.8	8.3±0.4
Group 2	0.8	1.6	8.2±0.4
Antibiotic use			
Group 3	0.8	5.8	12.3±1.1
Group 4A	1.4	2.4	10.7±0.3
Group 4B	3.9	10.8	18.6±1.5
Group 5	6.6	28.9	22.9±1.6

Definition of groups is described in Figure 11.

6.2.3.3 Details of antibiotic treatment

If we consider those patients receiving ABs (that is, Groups 3–5), the therapy was started in 74% of the cases on the first day and in 11% on the second day of hospital stay. These numbers were similar across groups. 52% of the cases were treated with a single AB; the others received combined AB treatment. In 75% of the cases, the initial treatment was continued while the remaining individuals required at least one switch in AB therapy (21 and 4% required one and two switches, respectively). In general, AB switch was associated with a more severe disease course.

Distribution of ABs across groups by status of infection and by severity of AP are shown in Table 8. Almost 30% of the cases received cephalosporins alone, followed by the combination of ciprofloxacin with metronidazole and cephalosporin with metronidazole. The pattern was similar in the subgroup of MAP, whereas imipenem was favoured in SAP.

6.2.3.4 Biomarkers and the initiation of antibiotic treatment

Figure 12A–D shows the on-admission levels of amylase, lipase, CRP and WBC across groups by status of infection. Patients receiving ABs (Groups 3–5) have significantly higher amylase, lipase, CRP and WBC compared to those not receiving ABs (Groups 1, 2). Patients with positive culturing (Group 5) did not have significantly higher amylase, lipase, CRP or WBC compared to those who did have negative culturing (Group 4b). Those receiving prophylactic ABs (Group 3) had significantly higher levels of amylase, lipase, CRP and WBC compared to those not receiving ABs and were not suspected of having infection (Group 1).

Figure 12E–H shows the on-admission levels of amylase, lipase, CRP and WBC across groups by severity. CRP but not amylase and lipase differed significantly by severity: the highest CRP level was measured in SAP, whereas the lowest in MAP (Figure 12G).

6.2.3.5 Changes in biomarkers during the disease course

Figure 13 shows the changes in CRP and WBC across groups by status of infection. Regarding CRP, only the comparison of Groups 4a vs 4b attained the level of significance (Figure 13D), while we observed no significant difference regarding WBC (Figure 13F–J). Considering the changes in PCT, we observed a tendency when comparing Groups 4b vs 5 ($p=0.052$), indicating a higher level of PCT in those with positive culturing.

When we tested if these biomarkers can distinguish cases with infection from those without infection, AUCs were poor for CRP and WBC (AUC=0.510 and 0.454, respectively) and fair for PCT (AUC=0.729) (Figure 14).

6.2.3.6 Outcomes and pathogens of cases with infections

IPN had spiking high mortality (25.0%). Other sources of infection (biliary, urogenital, pulmonary) were associated with moderate-high mortality ranging from 8.3 to 14.3%. Pathogens were dominantly Staphylococci (34.2%), Enterococci (27.4%), *Clostridium difficile* (22.4%), *Escherichia coli* (18.4%), *Pseudomonas* (13.2%) and *Klebsiella* species (9.2%).

Table 8. Distribution of antibiotics across groups by status of infection and by severity of acute pancreatitis.

	Single AB				Dual AB			Triple AB
	Cephalosporin	Ciprofloxacin	Imipenem	Other	Ciprofloxacin + metronidazole	Cephalosporin + metronidazole	Other	
Distribution across groups (%)								
Group 3	30.0	15.8	6.7	0.0	22.5	18.3	3.3	3.3
Group 4a	34.0	13.6	2.6	2.1	23.3	18.6	3.3	2.4
Group 4b	18.6	11.8	15.7	4.9	15.7	19.6	5.9	7.8
Group 5	18.4	11.8	14.5	6.6	13.2	13.2	11.8	10.5
Distribution across severity (%)								
Mild	31.9	15.4	3.1	1.6	24.6	18.1	2.5	2.9
Moderate	27.7	11.4	8.6	3.2	17.3	19.1	7.7	5.0
Severe	16.0	6.0	26.0	10.0	6.0	14.0	10.0	12.0
Summary (%)	29.5	13.5	6.4	2.6	21.0	18.1	4.6	4.2

Values are given in % of row total. Definition of groups is described in Figure 11. AB: antibiotic.

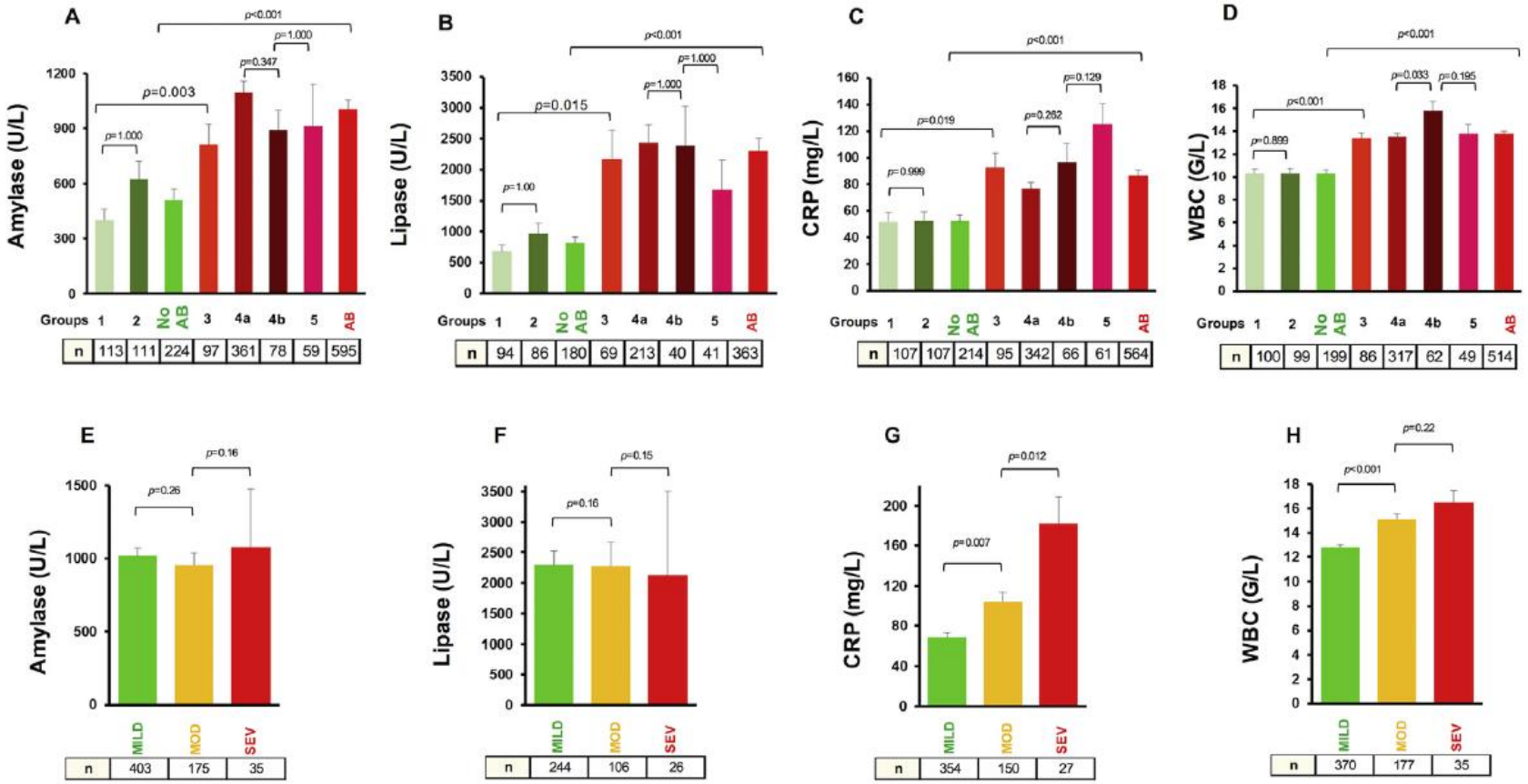


Figure 12. On-admission laboratory markers by antibiotic therapy and status of infection (A–D) and by severity of acute pancreatitis (E–H). In non-AB groups, day-matched controls were selected. Values are given as mean ± standard deviation. For the definitions of groups, see Figure 11. **(A)** Average amylase in non-AB group (510.01 ± 57.91 U/L) compared to AB group (1004.15 ± 50.22 U/L) differed significantly (p<0.001). **(B):** There was 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 level 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), **(D)** similar trends were detected with regards to WBC levels (10.32 ± 0.28 G/L vs 13.8 ± 0.2 G/L, p<0.001). **(E)** Average amylase (1015.25 ± 55.10 U/L, 957.41 ± 83.33 U/L, 1077.48 ± 397.02 U/l) and **(F)** lipase (2303.05 ± 219.19 U/L, 2286.82 ± 378.21 U/L, 2131.42 ± 1377.75 U/L) did not differ across mild, moderate and severe cases, respectively. **(G)** Average CRP (68.77 ± 4.32 mg/L, 104.56 ± 8.71 mg/L, 181.7 ± 27.26 mg/L) and **(H)** WBC (12.83 ± 0.21 G/L, 15.11 ± 0.49 G/L, 16.5 ± 0.98 G/L) positively correlated with the severity of acute pancreatitis. AB: antibiotic, CRP: C-reactive protein, WBC: white blood cell count. Reprinted from *'Antibiotic Therapy in Acute Pancreatitis: From Global Overuse to Evidence Based Recommendations'* by Párniczky et al., 2019, *Pancreatology.*

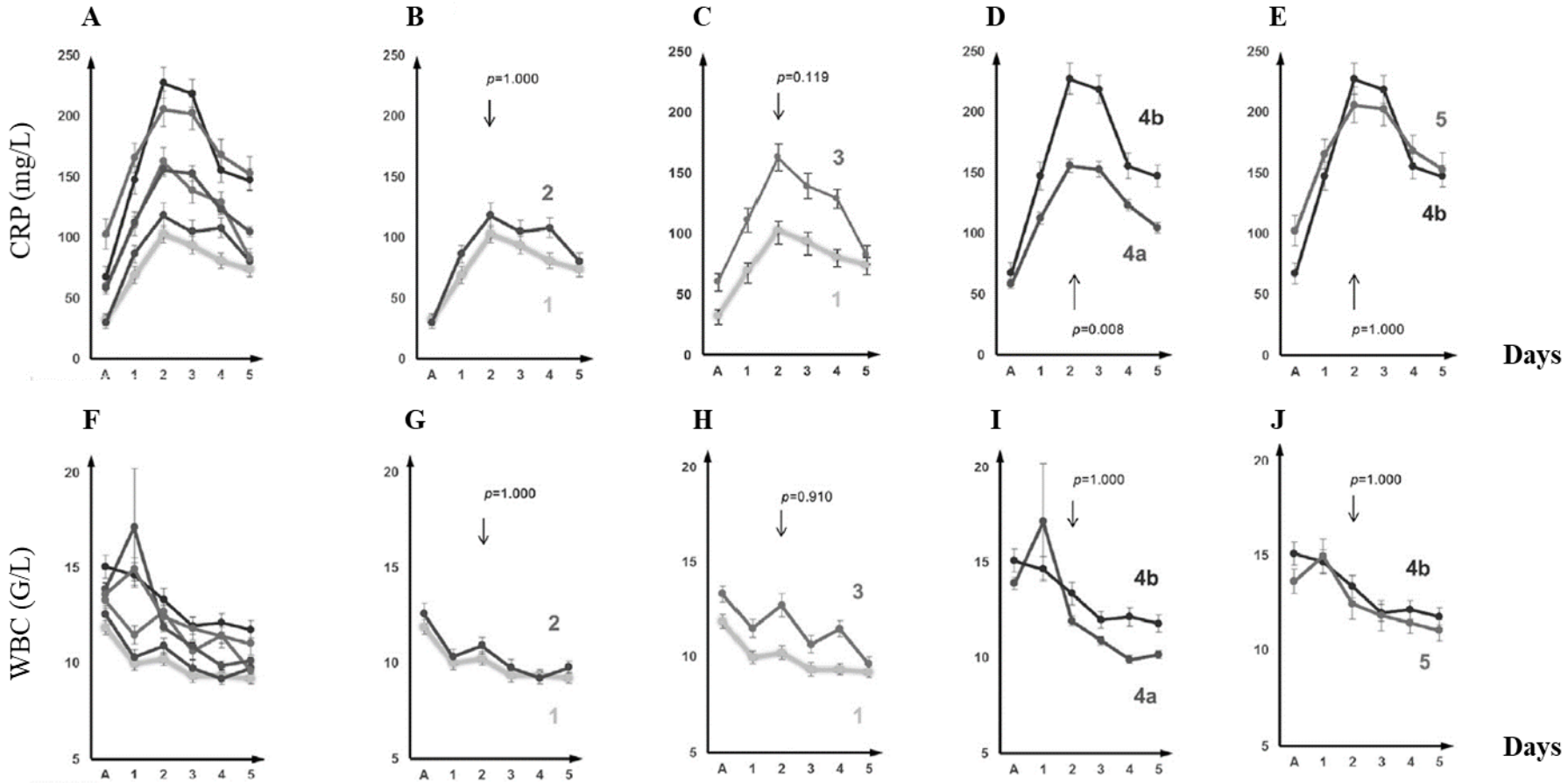


Figure 13. Changes in biomarkers during disease course across groups by antibiotic treatment and status of infection. (A) All groups (for illustrative purpose only), **(B)** Groups 1 vs 2, **(C)** Groups 1 vs 3, **(D)**, Groups 4a vs 4b and **(E)** Groups 4b vs 5 with the corresponding p-values embedded in the figures. Group are indicated with numbers in the figures, for the definitions of groups, see Figure 11. The horizontal axis represents the days of hospital stay (A: admission). CRP: C-reactive protein, WBC: white blood cell count. Adapted and reprinted from *'Antibiotic Therapy in Acute Pancreatitis: From Global Overuse to Evidence Based Recommendations'* by Párniczky et al., 2019, *Pancreatology.*

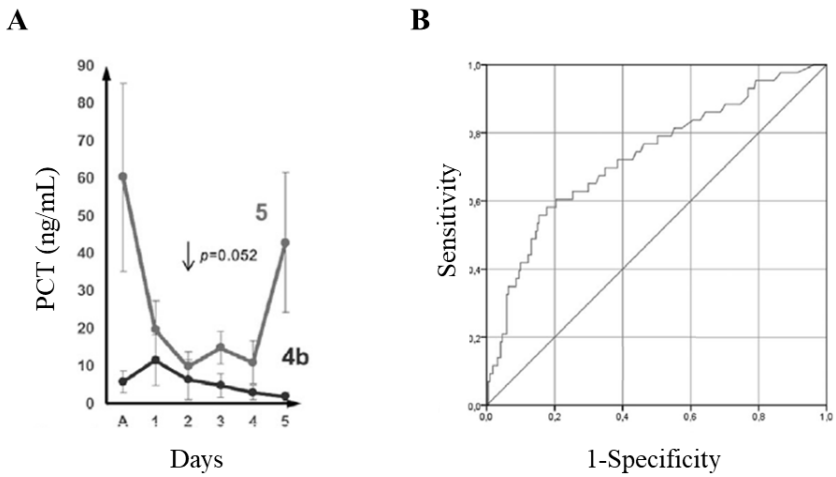


Figure 14. Procalcitonin and infections in acute pancreatitis. (A) Changes of procalcitonin level during disease course in Groups 4b vs 5 with the corresponding p-value embedded in the figure. **(B)** Diagnostic accuracy of procalcitonin in discriminating pancreatic infections: area under the curve was 0.729, indicating a fair discriminative ability. PCT: procalcitonin. Adapted and reprinted from *'Antibiotic Therapy in Acute Pancreatitis: From Global Overuse to Evidence Based Recommendations'* by Párniczky et al., 2019, *Pancreatology.*

6.3 Metabolic syndrome and acute pancreatitis

6.3.1 Characteristics of the study population

A total of 1,435 cases were identified in the AP Registry, of which 1,257 were included in the analysis (for sites of recruitment, see Supplementary Figure 1). The study population proved to be representative of the total population of the registry regarding age, sex, severity of AP, mortality, length of hospital stay and complications. All cases had available information about hypertension and obesity (defined as a BMI≥30 kg/m^2), 1,127 cases about diabetes mellitus and 1,036 cases about hyperlipidaemia. All four variables were available for 906 cases. Baseline characteristics of the population are summarized in Table 9. Obesity, hypertension, hyperlipidaemia and diabetes mellitus accounted for 29.5, 60.0, 33.6 and 16.4% of the cases.

6.3.2 Association of components of metabolic syndrome with disease outcomes

Table 9 summarizes the characteristics of the study population, and Table 10 shows the outcomes of patients with and without the components of MetS in univariate analysis. Mortality was similar across groups. Obesity and hypertension were associated with a more severe disease course (OR: 2.15, CI: 1.31–3.54 and OR: 2.39, CI: 1.30–4.38, respectively), more systemic complications (OR: 1.99, CI: 1.30–3.05 and OR: 2.83, CI: 1.64–4.88, respectively) and longer hospital stay (12.1 vs 10.4 days with p=0.008 and 11.8 vs 10.5 days with p=0.020, respectively). Local complications were rather more

common with hyperlipidaemia (OR: 1.55, CI: 1.17–2.05). Interestingly, diabetes mellitus was not associated with untoward outcomes of AP.

Based on the data of 906 patients having had available data for all the four variables, 189 patients (20.9%) had no components of MetS, 294 (32.5%) had obesity, 560 (61.8%) had hypertension, 316 (34.9%) had hyperlipidaemia, and 162 (17.9%) had diabetes mellitus. In logistic regression analysis adjusted for age and other components of MetS, obesity predicted renal failure (OR: 2.98, CI: 1.33–6.66); hypertension predicted SAP (OR: 3.41, CI: 1.39–8.37), systemic complications (OR: 2.64, CI: 1.27–5.51) and renal failure (OR: 7.46, CI: 1.61–34.49); hyperlipidaemia predicted local complications (OR: 1.51, CI: 1.10–2.07) and new diagnosis of DM (OR: 2.55, CI: 1.26–5.19); whereas diabetes mellitus was not a significant predictor of any outcomes. The presence of two, three, or four components of MetS significantly increased the rate of untoward outcomes by 9.5, 24.1, and 66.7%, respectively.

Table 9. Characteristics of the study population.

	Total (n=1,257)	Obesity		Hypertension		Hyperlipidaemia		Diabetes mellitus	
		No (n=886)	Yes (n=371)	No (n=451)	Yes (n=676)	No (n=687)	Yes (n=349)	No (n=1051)	Yes (n=206)
Demography									
Age (mean±SD, years)	55.7±17	55.4±17.7	56.3±15.2	46.2±15.2	63.8±14.1*	56.4±17.8	54.0±14.5*	54.5±17.3	61.7±13.9*
Female (% of total)	42.9	40.7	48.0*	38.1	48.2*	44.4	35.2	43.6	39.3
CCI (mean±SD, point)	1.4±1.6	1.3±1.6	1.6±1.7	0.9±1.4	1.7±1.7	1.3±1.6	1.7±1.8	1.0±1.4	2.9±1.7
Aetiology (% of total)									
Biliary	37.8	33.6	47.7*	31.3	44.1	41.3	26.4	38.2	35.9
Alcoholic	18.5	21.1	12.1	20.2	12.4	21.4	17.2	19.0	15.5
Hypertriglicerdaemic	3.7	3.0	5.4	3.3	3.7	0.1	12.9*	2.8	8.7*
Alcoholic + Hypertriglicerdaemic	1.8	1.9	1.6	1.6	1.9	0.0	6.6	1.8	1.9
Post-ERCP	2.6	3.0	1.6	3.1	2.8	2.9	0.9	2.6	2.9
Combined	8.0	7.1	10.0	11.1	7.0	7.7	7.2	7.9	8.3
Idiopathic	20.5	22.0	17.0	21.5	20.7	18.8	23.8	20.6	20.4
Other	7.1	8.1	4.6	8.0	7.4	7.7	5.2	7.2	6.3

*indicates a statistically significant difference between groups in univariate analysis (condition vs no condition). ERCP: endoscopic retrograde cholangiopancreatography, SD: standard deviation.

Table 10. Disease outcomes.

	Total (n=1,257)	Obesity		Hypertension		Hyperlipidaemia		Diabetes mellitus	
		No (n=886)	Yes (n=371)	No (n=451)	Yes (n=676)	No (n=687)	Yes (n=349)	No (n=1051)	Yes (n=206)
Severity (% of total)									
Mild	69.6	69.9	69.0	70.1	69.5	73.5	64.2*	69.7	68.9
Moderate	25.1	26.1	22.6	26.8	23.4	22.1	29.5	24.9	25.7
Severe	5.3	4.1	8.4*	3.1	7.1*	4.4	6.3	5.3	5.3
Mortality	2.4	2.1	3.0	1.3	3.1	2.3	1.4	2.5	1.9
Length of hospital stay (mean±SD, days)	10.9±9.3	10.4±8.6	12.1±10.6*	10.5±7.9	11.8±10.1*	10.5±9	11.4±10.3	10.7±9	11.8±10.6
Complications (% of total)									
Local	29.0	28.6	30.2	29.5	28.3	25.3	34.7*	29.1	28.6
Fluid collection	25.0	24.7	26.7	23.9	25.3	22.1	29.8*	24.9	27.2
Pseudocyst	7.6	7.8	7.3	6.9	9.3	6.0	10.6*	7.6	7.8
Necrosis	8.0	7.1	10.2	7.8	8.0	8.2	8.9	8.3	6.8
New onset diabetes mellitus	3.8	3.5	4.6	2.7	4.1	3.6	5.2	4.6	N/A
Systemic	7.6	6.0	11.3*	3.8	10.1*	6.6	9.5	7.0	10.2
Respiratory failure	4.6	3.5	7.3*	2.0	6.1*	4.5	4.9	4.1	7.3
Heart failure	1.8	1.4	3.0	0.7	2.5*	1.9	2.0	1.9	1.5
Renal failure	2.7	1.4	5.9*	0.7	4.1*	2.2	4.6*	2.8	2.4

*indicates a statistically significant difference between groups in univariate analysis (condition vs no condition). N/A: not applicable, SD: standard deviation.

7. Discussion

7.1 Scope and main findings

In this dissertation, findings from three cohort studies covering different aspects of the management of AP were introduced. We aimed to investigate the effects of centralized care, features and indications of AB use and the associations between the components of MetS and outcomes of AP. In our first study, centralized care proved to be superior regarding outcomes, quality indicators and cost of care (92). In our second study, early rise in CRP proved to be inaccurate for guiding the initiation of AB therapy, whereas PCT was a more promising biomarker (93). In the third study, MetS and its components predisposed patients to develop a more severe disease course (94).

7.2 Explanation and elaboration

7.2.1 Centralized care

To our best knowledge, five studies investigated the role of hospital volume on the outcomes of AP (7, 118-121). The definition for high hospital volume varied across studies fundamentally: cut-offs for annual case numbers ranged from 16 to 118. In contrast in our study, 195 cases were treated in the specialist unit (centralized care), and only 81 cases were treated in the tertiary pancreatic centre in the non-centralized setting (the others were treated in smaller wards receiving ≤30 cases, as shown by Figure 7). Comparing our centres to the international data, Healthcare Model A should be taken as a high volume centre whereas Healthcare Model B consists of of a moderate volume and multiple low volume centres.

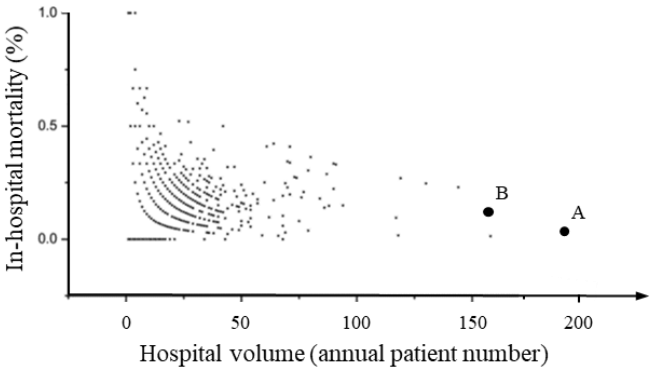


Figure 15. The association between hospital volume and in-hospital mortality. The higher the hospital volume, the lower the in-hospital mortality. In our study, in-hospital mortality was 1 and 6.3% with annual case numbers 195 and 160 in Healthcare Models A and B, respectively (represented by the larger black dots with the corresponding letters in the figure). Of note, only 81 patients were treated in the tertiary pancreatic centre in Healthcare Model B. Adapted and reprinted from *'The effect of hospital volume on patient outcomes in severe acute pancreatitis'* by Shen et al., 2012, *BMC Gastroenterology.*

Four studies provided evidence that a higher hospital volume has a favourable impact on mortality of AP (for an example, see Figure 15) (7, 118, 119, 121), the fifth found no benefit (120). Length of hospital stay consistently reduced in four studies (7, 118-120). Cost of

care was reduced in one study (7); however, another one reported no change (120). The benefit of a higher hospital volume remained stable even after propensity matching and/or adjustment for significant covariates, such as baseline disease severity (patients with SAP are probably more likely to be referred to a centre of higher progressivity level thereby increasing adverse outcomes, the phenomenon is termed as 'referral bias' (122)). It must be noted, however, that our study did not investigate the effect of hospital volume directly since this is only one component of centralized care. In our study, better guideline adherence (i.e. evidence-based care, reflected by the lower rate AB use and the higher rate of nasoenteral nutrition) served with an additional benefit for patients, making our study setting unique.

To sum up, providing care of AP in specialised units (i.e. centralization) is supported by several theoretical and practical arguments.

1) Both hospital volume and physician volume can exceed that of general units multiple times: along the 'Practice makes one better' principle, management skills (i.e. expertise) can be gained with the increasing number of cases.
2) Access to state-of-the-art facilities and services, including multidisciplinary consultations, is usually better in specialized units. Instant availability of ICU should be highlighted. Besides, access to diagnostic and therapeutic endoscopic procedures is a must-have-item in specialist units: EUS/ERCP should be performed by an expert operator for selected cases of biliary AP (123), and endoscopic debridement/stent insertion might be required for certain cases of local complications.
3) Adherence to evidence-based guidelines is better in specialist units as treating physicians are motivated to keep pace with changes in recommendations. Although most efforts for pharmacological interventions failed to achieve success in AP (72), pre-existing comorbidities can be decompensated, thereby requiring further care. Secondary prevention aiming to reduce the rate of recurrent AP might be more structured by providing the required intervention through strict follow-up of cases (such as same-admission cholecystectomy in biliary AP (124), encouragement for alcohol withdrawal in alcohol-induced AP (125) or lipid-control in hypertriglyceridaemic AP (126)).
4) Specialized units contribute to research activity to a considerable extent, which provides further financial and infrastructural access and promote guideline adherence (49). A good example could be the operation of the AP Registry, which

requires to acquire extremely detailed past medical history and strict recording of vital signs, laboratory parameters, finding on physical examination and imaging daily.

These arguments are entirely in line with the principles of evidence-based medicine regarding decision making: evidence from research should be complemented with personal expertise and the patient's preferences to make the optimal decision (Figure 16).

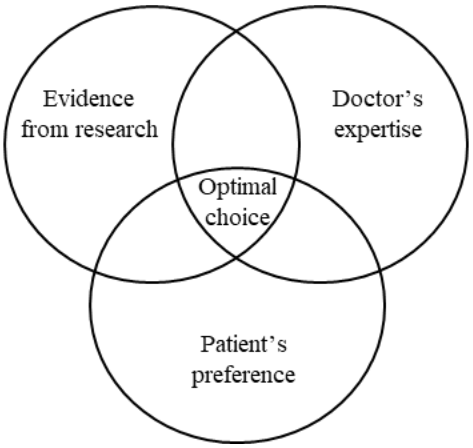


Figure 16. The model of evidence-based medicine. Centralized care in specialist units allows to meet 'Optimal choice'. The figure is the author's own work.

7.2.2 Antibiotic use

In 1975, two RCTs were published which investigated the efficacy of prophylactic AB use in AP (98, 103), writing the first pages of the saga of ABs in AP. Although now we consider prophylactic AB use ineffective (72), defining the population which benefits from ABs has remained an open debate. Although extrapancreatic infections, e.g. acute cholangitis, obviously require treatment (40, 43, 44), identifying those who already have or are particularly vulnerable to develop IPN is challenging.

Considering the direct and indirect strategies implemented to verify IPN and justify AB use, even the top-quality studies used inconsistent definitions, as indicated by our systematic review (see Supplementary Table 1). Despite the known drawbacks (invasivity, costs, difficult sampling, need for imaging-guidance), FNAB followed by culturing should be considered the single direct method for detecting bacteria from IPN and initiating targeted AB treatment, though empirical AB therapy is pervasively used (40, 43, 44). A meta-analysis of 14 studies reported that the incidence of IPN could be as high as 21% (314 cases of IPN out of 1,478 cases of AP) and IPN posed a considerable burden of mortality (127). In our data analysis of 962 AP cases, 76 had a culturing-confirmed infection (7.9%), which is considerably lower than the reported average. Of note, the number of cases with negative culturing was low as well (102 cases, 10.5%). A total of 420 cases (43.4%) were considered to show signs of suspected infection and were treated accordingly with ABs, which rather reflects that our practice follows the empirical treatment strategy instead of the culturing-based targeted AB therapy (Figure 11). Nevertheless, no RCTs have compared FNA-guided vs empirical initiation of ABs.

In line with our preliminary publication (25), our study indicated that 74.7% of cases received ABs during hospital stay in Hungary. In the context of the fraction of cases with confirmed or suspected infection, this number is almost double of the expectations. Findings from the Western countries fell far from that reported in Hungary while most Asian countries performed similarly as we did (map of worldwide AB use is shown in Figure 10). These findings are in line with previous observations from Japan (74%) (128), India (67%) (129), the UK (58%) (130) and the US (41%) (131) and findings of a summary publication from 2016 (41–88%) (132). If we consider AB use as an indicator of guideline adherence, Hungary performed poorly. Regular in-hospital audits and establishment of specialist units may facilitate guideline adherence regarding AB use, as shown by our study on the efficacy of centralized care (92).

AB overuse has long-lasting implications: it encourages the emergence of AB-resistant bacteria, thereby reducing the available treatment options not only in AP but also in other medical conditions (133). The background of AB over- or misuse is multifactorial but the development of SIRS with elevating WBC, CRP and, sometimes, rising body temperature – as the consequence of sterile inflammation – resembles an ongoing infection, deciphering clinicians. To address this issue, biomarker research tended to focus on new and newly emerging laboratory parameters (such as CRP, PCT, cytokines and chemokines) assumed to have the potential of distinguishing IPN from sterile ANP (see the paper of Quenot et al. for an up-to-date review on biomarkers (134)). In these studies, the level of biomarkers often showed a statistically significant difference between cases with and without IPN with varying diagnostic performance across studies. AUC for CRP ranged from 76 to 86% whereas that of PCT often exceeded 90%. In a meta-analysis of 7 studies, sensitivity and specificity of PCT proved to be 80 and 91%, respectively; with an AUC of 0.91 (135). Surprisingly, AUC for on-admission PCT was measured only 0.729 in our cohort of patients (Figure 14) while on-admission CRP had an even worse poor diagnostic performance. The difference between our results might root in the selection of the sample: earlier studies often included patients from ICU so that the pre-test probability of having IAP was substantially higher. Besides, a lot of patients in our database did not have valid PCT measurement; therefore, our confidence in the representativity of this result is low.

Biomarker-guided initiation of AB therapy is an enticing possibility. Convincing quality of evidence on safety and efficacy can only be obtained from RCTs. The single study we found on PCT-guided AB therapy had a limited sample size to estimate the

effects on hard outcomes reliably; therefore, it should be considered a pilot study (95). Another ongoing RCT from the UK under the acronym PROCAP has similar objectives and presumably has more extensive resources (136). Further studies on the topic are very welcomed.

7.2.3 Metabolic syndrome

According to data of the Hungarian Central Statistical Office, 40.3% of the population had normal BMI, 35.8% had a BMI between 25 and 30 kg/m^2 (i.e. overweight) and 19.7% had a BMI>30 kg/m^2 (i.e. obese) in 2017 (further data are available at www.ksh.hu). In contrast, prevalence of obesity was almost 30% in our study. Indeed, it is not surprising because obesity is known to increase the risk of AP: in a Chinese prospective cohort study including more than half-million participants, waist circumference was an independent risk factor of AP (adjusted hazard ratio [HR]: 1.35, CI: 1.27-1.43) (137). Observations posed that the amount (and maybe the distribution) of visceral fat is related to the severity of AP (138, 139). The theory on how obesity aggravates the clinical course of AP involves the role of abundant peripancreatic adipose tissue, which is vulnerable to necrosis, in which unsaturated fatty acids, cytokines, chemokines and other biologically active molecules are released, triggering the cascade of systemic effects (for details, see the review of Khatua et al. (140)). The previous results were supported by our findings based on calculations from BMI instead of waist circumference (as the latter is not routinely recorded in the AP Registry). Hyperlipidaemia was reported to be associated with adverse disease course in multiple studies (79, 141, 142) whereas, in our study, hyperlipidaemia was independently associated only with the frequency of local complications. By mechanism, lipotoxicity and endoplasmic reticulum stress were implicated (143). Surprisingly, we found no association between diabetes mellitus and disease outcomes in this study, opposing other evidence (144).

In line with other reports (30, 90, 91), the association between the effects of MetS on adverse disease outcomes was convincing in our study as well. Considering the individual effects of components of MetS, there is substantial heterogeneity in the measured effects across the studies. This roots in the fact that the components of MetS do associate with other prognostic factors (such as age or comorbidities), aggravating the disease course. This question can only be approached with multivariate analysis (in our study, with logistic regression) to control for confounding factors. However, studies

included various confounding factors in the analysis, potentially leading to divergent conclusions. Consequently, the findings of studies in the literature should not be considered comparable with each other.

7.3 Strengths and limitations

Although the AP Registry records are based on multicentre data, it must be noted that the population of the registry is not nationwide; therefore, we do not have evidence that it is undoubtedly representative of the whole Hungarian set of cases with AP (out of the estimated 5,000–5,500 cases in the country, an average of 500–600 cases are uploaded in the registry annually). Centres which cannot afford to employ CRAs may upload MAP with shorter hospitalization more frequently because the longer the hospitalization, the more B forms are required to be completed, imposing an extra administrative burden on the medical staff. Consequently, data from the registry may underestimate the rate of SAP and mortality.

Regarding internationality, the registry is open to join for all centres providing care for AP (irrespective of the level of care or centralization). However, the majority of the study population was recruited from Hungary (shown in Supplementary Figure 1). Of note, baseline characteristics of the study population (age, sex, comorbidities) and disease outcomes (mortality and severity) resemble that published in the literature.

Guideline adherence may differ across centres, so does diagnostic and therapeutic approaches, both having the potential to modify disease outcomes. Local complications are especially vulnerable to detection bias: while in our specialist unit, follow-up imaging (US or CECT) is arranged for the 1-month visit, some centres do not invite patients for follow-up at all. Therefore, incidence of local complications is probably underestimated, affecting the categorization of disease severity (i.e. the differentiation between MAP and MSAP, see Table 1 for definitions). Besides, transient and permanent organ failure are sometimes hard to be distinguished (e.g. if one does not have data on kidney functions prior to the acute episode, the length of recovery cannot be judged reliably). Access to interventions may affect outcomes as well: centres cannot adhere to the step-up approach if endoscopic or percutaneous interventions are not available (145). Limited laboratory and imaging capacities (e.g. measurement of IgG4, detection of pancreatic malformations or microlithiasis, identification of genetic mutations) may affect the investigation for rare aetiologies so that classification bias might occur.

The AP Registry is a unique source of data on AP cases with excellent data quality for hard outcomes, ensured by the four-level quality control systems. The high total case number (>1,000 cases) allows a detailed analysis of rare conditions as well. Although data quality for disease outcomes (e.g. severity, mortality) and certain baseline parameters (e.g. age, sex, aetiology, on-admission vital parameters) are almost 100%, other data are not always systematically documented. Missing data limits the use of logistic regression model because some potential confounding factors cannot be added or can be replaced with imputation. Besides, from a statistical point of view, mortality and severity should be considered rare events in AP, which reduce statistical power in the analysis even if the total case number is high.

Theoretically, the comparison of centralized vs non-centralized care would have the highest level of evidence from a cluster RCT. This setting is not feasible to be organized due to various logistical and ethical reasons. However, since consecutive cases were included in the analysis from both centres in this study, we assume that baseline factors were approximately balanced between groups (as shown by the age and sex of the cases in Table 3). The question if PCT-guided AB treatment is superior to standard of care or other biomarker-guided treatment regarding efficacy and safety can be best answered with a parallel RCT.

8. Conclusions and perspectives

1. **Centralized care is superior to non-centralized care in AP regarding mortality, severity and quality indicators of care, such as the use of ABs and enteral feeding, while the cost of care is reduced by a quarter in the specialist unit.**
   Further research is needed to investigate which component(s) of centralized care might be responsible for its benefit and which annual minimum volume of centres is needed to observe improvement in care.
2. **ABs are overused in AP both worldwide and in Hungary. Early AB treatment should not be initiated based on initially elevated CRP because it does not indicate infections reliably in AP. PCT shows fair diagnostic performance in detecting infections so that it may be a better driver of AB therapy than CRP.**
   Further research is needed to clarify if changes in biomarkers, such as persistently elevated or suddenly rising CRP, can establish the rationale for the initiation of AB treatment. The diagnostic performance of other biomarkers of the acute-phase response, e.g. cytokines and chemokines, warrants further investigation. Regular in-house audits might help to reduce the unnecessary AB treatment, thereby the cost of care in specialist units.
3. **Components of MetS are present in a considerable fraction of AP patients and are independent predictors of various outcomes. Hypertension predicts severity, systematic complications and renal failure; obesity predicts renal failure, and hyperlipidaemia predicts local complications and newly onset diabetes mellitus. The more components of MetS a patient has, the worse the clinical outcome is.**
   Further research is needed to investigate the interplay of the components of MetS during the clinical course of AP. In addition, the difference between well- and poorly treated comorbidities should be assessed as well. Prognostic scores might benefit from incorporating MetS or items of MetS.

9. Acknowledgements

I want to express my profound gratitude to my supervisor Áron Vincze for his guidance and help during my clinical and scientific work. Without him, this work would not have been possible.

I want to thank Péter Hegyi, who offered me the opportunity to participate in the operation of the AP Registry actively and supported me throughout the entire work. The efforts of all treating physicians and clinical research administrators who contributed to data acquisition and upload of patients' files must be acknowledged as well. The operation of the AP Registry would not be possible without the financial support of an Economic Development and Innovation Operative Programme Grant (GINOP 2.3.2.-15-2016-00048) and a Human Resources Development Operative Programme Grant (EFOP-3.6.2-16-2017-00006) of the National Research, Development and Innovation Office, Hungary.

I want to thank the biostatistical team of the Center for Translational Medicine, led by Nelli Farkas, for her help with the statistical analysis, and I am very grateful to Zsolt Szakács for his contribution to the methodology and critical review of the projects.

Finally, I would like to thank my family members, who always encouraged and supported me during my study.

10. References

1. Whitcomb DC, Shimosegawa T, Chari ST, Forsmark CE, Frulloni L, Garg P, et al. International consensus statements on early chronic Pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with The International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest Working Group and European Pancreatic Club. Pancreatology. 2018. DOI: 10.1016/j.pan.2018.05.008.
2. Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, et al. Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2018. Gastroenterology. 2019;156:254-72.e11. DOI: 10.1053/j.gastro.2018.08.063.
3. Szentesi A, Tóth E, Bálint E, Fanczal J, Madácsy T, Laczkó D, et al. Analysis of Research Activity in Gastroenterology: Pancreatitis Is in Real Danger. PLoS One. 2016;11:e0165244. DOI: 10.1371/journal.pone.0165244.
4. Xiao AY, Tan ML, Wu LM, Asrani VM, Windsor JA, Yadav D, et al. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. Lancet Gastroenterol Hepatol. 2016;1:45-55. DOI: 10.1016/s2468-1253(16)30004-8.
5. Oskarsson V, Hosseini S, Discacciati A, Videhult P, Jans A, Ekbom A, et al. Rising incidence of acute pancreatitis in Sweden: National estimates and trends between 1990 and 2013. United European Gastroenterol J. 2020;8:472-80. DOI: 10.1177/2050640620913737.
6. Brindise E, Elkhatib I, Kuruvilla A, Silva R. Temporal Trends in Incidence and Outcomes of Acute Pancreatitis in Hospitalized Patients in the United States From 2002 to 2013. Pancreas. 2019;48:169-75. DOI: 10.1097/mpa.0000000000001228.
7. Singla A, Simons J, Li Y, Csikesz NG, Ng SC, Tseng JF, et al. Admission volume determines outcome for patients with acute pancreatitis. Gastroenterology. 2009;137:1995-2001. DOI: 10.1053/j.gastro.2009.08.056.
8. Sahin-Tóth M, Hegyi P. Smoking and Drinking Synergize in Pancreatitis: Multiple Hits on Multiple Targets. Gastroenterology. 2017;153:1479-81. DOI: 10.1053/j.gastro.2017.10.031.

9. Mayerle J, Sendler M, Hegyi E, Beyer G, Lerch MM, Sahin-Tóth M. Genetics, Cell Biology, and Pathophysiology of Pancreatitis. Gastroenterology. 2019;156:1951-68.e1. DOI: 10.1053/j.gastro.2018.11.081.

10. Whitcomb DC. Genetic risk factors for pancreatic disorders. Gastroenterology. 2013;144:1292-302. DOI: 10.1053/j.gastro.2013.01.069.

11. Sahin-Tóth M, Tóth M. Significance of trypsinogen gene mutations in the etiology of hereditary pancreatitis. Orv Hetil. 2001;142:603-6. DOI: not available.

12. Alexakis N, Lombard M, Raraty M, Ghaneh P, Smart HL, Gilmore I, et al. When is pancreatitis considered to be of biliary origin and what are the implications for management? Pancreatology. 2007;7:131-41. DOI: 10.1159/000104238.

13. Apte MV, Pirola RC, Wilson JS. Mechanisms of alcoholic pancreatitis. J Gastroenterol Hepatol. 2010;25:1816-26. DOI: 10.1111/j.1440-1746.2010.06445.x.

14. Del Vecchio Blanco G, Gesuale C, Varanese M, Monteleone G, Paoluzi OA. Idiopathic acute pancreatitis: a review on etiology and diagnostic work-up. Clin J Gastroenterol. 2019;12:511-24. DOI: 10.1007/s12328-019-00987-7.

15. Makhija R, Kingsnorth AN. Cytokine storm in acute pancreatitis. J Hepatobiliary Pancreat Surg. 2002;9:401-10. DOI: 10.1007/s005340200049.

16. Telek G, Fehér J, Jakab F, Claude R. Acute pancreatitis: recent advances in understanding its pathophysiology. Orv Hetil. 2000;141:267-78. DOI: not available.

17. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62:102-11. DOI: 10.1136/gutjnl-2012-302779.

18. Dhaka N, Samanta J, Kochhar S, Kalra N, Appasani S, Manrai M, et al. Pancreatic fluid collections: What is the ideal imaging technique? World journal of gastroenterology. 2015;21:13403-10. DOI: 10.3748/wjg.v21.i48.13403.

19. Porter KK, Zaheer A, Kamel IR, Horowitz JM, Arif-Tiwari H, Bartel TB, et al. ACR Appropriateness Criteria; Acute Pancreatitis. Journal of the American College of Radiology. 2019;16:S316-S30. DOI: 10.1016/j.jacr.2019.05.017.

20. Rana SS. An overview of walled-off pancreatic necrosis for clinicians. Expert Rev Gastroenterol Hepatol. 2019;13:331-43. DOI: 10.1080/17474124.2019.1574568.

21. Manrai M, Kochhar R, Gupta V, Yadav TD, Dhaka N, Kalra N, et al. Outcome of Acute Pancreatic and Peripancreatic Collections Occurring in Patients With Acute Pancreatitis. Ann Surg. 2018;267:357-63. DOI: 10.1097/sla.0000000000002065.

22. Cui ML, Kim KH, Kim HG, Han J, Kim H, Cho KB, et al. Incidence, risk factors and clinical course of pancreatic fluid collections in acute pancreatitis. Dig Dis Sci. 2014;59:1055-62. DOI: 10.1007/s10620-013-2967-4.

23. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med. 1995;23:1638-52. DOI: 10.1097/00003246-199510000-00007.

24. Dombernowsky T, Kristensen M, Rysgaard S, Gluud LL, Novovic S. Risk factors for and impact of respiratory failure on mortality in the early phase of acute pancreatitis. Pancreatology. 2016;16:756-60. DOI: 10.1016/j.pan.2016.06.664.

25. Párniczky A, Kui B, Szentesi A, Balázs A, Szűcs Á, Mosztbacher D, et al. Prospective, Multicentre, Nationwide Clinical Data from 600 Cases of Acute Pancreatitis. PLoS One. 2016;11:e0165309. DOI: 10.1371/journal.pone.0165309.

26. Besselink MG, Verwer TJ, Schoenmaeckers EJ, Buskens E, Ridwan BU, Visser MR, et al. Timing of surgical intervention in necrotizing pancreatitis. Arch Surg. 2007;142:1194-201. DOI: 10.1001/archsurg.142.12.1194.

27. Werge M, Novovic S, Schmidt PN, Gluud LL. Infection increases mortality in necrotizing pancreatitis: A systematic review and meta-analysis. Pancreatology. 2016;16:698-707. DOI: 10.1016/j.pan.2016.07.004.

28. Freeman ML, Werner J, van Santvoort HC, Baron TH, Besselink MG, Windsor JA, et al. Interventions for necrotizing pancreatitis: summary of a multidisciplinary consensus conference. Pancreas. 2012;41:1176-94. DOI: 10.1097/MPA.0b013e318269c660.

29. Bradley EL, 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. Arch Surg. 1993;128:586-90. DOI: 10.1001/archsurg.1993.01420170122019.

30. Niknam R, Moradi J, Jahanshahi KA, Mahmoudi L, Ejtehadi F. Association Between Metabolic Syndrome and Its Components with Severity of Acute Pancreatitis. Diabetes Metab Syndr Obes. 2020;13:1289-96. DOI: 10.2147/dmso.S249128.

31. Pongprasobchai S, Vibhatavata P, Apisarnthanarak P. Severity, Treatment, and Outcome of Acute Pancreatitis in Thailand: The First Comprehensive Review Using Revised Atlanta Classification. Gastroenterol Res Pract. 2017;2017:3525349. DOI: 10.1155/2017/3525349.

32. Zhu Y, Pan X, Zeng H, He W, Xia L, Liu P, et al. A Study on the Etiology, Severity, and Mortality of 3260 Patients With Acute Pancreatitis According to the Revised Atlanta Classification in Jiangxi, China Over an 8-Year Period. Pancreas. 2017;46:504-9. DOI: 10.1097/mpa.0000000000000776.

33. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: a large population-based study. Gut. 2008;57:1698-703. DOI: 10.1136/gut.2008.152702.

34. Devani K, Charilaou P, Radadiya D, Brahmbhatt B, Young M, Reddy C. Acute pancreatitis: Trends in outcomes and the role of acute kidney injury in mortality- A propensity-matched analysis. Pancreatology. 2018;18:870-7. DOI: 10.1016/j.pan.2018.10.002.

35. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JH. Acute pancreatitis: value of CT in establishing prognosis. Radiology. 1990;174:331-6. DOI: 10.1148/radiology.174.2.2296641.

36. Mortele KJ, Wiesner W, Intriere L, Shankar S, Zou KH, Kalantari BN, et al. A modified CT severity index for evaluating acute pancreatitis: improved correlation with patient outcome. AJR Am J Roentgenol. 2004;183:1261-5. DOI: 10.2214/ajr.183.5.1831261.

37. Ranson JH, Pasternack BS. Statistical methods for quantifying the severity of clinical acute pancreatitis. J Surg Res. 1977;22:79-91. DOI: 10.1016/0022-4804(77)90045-2.

38. Yeung YP, Lam BY, Yip AW. APACHE system is better than Ranson system in the prediction of severity of acute pancreatitis. Hepatobiliary Pancreat Dis Int. 2006;5:294-9.

39. Mikó A, Vigh É, Mátrai P, Soós A, Garami A, Balaskó M, et al. Computed Tomography Severity Index vs. Other Indices in the Prediction of Severity and Mortality in Acute Pancreatitis: A Predictive Accuracy Meta-analysis. Front Physiol. 2019;10:1002. DOI: 10.3389/fphys.2019.01002.

40. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology. 2013;13:e1-15. DOI: 10.1016/j.pan.2013.07.063.

41. Hritz I, Czakó L, Dubravcsik Z, Farkas G, Kelemen D, Lásztity N, et al. Acute pancreatitis. Evidence-based practice guidelines, prepared by the Hungarian Pancreatic Study Group. Orv Hetil. 2015;156:244-61. DOI: 10.1556/oh.2015.30059.

42. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336:924-6. DOI: 10.1136/bmj.39489.470347.AD.

43. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108:1400-15; 16. DOI: 10.1038/ajg.2013.218.

44. Yokoe M, Takada T, Mayumi T, Yoshida M, Isaji S, Wada K, et al. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. J Hepatobiliary Pancreat Sci. 2015;22:405-32. DOI: 10.1002/jhbp.259.

45. Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. Gastroenterology. 2018;154:1096-101. DOI: 10.1053/j.gastro.2018.01.032.

46. Leppäniemi A, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick AW, et al. 2019 WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg. 2019;14:27. DOI: 10.1186/s13017-019-0247-0.

47. Greenberg JA, Hsu J, Bawazeer M, Marshall J, Friedrich JO, Nathens A, et al. Clinical practice guideline: management of acute pancreatitis. Can J Surg. 2016;59:128-40. DOI: 10.1503/cjs.015015.

48. Pezzilli R, Zerbi A, Campra D, Capurso G, Golfieri R, Arcidiacono PG, et al. Consensus guidelines on severe acute pancreatitis. Dig Liver Dis. 2015;47:532-43. DOI: 10.1016/j.dld.2015.03.022.

49. Hegyi P, Petersen OH, Holgate S, Erőss B, Garami A, Szakács Z, et al. Academia Europaea Position Paper on Translational Medicine: The Cycle Model for Translating Scientific Results into Community Benefits. J Clin Med. 2020;9. DOI: 10.3390/jcm9051532.

50. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med. 2003;349:2117-27. DOI: 10.1056/NEJMsa035205.

51. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, et al. Hospital volume and surgical mortality in the United States. N Engl J Med. 2002;346:1128-37. DOI: 10.1056/NEJMsa012337.

52. Mamidanna R, Ni Z, Anderson O, Spiegelhalter SD, Bottle A, Aylin P, et al. Surgeon Volume and Cancer Esophagectomy, Gastrectomy, and Pancreatectomy: A

Population-based Study in England. Ann Surg. 2016;263:727-32. DOI: 10.1097/sla.0000000000001490.

53. Finlayson EV, Birkmeyer JD. Effects of hospital volume on life expectancy after selected cancer operations in older adults: a decision analysis. J Am Coll Surg. 2003;196:410-7. DOI: 10.1016/s1072-7515(02)01753-2.

54. Palser TR, Cromwell DA, Hardwick RH, Riley SA, Greenaway K, Allum W, et al. Re-organisation of oesophago-gastric cancer care in England: progress and remaining challenges. BMC Health Serv Res. 2009;9:204. DOI: 10.1186/1472-6963-9-204.

55. Moxey PW, Hofman D, Hinchliffe RJ, Poloniecki J, Loftus IM, Thompson MM, et al. Volume-outcome relationships in lower extremity arterial bypass surgery. Ann Surg. 2012;256:1102-7. DOI: 10.1097/SLA.0b013e31825f01d1.

56. Karthikesalingam A, Hinchliffe RJ, Poloniecki JD, Loftus IM, Thompson MM, Holt PJ. Centralization harnessing volume-outcome relationships in vascular surgery and aortic aneurysm care should not focus solely on threshold operative caseload. Vasc Endovascular Surg. 2010;44:556-9. DOI: 10.1177/1538574410375130.

57. Birkmeyer JD, Sun Y, Goldfaden A, Birkmeyer NJ, Stukel TA. Volume and process of care in high-risk cancer surgery. Cancer. 2006;106:2476-81. DOI: 10.1002/cncr.21888.

58. Sanaiha Y, Khoury H, Kavianpour B, Yazdani S, Gowland L, Iyengar A, et al. Impact of Approach and Hospital Volume on Cardiovascular Complications After Pulmonary Lobectomy. J Surg Res. 2019;235:202-9. DOI: 10.1016/j.jss.2018.09.062.

59. Benlice C, Baca B, Firidin SN, Muti A, Aytac E, Erguner I, et al. Increased Caseload Volume is Associated With Better Oncologic Outcomes After Laparoscopic Resections for Colorectal Cancer. Surg Laparosc Endosc Percutan Tech. 2016;26:49-53. DOI: 10.1097/sle.0000000000000221.

60. Axelrod DA, Guidinger MK, McCullough KP, Leichtman AB, Punch JD, Merion RM. Association of center volume with outcome after liver and kidney transplantation. Am J Transplant. 2004;4:920-7. DOI: 10.1111/j.1600-6143.2004.00462.x.

61. Kapral C, Duller C, Wewalka F, Kerstan E, Vogel W, Schreiber F. Case volume and outcome of endoscopic retrograde cholangiopancreatography: results of a nationwide Austrian benchmarking project. Endoscopy. 2008;40:625-30. DOI: 10.1055/s-2008-1077461.

62. Varadarajulu S, Kilgore ML, Wilcox CM, Eloubeidi MA. Relationship among hospital ERCP volume, length of stay, and technical outcomes. Gastrointest Endosc. 2006;64:338-47. DOI: 10.1016/j.gie.2005.05.016.

63. Wani S, Han S, Simon V, Hall M, Early D, Aagaard E, et al. Setting minimum standards for training in EUS and ERCP: results from a prospective multicenter study evaluating learning curves and competence among advanced endoscopy trainees. Gastrointest Endosc. 2019;89:1160-8.e9. DOI: 10.1016/j.gie.2019.01.030.

64. Testoni PA, Mariani A, Giussani A, Vailati C, Masci E, Macarri G, et al. Risk factors for post-ERCP pancreatitis in high- and low-volume centers and among expert and non-expert operators: a prospective multicenter study. Am J Gastroenterol. 2010;105:1753-61. DOI: 10.1038/ajg.2010.136.

65. Williams EJ, Ogollah R, Thomas P, Logan RF, Martin D, Wilkinson ML, et al. What predicts failed cannulation and therapy at ERCP? Results of a large-scale multicenter analysis. Endoscopy. 2012;44:674-83. DOI: 10.1055/s-0032-1309345.

66. Min JK, Cha JM, Kwak MS, Yoon JY, Jung Y, Shin JE, et al. Quality Indicators and Outcome Measures of Endoscopy in the National Cancer Screening Program. Yonsei Med J. 2019;60:1054-60. DOI: 10.3349/ymj.2019.60.11.1054.

67. Lipman G, Markar S, Gupta A, Haidry RJ, Lovat LB. Learning curves and the influence of procedural volume for the treatment of dysplastic Barrett's. Gastrointest Endosc. 2020. DOI: 10.1016/j.gie.2020.02.041.

68. Sarwar A, Zhou L, Novack V, Tapper EB, Curry M, Malik R, et al. Hospital volume and mortality after transjugular intrahepatic portosystemic shunt creation in the United States. Hepatology. 2018;67:690-9. DOI: 10.1002/hep.29354.

69. Dy SM, Cromwell DM, Thuluvath PJ, Bass EB. Hospital experience and outcomes for esophageal variceal bleeding. Int J Qual Health Care. 2003;15:139-46. DOI: 10.1093/intqhc/mzg016.

70. Myers RP, Papay KD, Shaheen AA, Kaplan GG. Relationship between hospital volume and outcomes of esophageal variceal bleeding in the United States. Clin Gastroenterol Hepatol. 2008;6:789-98. DOI: 10.1016/j.cgh.2008.03.007.

71. Ananthakrishnan AN, McGinley EL, Saeian K. Higher hospital volume predicts endoscopy but not the in-hospital mortality rate in patients with acute variceal hemorrhage. Gastrointest Endosc. 2009;69:221-9. DOI: 10.1016/j.gie.2008.04.065.

72. Moggia E, Koti R, Belgaumkar AP, Fazio F, Pereira SP, Davidson BR, et al. Pharmacological interventions for acute pancreatitis. Cochrane Database Syst Rev. 2017;4:Cd011384. DOI: 10.1002/14651858.CD011384.pub2.

73. Staubli SM, Oertli D, Nebiker CA. Laboratory markers predicting severity of acute pancreatitis. Crit Rev Clin Lab Sci. 2015;52:273-83. DOI: 10.3109/10408363.2015.1051659.

74. Mándi Y, Farkas G, Takács T, Boda K, Lonovics J. Diagnostic relevance of procalcitonin, IL-6, and sICAM-1 in the prediction of infected necrosis in acute pancreatitis. Int J Pancreatol. 2000;28:41-9. DOI: 10.1385/ijgc:28:1:41.

75. Müller CA, Uhl W, Printzen G, Gloor B, Bischofberger H, Tcholakov O, et al. Role of procalcitonin and granulocyte colony stimulating factor in the early prediction of infected necrosis in severe acute pancreatitis. Gut. 2000;46:233-8. DOI: 10.1136/gut.46.2.233.

76. Márta K, Lazarescu AM, Farkas N, Mátrai P, Cazacu I, Ottóffy M, et al. Aging and Comorbidities in Acute Pancreatitis I: A Meta-Analysis and Systematic Review Based on 194,702 Patients. Front Physiol. 2019;10:328. DOI: 10.3389/fphys.2019.00328.

77. Szakács Z, Gede N, Pécsi D, Izbéki F, Papp M, Kovács G, et al. Aging and Comorbidities in Acute Pancreatitis II.: A Cohort-Analysis of 1203 Prospectively Collected Cases. Front Physiol. 2018;9:1776. DOI: 10.3389/fphys.2018.01776.

78. He WH, Zhu Y, Zhu Y, Liu P, Zeng H, Xia L, et al. Comparison of severity and clinical outcomes between hypertriglyceridemic pancreatitis and acute pancreatitis due to other causes. Zhonghua Yi Xue Za Zhi. 2016;96:2569-72. DOI: 10.3760/cma.j.issn.0376-2491.2016.32.011.

79. Pascual I, Sanahuja A, García N, Vázquez P, Moreno O, Tosca J, et al. Association of elevated serum triglyceride levels with a more severe course of acute pancreatitis: Cohort analysis of 1457 patients. Pancreatology. 2019;19:623-9. DOI: 10.1016/j.pan.2019.06.006.

80. Mosztbacher D, Hanák L, Farkas N, Szentesi A, Mikó A, Bajor J, et al. Hypertriglyceridemia-induced acute pancreatitis: A prospective, multicenter, international cohort analysis of 716 acute pancreatitis cases. Pancreatology. 2020;20:608-16. DOI: 10.1016/j.pan.2020.03.018.

81. Samanta J, Dhaka N, Gupta P, Singh AK, Yadav TD, Gupta V, et al. Comparative study of the outcome between alcohol and gallstone pancreatitis in a high-volume tertiary care center. JGH Open. 2019;3:338-43. DOI: 10.1002/jgh3.12169.

82. Uhl W, Isenmann R, Curti G, Vogel R, Beger HG, Büchler MW. Influence of etiology on the course and outcome of acute pancreatitis. Pancreas. 1996;13:335-43. DOI: 10.1097/00006676-199611000-00002.

83. Kotán R, Pósán J, Sápy P, Damjanovich L, Szentkereszty Z. Analysis of clinical course of severe acute biliary and non biliary pancreatitis: a comparative study. Orv Hetil. 2010;151:265-8. DOI: 10.1556/oh.2010.28760.

84. Lankisch PG, Burchard-Reckert S, Petersen M, Lehnick D, Schirren CA, Stöckmann F, et al. Etiology and age have only a limited influence on the course of acute pancreatitis. Pancreas. 1996;13:344-9. DOI: 10.1097/00006676-199611000-00003.

85. Sankaran SJ, Xiao AY, Wu LM, Windsor JA, Forsmark CE, Petrov MS. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. Gastroenterology. 2015;149:1490-500.e1. DOI: 10.1053/j.gastro.2015.07.066.

86. Ahmed Ali U, Issa Y, Hagenaars JC, Bakker OJ, van Goor H, Nieuwenhuijs VB, et al. Risk of Recurrent Pancreatitis and Progression to Chronic Pancreatitis After a First Episode of Acute Pancreatitis. Clin Gastroenterol Hepatol. 2016;14:738-46. DOI: 10.1016/j.cgh.2015.12.040.

87. Smeets X, Knoester I, Grooteman KV, Singh VK, Banks PA, Papachristou GI, et al. The association between obesity and outcomes in acute pancreatitis: an individual patient data meta-analysis. Eur J Gastroenterol Hepatol. 2019;31:316-22. DOI: 10.1097/meg.0000000000001300.

88. Dobszai D, Mátrai P, Gyöngyi Z, Csupor D, Bajor J, Erőss B, et al. Body-mass index correlates with severity and mortality in acute pancreatitis: A meta-analysis. World J Gastroenterol. 2019;25:729-43. DOI: 10.3748/wjg.v25.i6.729.

89. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640-5. DOI: 10.1161/circulationaha.109.192644.

90. Mikolasevic I, Milic S, Orlic L, Poropat G, Jakopcic I, Franjic N, et al. Metabolic syndrome and acute pancreatitis. Eur J Intern Med. 2016;32:79-83. DOI: 10.1016/j.ejim.2016.04.004.

91. Sawalhi S, Al-Maramhy H, Abdelrahman AI, Allah SE, Al-Jubori S. Does the presence of obesity and/or metabolic syndrome affect the course of acute pancreatitis?: A prospective study. Pancreas. 2014;43:565-70. DOI: 10.1097/mpa.0000000000000028.

92. Gódi S, Erőss B, Gyömbér Z, Szentesi A, Farkas N, Párniczky A, et al. Centralized care for acute pancreatitis significantly improves outcomes. J Gastrointestin Liver Dis. 2018;27:151-7. DOI: 10.15403/jgld.2014.1121.272.pan.

93. Párniczky A, Lantos T, Tóth EM, Szakács Z, Gódi S, Hágendorn R, et al. Antibiotic therapy in acute pancreatitis: From global overuse to evidence based recommendations. Pancreatology. 2019;19:488-99. DOI: 10.1016/j.pan.2019.04.003.

94. Szentesi A, Párniczky A, Vincze Á, Bajor J, Gódi S, Sarlós P, et al. Multiple Hits in Acute Pancreatitis: Components of Metabolic Syndrome Synergize Each Other's Deteriorating Effects. Front Physiol. 2019;10:1202. DOI: 10.3389/fphys.2019.01202.

95. Qu R, Ji Y, Ling Y, Ye CY, Yang SM, Liu YY, et al. Procalcitonin is a good tool to guide duration of antibiotic therapy in patients with severe acute pancreatitis. A randomized prospective single-center controlled trial. Saudi Med J. 2012;33:382-7. DOI: not available.

96. Barreda L, Targarona J, Milian W, Portugal J, Sequeiros J, Pando E, et al. Is the prophylactic antibiotic therapy with Imipenem effective for patients with pancreatic necrosis? Acta Gastroenterol Latinoam. 2009;39:24-9. DOI: not available.

97. Bassi C, Falconi M, Talamini G, Uomo G, Papaccio G, Dervenis C, et al. Controlled clinical trial of pefloxacin versus imipenem in severe acute pancreatitis. Gastroenterology. 1998;115:1513-7. DOI: 10.1016/s0016-5085(98)70030-7.

98. Craig RM, Dordal E, Myles L. Letter: The use of ampicillin in acute pancreatitis. Ann Intern Med. 1975;83:831-2. DOI: 10.7326/0003-4819-83-6-831.

99. Delcenserie R, Yzet T, Ducroix JP. Prophylactic antibiotics in treatment of severe acute alcoholic pancreatitis. Pancreas. 1996;13:198-201. DOI: not available.

100. Dellinger EP, Tellado JM, Soto NE, Ashley SW, Barie PS, Dugernier T, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. Ann Surg. 2007;245:674-83. DOI: 10.1097/01.sla.0000250414.09255.84.

101. Finch WT, Sawyers JL, Schenker S. A prospective study to determine the efficacy of antibiotics in acute pancreatitis. Ann Surg. 1976;183:667-71. DOI: 10.1097/00000658-197606000-00008.

102. García-Barrasa A, Borobia FG, Pallares R, Jorba R, Poves I, Busquets J, et al. A double-blind, placebo-controlled trial of ciprofloxacin prophylaxis in patients with acute necrotizing pancreatitis. J Gastrointest Surg. 2009;13:768-74. DOI: 10.1007/s11605-008-0773-7.

103. Howes R, Zuidema GD, Cameron JL. Evaluation of prophylactic antibiotics in acute pancreatitis. J Surg Res. 1975;18:197-200. DOI: 10.1016/0022-4804(75)90016-5.

104. Isenmann R, Rünzi M, Kron M, Kahl S, Kraus D, Jung N, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. Gastroenterology. 2004;126:997-1004. DOI: 10.1053/j.gastro.2003.12.050.

105. Luiten EJ, Hop WC, Lange JF, Bruining HA. Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis. Ann Surg. 1995;222:57-65. DOI: 10.1097/00000658-199507000-00010.

106. Manes G, Rabitti PG, Menchise A, Riccio E, Balzano A, Uomo G. Prophylaxis with meropenem of septic complications in acute pancreatitis: a randomized, controlled trial versus imipenem. Pancreas. 2003;27:e79-83. DOI: 10.1097/00006676-200311000-00018.

107. Manes G, Uomo I, Menchise A, Rabitti PG, Ferrara EC, Uomo G. Timing of antibiotic prophylaxis in acute pancreatitis: a controlled randomized study with meropenem. Am J Gastroenterol. 2006;101:1348-53. DOI: 10.1111/j.1572-0241.2006.00567.x.

108. Maraví-Poma E, Gener J, Alvarez-Lerma F, Olaechea P, Blanco A, Domínguez-Muñoz JE. Early antibiotic treatment (prophylaxis) of septic complications in severe acute necrotizing pancreatitis: a prospective, randomized, multicenter study comparing two regimens with imipenem-cilastatin. Intensive Care Med. 2003;29:1974-80. DOI: 10.1007/s00134-003-1956-z.

109. Nordback I, Sand J, Saaristo R, Paajanen H. Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis--a single-center randomized study. J Gastrointest Surg. 2001;5:113-8; discussion 8-20. DOI: 10.1016/s1091-255x(01)80021-4.

110. Pederzoli P, Bassi C, Vesentini S, Campedelli A. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. Surg Gynecol Obstet. 1993;176:480-3. DOI: not available.

111. Røkke O, Harbitz TB, Liljedal J, Pettersen T, Fetvedt T, Heen L, et al. Early treatment of severe pancreatitis with imipenem: a prospective randomized clinical trial. Scand J Gastroenterol. 2007;42:771-6. DOI: 10.1080/00365520601173855.

112. Sainio V, Kemppainen E, Puolakkainen P, Taavitsainen M, Kivisaari L, Valtonen V, et al. Early antibiotic treatment in acute necrotising pancreatitis. Lancet. 1995;346:663-7. DOI: 10.1016/s0140-6736(95)92280-6.

113. Schwarz M, Isenmann R, Meyer H, Beger HG. Antibiotic use in necrotizing pancreatitis. Results of a controlled study. Dtsch Med Wochenschr. 1997;122:356-61. DOI: 10.1055/s-2008-1047621.

114. Spicak J, Hubaczova M, Antos F, Bartova J, Cech P, Kasalicky M, et al. Antibiotics in the treatment of acute pancreatitis-findings from a randomized multi-centre prospective study. Ceska a Slovenska Gastroenterologie a Hepatologie. 2002;56:183-9.

115. Spicak J, Hejtmankova S, Cech P, Hoskovec D, Kostka R, Leffler J, et al. Antibiotic Prophylaxis in Severe Acute Pancreatitis: Randomized Multicenter Prospective Trial with Meropenem. Ceska a Slovenska Gastroenterologie a Hepatologie. 2003;57. DOI: not available.

116. Xue P, Deng LH, Zhang ZD, Yang XN, Wan MH, Song B, et al. Effect of antibiotic prophylaxis on acute necrotizing pancreatitis: results of a randomized controlled trial. J Gastroenterol Hepatol. 2009;24:736-42. DOI: 10.1111/j.1440-1746.2008.05758.x.

117. Yang XN, Deng LH, Xue P, Zhao L, Jin T, Wan MH, et al. Non-preventive use of antibiotics in patients with severe acute pancreatitis treated with integrated traditional Chinese and Western medicine therapy: a randomized controlled trial. Zhong Xi Yi Jie He Xue Bao. 2009;7:330-3. DOI: 10.3736/jcim20090406.

118. Murata A, Matsuda S, Mayumi T, Yokoe M, Kuwabara K, Ichimiya Y, et al. Effect of hospital volume on clinical outcome in patients with acute pancreatitis, based on a national administrative database. Pancreas. 2011;40:1018-23. DOI: 10.1097/MPA.0b013e31821bd233.

119. Shen HN, Lu CL, Li CY. The effect of hospital volume on patient outcomes in severe acute pancreatitis. BMC Gastroenterol. 2012;12:112. DOI: 10.1186/1471-230x-12-112.

120. Hamada T, Yasunaga H, Nakai Y, Isayama H, Horiguchi H, Fushimi K, et al. Impact of hospital volume on outcomes in acute pancreatitis: a study using a nationwide administrative database. J Gastroenterol. 2014;49:148-55.

121. Kamal A, Sinha A, Hutfless SM, Afghani E, Faghih M, Khashab MA, et al. Hospital admission volume does not impact the in-hospital mortality of acute pancreatitis. 2017;19:21-8.
122. Wu BU. The impact of hospital volume on outcomes in acute pancreatitis: a case for centers of excellence? Gastroenterology. 2009;137:1886-8. DOI: 10.1053/j.gastro.2009.10.016.
123. Halász A, Pécsi D, Farkas N, Izbéki F, Gajdán L, Fejes R, et al. Outcomes and timing of endoscopic retrograde cholangiopancreatography for acute biliary pancreatitis. Dig Liver Dis. 2019;51:1281-6. DOI: 10.1016/j.dld.2019.03.018.
124. da Costa DW, Bouwense SA, Schepers NJ, Besselink MG, van Santvoort HC, van Brunschot S, et al. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. Lancet. 2015;386:1261-8. DOI: 10.1016/s0140-6736(15)00274-3.
125. Nordback I, Pelli H, Lappalainen-Lehto R, Järvinen S, Räty S, Sand J. The recurrence of acute alcohol-associated pancreatitis can be reduced: a randomized controlled trial. Gastroenterology. 2009;136:848-55. DOI: 10.1053/j.gastro.2008.11.044.
126. Rawla P, Sunkara T, Thandra KC, Gaduputi V. Hypertriglyceridemia-induced pancreatitis: updated review of current treatment and preventive strategies. Clin J Gastroenterol. 2018;11:441-8. DOI: 10.1007/s12328-018-0881-1.
127. Petrov MS, Shanbhag S, Chakraborty M, Phillips AR, Windsor JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. Gastroenterology. 2010;139:813-20. DOI: 10.1053/j.gastro.2010.06.010.
128. Nakaharai K, Morita K, Jo T, Matsui H, Fushimi K, Yasunaga H. Early prophylactic antibiotics for severe acute pancreatitis: A population-based cohort study using a nationwide database in Japan. J Infect Chemother. 2018;24:753-8. DOI: 10.1016/j.jiac.2018.05.009.
129. Talukdar R, Ingale P, Choudhury HP, Dhingra R, Shetty S, Joshi H, et al. Antibiotic use in acute pancreatitis: an Indian multicenter observational study. Indian J Gastroenterol. 2014;33:458-65. DOI: 10.1007/s12664-014-0494-7.
130. Baltatzis M, Mason JM, Chandrabalan V, Stathakis P, McIntyre B, Jegatheeswaran S, et al. Antibiotic use in acute pancreatitis: An audit of current practice in a tertiary centre. Pancreatology. 2016;16:946-51. DOI: 10.1016/j.pan.2016.08.012.
131. Koutroumpakis E, Slivka A, Furlan A, Dasyam AK, Dudekula A, Greer JB, et al. Management and outcomes of acute pancreatitis patients over the last decade: A US

tertiary-center experience. Pancreatology. 2017;17:32-40. DOI: 10.1016/j.pan.2016.10.011.

132. Baltatzis M, Jegatheeswaran S, O'Reilly DA, Siriwardena AK. Antibiotic use in acute pancreatitis: Global overview of compliance with international guidelines. Pancreatology. 2016;16:189-93. DOI: 10.1016/j.pan.2015.12.179.

133. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. Lancet Infect Dis. 2013;13:1057-98. DOI: 10.1016/s1473-3099(13)70318-9.

134. Quenot JP, Luyt CE, Roche N, Chalumeau M, Charles PE, Claessens YE, et al. Role of biomarkers in the management of antibiotic therapy: an expert panel review II: clinical use of biomarkers for initiation or discontinuation of antibiotic therapy. Ann Intensive Care. 2013;3:21. DOI: 10.1186/2110-5820-3-21.

135. Mofidi R, Suttie SA, Patil PV, Ogston S, Parks RW. The value of procalcitonin at predicting the severity of acute pancreatitis and development of infected pancreatic necrosis: systematic review. Surgery. 2009;146:72-81. DOI: 10.1016/j.surg.2009.02.013.

136. Siriwardena AK, Jegatheeswaran S, Mason JM, Baltatzis M, Chan A, Sheen AJ, et al. PROCalcitonin-based algorithm for antibiotic use in Acute Pancreatitis (PROCAP): study protocol for a randomised controlled trial. Trials. 2019;20:463. DOI: 10.1186/s13063-019-3549-3.

137. Pang Y, Kartsonaki C, Turnbull I, Guo Y, Yang L, Bian Z, et al. Metabolic and lifestyle risk factors for acute pancreatitis in Chinese adults: A prospective cohort study of 0.5 million people. PLoS Med. 2018;15:e1002618. DOI: 10.1371/journal.pmed.1002618.

138. Yashima Y, Isayama H, Tsujino T, Nagano R, Yamamoto K, Mizuno S, et al. A large volume of visceral adipose tissue leads to severe acute pancreatitis. J Gastroenterol. 2011;46:1213-8. DOI: 10.1007/s00535-011-0430-x.

139. O'Leary DP, O'Neill D, McLaughlin P, O'Neill S, Myers E, Maher MM, et al. Effects of abdominal fat distribution parameters on severity of acute pancreatitis. World J Surg. 2012;36:1679-85. DOI: 10.1007/s00268-011-1414-y.

140. Khatua B, El-Kurdi B, Singh VP. Obesity and pancreatitis. Current opinion in gastroenterology. 2017;33:374-82. DOI: 10.1097/MOG.0000000000000386.

141. Ji T, Li X, Zhang X, Hui L, Shang F, Zhu X, et al. Evaluation of the Severity of Hyperlipidemia Pancreatitis Using CT-measured Visceral Adipose Tissue. J Clin Gastroenterol. 2019;53:e276-e83. DOI: 10.1097/mcg.0000000000001079.

142. Wang SH, Chou YC, Shangkuan WC, Wei KY, Pan YH, Lin HC. Relationship between Plasma Triglyceride Level and Severity of Hypertriglyceridemic Pancreatitis. PLoS One. 2016;11:e0163984. DOI: 10.1371/journal.pone.0163984.

143. Zeng Y, Wang X, Zhang W, Wu K, Ma J. Hypertriglyceridemia aggravates ER stress and pathogenesis of acute pancreatitis. Hepatogastroenterology. 2012;59:2318-26. DOI: 10.5754/hge12042.

144. Huh JH, Jeon H, Park SM, Choi E, Lee GS, Kim JW, et al. Diabetes Mellitus is Associated With Mortality in Acute Pancreatitis. J Clin Gastroenterol. 2018;52:178-83. DOI: 10.1097/mcg.0000000000000783.

145. Szakó L, Mátrai P, Hegyi P, Pécsi D, Gyöngyi Z, Csupor D, et al. Endoscopic and surgical drainage for pancreatic fluid collections are better than percutaneous drainage: Meta-analysis. Pancreatology. 2020;20:132-41. DOI: 10.1016/j.pan.2019.10.006.

11. Scientometrics and list of publications

Source: MTMT2. Date of update: 23th Jun 2020.

Impact factors

1. First author: 2.063
2. Cumulative: 52.075

Citations

1. Independent (from journal articles only): 166
2. Cumulative: 245
3. Hirsh index: 8

Publications directly related to the content of this PhD thesis (n=3, IF: 9.059)

1. **Gódi S**, Erőss B, Gyömbér Z, Szentesi A, Farkas N, Párniczky A, et al. Centralized care for acute pancreatitis significantly improves outcomes. J Gastrointestin Liver Dis. 2018;27:151-7. DOI: 10.15403/jgld.2014.1121.272.pan (**Q2, IF: 2.063**).
2. Párniczky A, Lantos T, Tóth EM, Szakács Z, **Gódi S**, Hágendorn R, et al. Antibiotic therapy in acute pancreatitis: From global overuse to evidence based recommendations. Pancreatology. 2019;19:488-99. DOI: 10.1016/j.pan.2019.04.003 (**Q1, IF: 3.629**).
3. Szentesi A, Párniczky A, Vincze Á, Bajor J, **Gódi S**, Sarlós P, et al. Multiple Hits in Acute Pancreatitis: Components of Metabolic Syndrome Synergize Each Other's Deteriorating Effects. Front Physiol. 2019;10:1202. DOI: 10.3389/fphys.2019.01202 (**Q2, IF: 3.367**).

Other publications (n=17, IF: 43.016)

1. Balázs A, Németh BC, Ördög B, Hegyi E, Hritz I, Czakó L, …**Gódi S**…, et al. A Common CCK-B Receptor Intronic Variant in Pancreatic Adenocarcinoma in a Hungarian Cohort. Pancreas. 2016;45:541-5. DOI: 10.1097/mpa.0000000000000539 (**Q1, IF: 2.967**).
2. Farkas N, Hanák L, Mikó A, Bajor J, Sarlós P, Czimmer J, …**Gódi S**…, et al. A Multicenter, International Cohort Analysis of 1435 Cases to Support Clinical Trial Design in Acute Pancreatitis. Front Physiol. 2019;10:1092. DOI: 10.3389/fphys.2019.01092 (**Q2, IF: 3.367**).

3. Hágendorn R, Vincze Á, Izbéki F, Gajdán L, **Gódi S**, Illés A, et al. Development of disturbance of consciousness is associated with increased severity in acute pancreatitis. Pancreatology. 2020 [Accepted for publication] (**Q1, IF: 3.629**).

4. Halász A, Pécsi D, Farkas N, Izbéki F, Gajdán L, Fejes R, …**Gódi S**…,, et al. Outcomes and timing of endoscopic retrograde cholangiopancreatography for acute biliary pancreatitis. Dig Liver Dis. 2019;51:1281-6. DOI: 10.1016/j.dld.2019.03.018 (**Q2, IF: 3.570**).

5. Kun J, Szitter I, Kemény A, Perkecz A, Kereskai L, Pohóczky K, …**Gódi S**…,, et al. Upregulation of the transient receptor potential ankyrin 1 ion channel in the inflamed human and mouse colon and its protective roles. PLoS One. 2014;9:e108164. DOI: 10.1371/journal.pone.0108164 (**Q1, IF: 3.234**).

6. Lakatos G, Balázs A, Kui B, **Gódi S**, Szücs Á, Szentesi A, et al. Pancreatic Cancer: Multicenter Prospective Data Collection and Analysis by the Hungarian Pancreatic Study Group. J Gastrointestin Liver Dis. 2016;25:219-25. DOI: 10.15403/jgld.2014.1121.252.pcr (**Q2, IF: 1.837**).

7. Madácsy L, Kurucsai G, Joó I, **Gódi S**, Fejes R, Székely A. Rescue ERCP and insertion of a small-caliber pancreatic stent to prevent the evolution of severe post-ERCP pancreatitis: a case-controlled series. Surg Endosc. 2009;23:1887-93. DOI: 10.1007/s00464-008-0199-z (**Q1, IF: 3.307**).

8. Márta K, Szabó AN, Pécsi D, Varjú P, Bajor J, **Gódi S**, et al. High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): protocol of a multicentre randomised double-blind clinical trial. BMJ Open. 2017;7:e015874. DOI: 10.1136/bmjopen-2017-015874 (**Q1, IF: 2.413**).

9. Meczker Á, Mikó A, Gede N, Szentesi A, Párniczky A, **Gódi S**, et al. Retrospective Matched-Cohort Analysis of Acute Pancreatitis Induced by 5-Aminosalicylic Acid-Derived Drugs. Pancreas. 2019;48:488-95. DOI: 10.1097/mpa.0000000000001297 (**Q1, IF: 2.920**).

10. Mosztbacher D, Hanák L, Farkas N, Szentesi A, Mikó A, Bajor J, …**Gódi S**…, et al. Hypertriglyceridemia-induced acute pancreatitis: A prospective, multicenter, international cohort analysis of 716 acute pancreatitis cases. Pancreatology. 2020;20:608-16. DOI: 10.1016/j.pan.2020.03.018 (**Q1, IF: 3.629**).

11. Pár G, Trosits A, Pakodi F, Szabó I, Czimmer J, Illés A, …**Gódi S**…, et al. Transient Elastography as a Predictor of Oesophageal Varices in Patients With Liver Cirrhosis. Orv Hetil. 2014;155:270-6. DOI: 10.1556/OH.2014.29824 (**Q3, IF: -**).

12. Párniczky A, Kui B, Szentesi A, Balázs A, Szűcs Á, Mosztbacher D, …**Gódi S**…, et al. Prospective, Multicentre, Nationwide Clinical Data from 600 Cases of Acute Pancreatitis. PLoS One. 2016;11:e0165309. DOI: 10.1371/journal.pone.0165309 (**Q1, IF: 2.806**).

13. Pécsi D, Hegyi P, Szentesi A, **Gódi S**, Pakodi F, Vincze Á. The Role of Endoscopy Registries in Quality Health Care. The First Data From the Hungarian Endoscopic Retrograde Cholangiopancreatography (ERCP) Registry. Orv Hetil. 2018;159:1506-15. DOI: 10.1556/650.2018.31145. DOI: not available (**Q3, IF: 0.564**).

14. Pécsi D, Paulovicsné KM, Czimmer J, **Gódi S**, Hunyady B, Illés A, et al. Livopan szedációval szerzett tapasztalataink kolonoszkópia során. Centr Eur J Gastroenterol Hepat. 2018;4:220-3 (**Q: -, IF: -**).

15. Szakács Z, Gede N, Pécsi D, Izbéki F, Papp M, Kovács G, …**Gódi S**…, et al. Aging and Comorbidities in Acute Pancreatitis II.: A Cohort-Analysis of 1203 Prospectively Collected Cases. Front Physiol. 2018;9:1776. DOI: 10.3389/fphys.2018.01776 (**Q2, IF: 3.201**).

16. Szentesi A, Tóth E, Bálint E, Fanczal J, Madácsy T, Laczkó D, …**Gódi S**…, et al. Analysis of Research Activity in Gastroenterology: Pancreatitis Is in Real Danger. PLoS One. 2016;11:e0165244. DOI: 10.1371/journal.pone.0165244 (**Q1, IF: 2.806**).

17. Szücs Á, Marjai T, Szentesi A, Farkas N, Párniczky A, Nagy G, …**Gódi S**…, et al. Chronic pancreatitis: Multicentre prospective data collection and analysis by the Hungarian Pancreatic Study Group. PLoS One. 2017;12:e0171420. DOI: 10.1371/journal.pone.0171420 (**Q1, IF: 2.766**).

12. Appendix

Supplementary Table 1. Characteristics of studies reporting on the guidance and initiation of antibiotic therapy in acute pancreatitis.

Studies reporting on the guidance of AB therapy					
Study	**Country (recruitment period)**	**Population**	**N^0 of pts.**	**Interventions**	**Definition for suspected infection => intervention**
Qu et al. 2012 (95)	China (2009-2011)	SAP (by Atlanta 1992)	71	PCT-guided (cut-off: 0.5 mg/ml) vs prophylactic ABs	clinical signs and symptoms
Studies testing the efficacy of ABs					
Barreda et al. 2009 (article in Spanish) (96)	Peru (2005-2007)	ANP (FNA confirmed)	58	imipenem vs no ABs	two or more criteria of sepsis after the second week of onset => FNA => surgery (culturing)
Bassi et al. 1998 (97)	Italy and Greek (1991-1997)	ANP: CECT-confirmed necrosis (at least 50%) and CRP>100 mg/l	60	imipenem vs pefloxacin	routine laboratory tests and markers by Bassi 1994 => FNA => surgery
Craig et al. 1975 (98)	The US	upper abdominal pain for at least 24 h + elevated serum amylase (>160 U/dl) or elevated urinary amylase	46	ampicillin vs no ABs	fever >38.3°C => blood culture
Delcenserie et al. 1996 (99)	France (1988-1993)	SAP: Alcoholic aetiology, CT-confirmed fluid collections	23	ceftazidime, amikacin, metronidazole vs no ABs	not stated => FNA
Dellinger et al. 2007 (100)	Multicenter (Europe and North America) (2003-2004)	ANP: 1, CECT-confirmed necrosis (at least 30%) 2, CT-confirmed fluid collections plus pancreatic edema (Balthazar E) and	100	meropenem vs no ABs	clinical deterioration, routine haematology and biochemistry => FNA or surgical samples

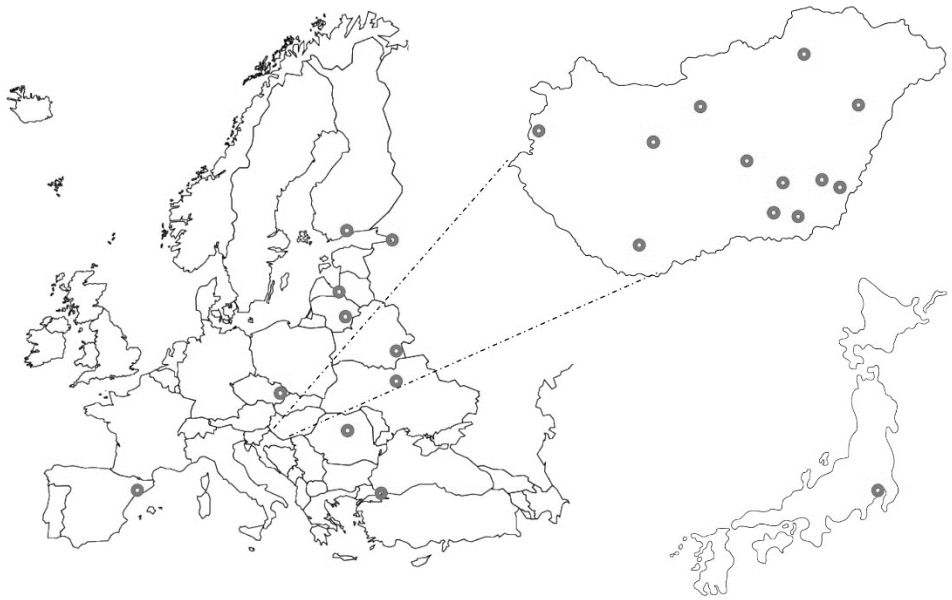
		(MOD score ≥2 and CRP>120 mg/l)			
Finch et al. 1976 (101)	The US (1971-1973)	alcoholic OR idiopathic AP confirmed by symptoms + amylase greater than 160 Somogyi U/100 ml	58	ampicillin or cefalotin vs no ABs	not stated => surgery
Garcia-Barassa et al. 2009 (102)	Spain (1999-2003)	AP: by Atlanta class ANP: CT-confirmed necrosis	41	ciprofloxacin vs no ABs	clinical deterioration, strong clinical suspicion => FNA
Howes et al. 1975 (103)	The US (1972-1974)	AP: symptoms + amylase	95	ampicillin or lincomycin vs no ABs	clinical or bacteriological evidence => AB
Isenmann et al. 2004 (104)	Germany (1999-2002)	AP: symptoms + (3x amylase OR 3x lipase) SAP: AP + (CRP>150 mg/l OR CECT-confirmed necrosis)	114	ciprofloxacin + metronidazole vs no ABs	SIRS OR MOF OR increase of CRP and clinically suspected infection (OR expancreatic inf.) => FNA or surgical sampling AND open-labelled AB treatment
Luiten et al. 1995 (105)	The Netherlands (1990-1993)	AP: symptoms + amylase > 1000 IU/l or laparotomy SAP: Imrie score ≥3 + CECT (Balthazar grades D-E)	102	cefotaxime + selective decontamination (colistin + amphotericin + norfloxacin) vs no ABs	clinical suspicion (not detailed), fever ≥ 39°C for blood culturing => FNA
Manes et al. 2003 (106)	Italy (1996-2001)	ANP: necrosis confirmed by CECT or by surgery + CRP >120 mg/l	176	meropenem vs imipenem	not stated (fever >38°C?) => FNA => surgery
Manes et al. 2006 (107)	Italy (2002-2005)	AP (no definition)	59	early vs late treatment	persistent fever (>38°C), increased CRP, leukocytosis, and lack of improvement under appropriate therapy, or

					air bubbles in the necrosis (CECT) => FNA => surgery
Maravi-Poma et al. 2003 (108)	Spain (not stated)	AP: abdominal pain + 3x amylase/3x lipase ICU + severe ANP: CTSI>4	92	long vs short treatment	signs of sepsis or organ failure for at least 3 days => FNA
Nordback et al. 2001 (109)	Finland (1995-1999)	AP: symptoms + 3x amylase + CT ANP: CRP > 150 mg/l within 48 h, CT-confirmed necrosis	58	imipenem vs no ABs	following an initial decrease, a recurrent parallel increases in inflammation variables (temperature, white blood cell count (+30%), CRP level (+30%)) => surgery recurrent non-parallel increases => FNA => surgery
Pederzoli et al. 1993 (110)	Italy (1989-1991)	ANP: CECT-confirmed necrosis	74	imipenem vs no ABs	suspected infected necrosis, infected pseudocyst, abscess => FNA => surgery
Rokke et al. 2007 (111)	Norway (1997-2002)	SAP: symptoms + 3x amylase + CT; CRP>120 mg/l within 24 h or >200 mg/l within 48 h or CT-confirmed necrosis	73	imipenem vs no ABs	clinical, radiological or laboratory signs of infection => AB => surgery (if indicated by the attending doctor)
Sainio et al. 1995 (112)	Finland (1989-1993)	SAP: CRP>120 mg/l within 48 h, low pancreatic contrast-enhancement on CECT, alcoholic aetiology	60	cefuroxime vs no ABs	persistent fever, rise in CRP, or fluid collections detected by CT => FNA
Schwarz et al. 1997 (article in German) (113)	Germany (1991-1994)	ANP	26	ofloxacin + metronidazole vs no ABs	FNA for all participants regularly in control group

Spicak et al. 2002 (article in Czech) (114)	Czech Republic (1999-2001)	SAP: symptoms + 3x amylase + CT (Atlanta (local compl.!) or CRP>150 mg/l	63	ciprofloxacin + metronidazole vs no ABs	control group: temperature 38°C for at least 24 h or infection => AB empirically, later culturing
Spicak et al. 2003 (article in Czech) (115)	Czech Republic (2001-2002)	SAP: symptoms + 3x amylase + CT (Atlanta: CRP>190 mg/l AND peripancreatic fluid)	41	meropenem vs no ABs	control group: temperature 38.5°C for at least 24 h or infection=> AB empirically suspicion => FNA
Xue et al. 2009 (116)	China (2007)	SAP (by Bangkok World Congress of Gastroenterology in Thailand 2002): CECT-confirmed necrosis > 30%	56	imipenem vs no ABs	a second continuous increase in temperature ≥38.5°C or white blood cell count ≥20x10^9/L or CRP≥30% or clinical deterioration => culture from the suspected organ + CECT => air bubbles in necrosis => FNA
Yang et al. 2009 (article in Chinese) (117)	China	SAP: organ failure OR Ranson > 3, APACHE II > 8, Balthazar CT grade II or above	54	imipenem vs no ABs	suspected pancreatic infection => AB change by resistance and surgery

APACHE II: acute physiology and chronic health evaluation, AB: antibiotic, ANP: acute necrotizing pancreatitis, AP: acute pancreatitis, CRP: C-reactive protein, ICU: intensive care unit, CT: computed tomography, CECT: contrast-enhanced computed tomography, FNA: fine-needle aspiration, MOD: multiple organ dysfunction, MOF: multi-organ failure, PCT: procalcitonin SAP: severe acute pancreatitis, SIRS: systemic inflammatory response syndrome.

Supplementary Figure 1. Sites of recruitment of the study population of the AP Registry



Country	City	Institute	No. of patients
Hungary	Pécs	First Department of Medicine, Medical School, University of Pécs	351
	Székesfehérvár	Szent György Teaching Hospital of County Fejér	181
	Szeged	First Department of Medicine, University of Szeged	149
		Second Department of Medicine, University of Szeged	25
		Department of Surgery, University of Szeged	4
	Budapest	Bajcsy-Zsilinszky Hospital	123
		Polyclinic of Hospitaller Brothers of Saint John of God	2
		Heim Pál National Institute of Pediatrics	1
	Debrecen	Department of Internal Medicine, University of Debrecen	75
		Institute of Surgery, University of Debrecen	5
	Békéscsaba	Dr. Réthy Pál Hospital, Gastroenterology Department	53
	Gyula	Békés County Central Hospital-Pandy Kálmán Hospital, Dept. of Internal Med. and Gastroent.	27
	Szentes	Dr. Bugyi István Hospital	16
	Miskolc	Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital	14
	Kecskemét	Bács-Kiskun County Hospital	11
	Makó	Healthcare Center of County Csongrád	9
	Szombathely	Markusovszky University Teaching Hospital	8
Romania	Targu Mures	Mures County Emergency Hospital	40
Lithuania	Vilnius	Vilnius University Hospital Santariskiu Klinikos	31
Spain	Barcelona	Consorci Sanitari del Garraf, sant Pere de Ribes	30
Finland	Helsinki	Department of Transplantation and Liver Surgery, Helsinki University Hospital and University of Helsinki	27
Turkey	Istanbul	Hospital of Bezmialem Vakif University, School of Medicine	20
Russia	St. Petersburg	Saint Luke Clinical Hospital	18
Czech Republic	Ostrava	Centrum péče o zažívací trakt, Vítkovická nemocnice a.s.	11
Belarus	Gomel	Gomel Regional Clinical Hospital	8
Latvia	Riga	Pauls Stradins Clinical University Hospital, Gastroent., Hep. and Nutr. Centre	8
Ukraine	Kiev	Bogomolets National Medical University	8
Japan	Tokyo	Keio University	2
		Total number of patients	**1257**

Grey circles on the map represent the sites of recruitment.

ORIGINAL PAPER

Available from: http://www.jgld.ro/wp/archive/y2018/n2/a7
DOI: http://dx.doi.org/10.15403/jgld.2014.1121.272.pan

Centralized Care For Acute Pancreatitis Significantly Improves Outcomes

Szilárd Gódi[1], Bálint Erőss[1,2], Zsuzsanna Gyömbér[3], Andrea Szentesi[2,3], Nelli Farkas[2,4], Andrea Párniczky[2,5], Patrícia Sarlós[1,2], Judit Bajor[1], József Czimmer[1,2], Alexandra Mikó[2], Katalin Márta[2], Roland Hágendorn[1], Zsolt Márton[1], Zsófia Verzár[6], László Czakó[3], Zoltán Szepes[3], Áron Vincze[1,2*], Péter Hegyi[1,2,3,7*] on behalf of the Hungarian Pancreatic Study Group

1) 1st Department of Medicine, University of Pécs Medical School, 7624 Pécs,
2) Institute for Translational Medicine, University of Pécs Medical School, 7624 Pécs,
3) 1st Department of Medicine, University of Szeged, 6720 Szeged,
4) Institute of Bioanalysis, University of Pécs Medical School, 7624 Pécs, Hungary
5) Department of Gastroenterology, Heim Pál Children's Hospital, 1098 Budapest,
6) Department of Emergency Medicine, University of Pécs School of Medicine, 7624 Pécs,
7) MTA-SZTE Momentum Gastroenterology Multidisciplinary Research Group, Hungary

Address for correspondence:
Péter Hegyi
Institute for Translational Medicine, University of Pécs
Szigeti út 12., II. em., H-7624 Pécs, Hungary
hegyi2009@gmail.com

Received: 15.02.2018
Accepted: 30.04.2018

*equally contributed. List of clinical collaborators contributors on page 156.

ABSTRACT

Aims: In this observational study, we investigated whether specialized care improves outcomes for acute pancreatitis (AP).

Methods: Consecutive patients admitted to two university hospitals with AP were enrolled in this study between 1 January 2016 and 31 December 2016 (Center A: specialized center; Center B: general hospital). Data on demographic characteristics and AP etiology, severity, mortality and quality of care (enteral nutrition and antibiotic use) were extracted from the Hungarian Acute Pancreatitis Registry. An independent sample *t*-test, Mann–Whitney test, chi-squared test or Fisher's test were used for statistical analyses. Costs of care were calculated and compared in the two models of care.

Results: There were 355 patients enrolled, 195 patients in the specialized center (Center A) and 160 patients in the general hospital (Center B). There was no difference in mean age (57.02 ±17.16 vs. 57.31 ±16.50 P=0.872) and sex ratio (56% males vs. 57% males, P=0.837) between centres, allowing a comparison without selection bias. Center A had lower mortality (n=2, 1.03% vs. n=16, 6.25%, p=0.007), more patients received enteral feeding (n=179, 91.8%, vs. n=36, 22.5%, p<0.001) and fewer patients were treated with antibiotics (n=85, 43.6% vs. n=123, 76.9%, p=0.001). In Center A the median length of hospitalization was shorter (Me 6, IQR 5–9 vs. Me 8, IQR 6–11, p=0.02) and the costs of care were by 25% lower.

Conclusion: Our data suggests that treatment of AP in specialized centers reduces mortality, length of hospitalization and thus might reduce the costs.

Key words: acute pancreatitis – costs – specialized center – outcome – mortality.

Abbreviations: ACG: American College of Gastroenterology; AP: Acute pancreatitis; ER: Emergency Unit; IAP/APA: International Association of Pancreatology and the American Pancreatic Association; ICU: Intensive Care Unit; LOH: Length of hospitalization; SD: Surgical Department; TIMD: Territorial Internal Medical Departments; TPC: Tertiary Pancreas Center.

INTRODUCTION

Medical care for acute diseases requiring hospitalization varies between countries and often within the same country. The same acute diseases are treated in hospitals with different profiles of expertise, different bed bases for specialties and different guidelines. There are two major pathways for admission with acute diseases.

One of the pathways is organized care in high-volume specialized centers for specific todiseases, where patients are directly admitted to a highly specialized ward, with a multidisciplinary team, strict adherence to guidelines and easy access to special procedures (Fig. 1A). There are examples of established specialized care models for the treatment of stroke and acute coronary syndrome [1, 2].

On the other pathway, patients are referred to general medical wards (internal medicine or surgery), and, depending on the progression of the disease, some patients are transferred to specialized wards. If there is further deterioration, transfer to an intensive care unit may be necessary. We define this as the general medical care model.

Outcomes for acute diseases can be significantly different depending on care, and there are examples of significantly improved outcomes for acute diseases treated in specialized centers. There is ample evidence that organized care for

stroke [1] and acute myocardial infarction with ST elevation in specialized centers have saved lives and reduced the burden of these diseases [2]. Based on this evidence, national and international stroke [3] and cardiology [4] associations organized care in specialized centers, with specific recommendations in their guidelines.

Acute pancreatitis (AP) is the most common acute presentation in gastroenterology requiring hospital admission in the USA [5]. According to data obtained from the Hungarian National Health Insurance Fund, there is an estimated 5500 AP hospital admissions/year for Hungary's population of 10 million. There have been significant efforts to improve outcomes and to reduce the disease burden in AP as suboptimal care can result in progression to severe forms of the disease, higher morbidity and mortality. The Working Group of the International Association of Pancreatology and the American Pancreatic Association (IAP/APA) updated and published evidence-based guidelines for the treatment of AP [6] most recently in 2013, and the American College of Gastroenterology (ACG) also published their guidelines [7] the same year. The Hungarian Pancreatic Study Group translated both and synthesized them in the Hungarian guidelines [8] in 2015.

The IAP/APA guidelines suggest intensive care for patients with severe AP and referral to a specialized center [6]. In defining a center specialized for AP, the guidelines specify the need for intensive care facilities for organ replacement therapy, continuous access to interventional radiology, endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasonography and surgical expertise in the treatment of necrotizing AP [6].

The ACG guidelines recommend risk stratification to identify patients who will need early transfer to an intensive care unit [7]. Referral to a specialized center in the case of severe AP is also recommended in the Hungarian guidelines [8]. However, there is no recommendation in these guidelines regarding whether all AP (mild and moderate) should be referred to centers with specialized care after diagnosis at the emergency unit. There is convincing evidence on improved outcomes for AP in high-volume centers (more than 118 admissions/year for AP), according to Singla et al. [9].

It is difficult to predict the severity of AP at the time of admission, and patients presenting with mild forms can develop fulminant AP within a few days. Current stratification systems for AP are unable to predict the course of the disease at the early stage unless the disease is severe at the time of admission. The revised Atlanta classification of AP severity is determined by clinical parameters recorded throughout the disease and provides disease severity in retrospect [10]. Therefore, it is not suitable for predicting the outcome.

The guidelines for the treatment of AP [7-9] recommend that the risk factors, the clinical prognostic factors and the response to the treatment should be monitored to predict the outcome. However, a reliable prediction system based on admission parameters is yet to be developed for the accurate prediction of the clinical course of and outcome for AP. Until now, no evidence has been published for or against the treatment of AP of all severities in specialized pancreatic centers.

Our aim was to investigate whether specialized care improves the outcomes for AP.

METHODS

The Hungarian Pancreatic Study Group was established in 2011 to improve care for pancreatic diseases. To date, the Hungarian Pancreatic Study Group has built up an international prospective registry for AP and organized five registered clinical trials to investigate AP under the acronyms PREPAST [11], APPLE [12], PINEAPPLE [13], GOULASH [14] and EASY [15].

Study design

In this observational cohort study, we analyzed and compared data from the prospectively collected AP Registry, specifically, outcomes, quality of care and costs for AP in two university hospitals with two different models for the management of AP.

Treatment Center A fulfilled the criteria for a specialized center for AP. Patients were admitted directly to the specialized ward from regional emergency departments. Center A admits patients from nine high-volume emergency units in the region. The specialized center has an integrated care pathway for patients requiring care in the high dependency unit or intensive care unit (Fig. 1A).

Treatment Center B admits patients with AP to general internal medicine wards from the emergency department, and patients are transferred to the specialized pancreatic ward, if there is deterioration. Treatment Center B transfers patients from the emergency department to one of the five general internal medicine wards or to a surgical ward, or if indicated by the patient's status, either to the tertiary pancreatic center or to the intensive care unit (Fig. 1B).

Both treatment centers (A and B) deal with high volumes, but their models of care for AP are different. Both institutions care for populations with nearly identical demographics.

Limitation

The study design and the differences between the two cohorts are potential sources of bias and limitation; therefore, both cohorts were carefully scrutinised through statistical analysis before comparing outcomes to ensure that they were comparable.

Ethical approval

The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council (22254-1/2012/EKU) on 15 August 2012 and conforms to the 1975 Declaration of Helsinki ethical guidelines as reflected in *a priori* approval by the institution's human research committee. The patients signed the relevant consent forms.

Statistical analyses

The demographics and the etiology in both samples were compared. To analyze the differences in the distribution of severity, complications (local and systemic), mortality and management (enteral feeding and antibiotic use) between the centers, we used Pearson's chi-squared test or Fisher's exact

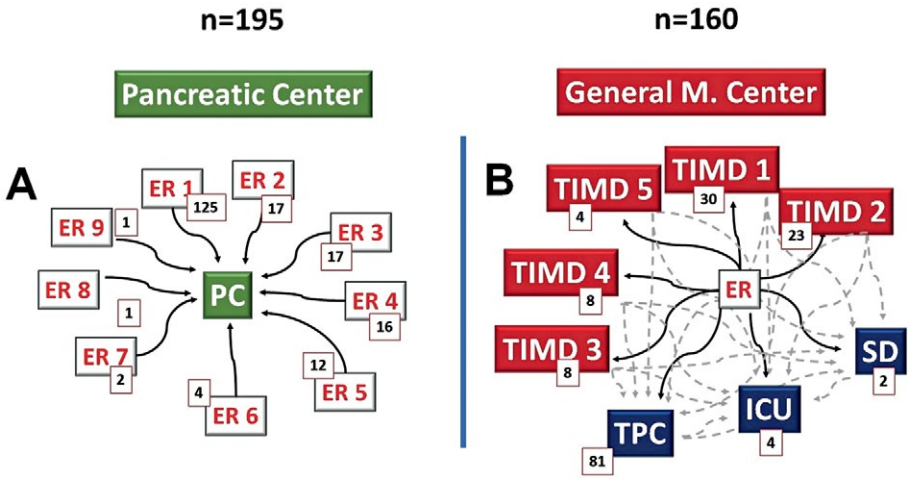


Fig. 1. A: Patient pathways in the specialized high-volume center from different Emergency Units (ER); B: Patient pathways in the step-up care pathway institution from Territorial Internal Medical Departments (TIMD), Intensive Care Units (ICU), the Tertiary Pancreas Center (TPC) and the Surgical Department (SD), number of cases (n).

test. We used the independent samples Student's *t*-test for age and the Mann–Whitney U test for comparison of hospital stay. P values under 0.05 were considered statistically significant. Where the p value was less than 0.1 but higher than 0.05, we only regarded the result as a tendency. All statistical analyses were performed by IBM SPSS Statistics v 24.0 (IBM, New York, NY, USA).

RESULTS

The best evidence in comparative medicine is always provided by the results from randomized clinical trials, as they ensure that there is no selection bias between cases and controls. However, in this observational trial, it was impossible to perform randomization, since there was only one model of care for AP in the two centers. In addition, these large centers are far away from each other; therefore, transfer of patients after randomization would not have been possible. Finally, and most importantly, randomization would have been unethical.

The two university centers are located in the same region of Europe with an ethnically homogeneous population, and 98% of the patients approached gave their consent at both centers.

Demographic characteristics

Treatment Center A with specialized care for AP admitted 195 patients, while treatment Center B treated 160 patients with AP in 2016 (Fig. 1A, B). A demographic analysis of the two cohorts showed no significant difference. Mean age was 57.02 (±17.16) in Center A and 57.31 (±16.50) in Center B (p=0.872). The proportion of males was 56% in Center A and 57% in Center B (p=0.837). Age did not differ significantly in males or females between the two cohorts (male mean age in center A: 54.16 ±16.96; in Center B: 57.03±16.01, p=0.221; female mean age in Center A: 60.71 ±16.80; in Center B: 57.68 ±17.26, p=0.276).

Although it was not intentional, the cohorts were matched for age and sex (Fig. 2 A, B).

The etiology of AP was similar in both cohorts. The major causes were biliary stones, alcohol, and idiopathic

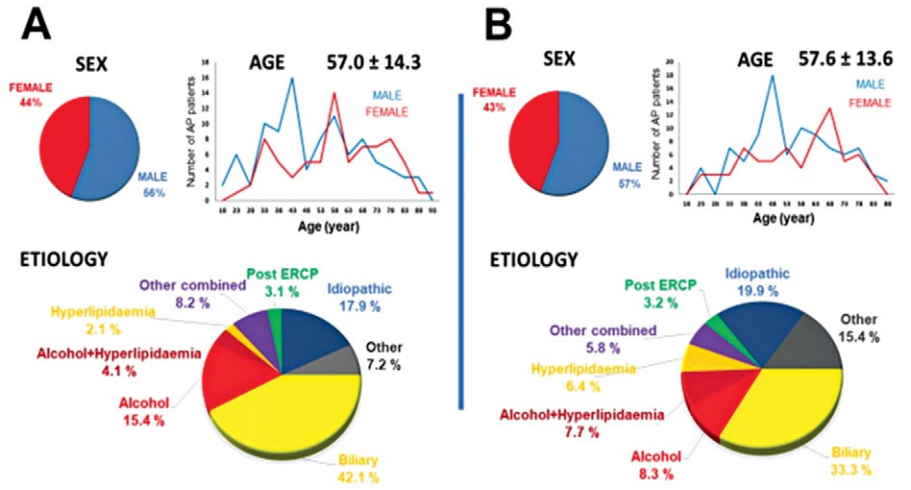


Fig. 2. A: The demographic characteristics and etiological factors of acute pancreatitis in the specialized high-volume center; B: The demographic characteristics and etiological factors of acute pancreatitis in the step-up care pathway institution.

and hyperlipidemia, accounting for the vast majority in both centers (Fig. 2).

This similarity, along with the matched age and sex ratio, allowed us to compare the outcomes for AP in both cohorts and reduced the selection bias of this observational cohort study.

Severity and mortality of AP

The distribution of the worst severity of AP was different in Centers A and B (Fig. 3 A, B). Center B had 67% more severe AP (n=19, 11.9%) than Center A (n=14, 7.1%); however, this was not statistically different (p=0.310), likely due to the small sample sizes, 14 patients in Center A and 19 in Center B.

The mortality of all AP in Center B was six times higher (n=16, 6.25%) than in Center A (n=2, 1.03%), and this difference proved to be statistically significant, p=0.007. Severe AP showed a threefold increase of mortality in Center B (n=8, 47.37% vs. n=2, 14.29%, p=0.067). There were no deaths from mild AP in either cohort.

The average hospital stay was significantly shorter in Center A (Me: 6 (IQR: 5–9) days vs. Me: 8 (IQR: 6–11) days, p=0.02) (Fig. 3 A, B). The subgroup analysis found shorter means of hospital stay for all grades of severity; however, it was only significant in mild AP, suggesting that mild cases of AP were discharged sooner from Center A.

Complications of AP

Our analysis found no differences between the local and systemic complications of AP between Centers A and B (n=43, 23.1% vs. n=35, 21.8%, p=0.872, and n=21, 10.5% vs. n=27, 16.9%, p=0.177, respectively). The detailed results are shown in Fig. 3C.

Interventions and therapy

There were no differences between Center A and B in the number of ERCP (n=85, 43.59% vs. n=59, 36.88%, p=0.143), necrosectomy (n=1, 0.5% vs. n=2, 1.25%, p=0.793) and radiological or endoscopic ultrasound-guided drainage procedures (n=8, 4.1% vs. n=2, 1.2%, p=0.118).

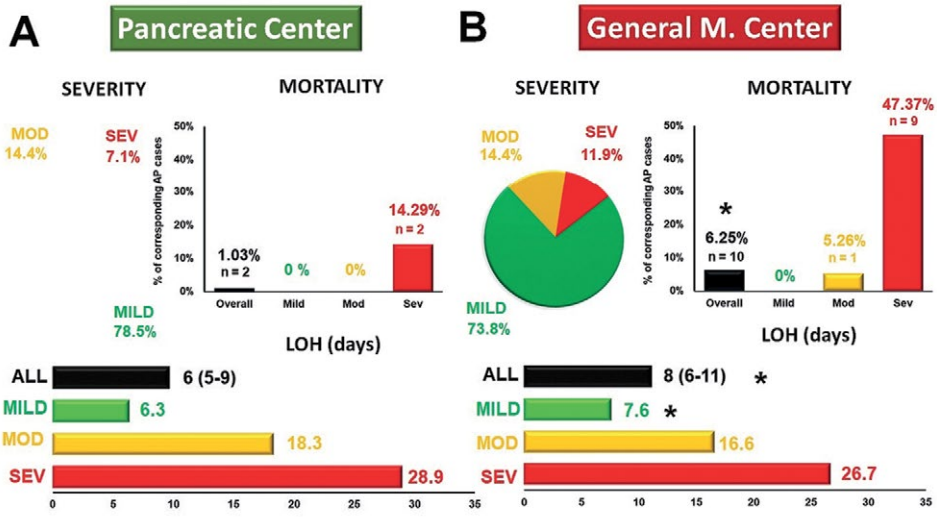
We found no differences in the number of ERCPs for biliary pancreatitis, n=69, 83% ERCPs in n=83 patients in Center A and n=45, 84.9% ERCPs in n=53 patients in Center B (p=0.817). The ERCPs in AP with biliary etiology were performed in n=60 mild, n=4 moderate, and n=5 severe AP cases in Center A and n=40, n=4 and n=1 in Center B. None of these were significantly different.

Quality of care and management

We investigated whether management of patients and adherence to the guidelines differed in the two centers. The best and most reliable management markers which we could identify were enteral feeding and the use of antibiotics (Fig. 4 A, B).

More patients had enteral feeding in Center A than in Center B (n=179, 91.8% vs. n=36, 22.5%, p<0.001) (Fig. 4 A,B).

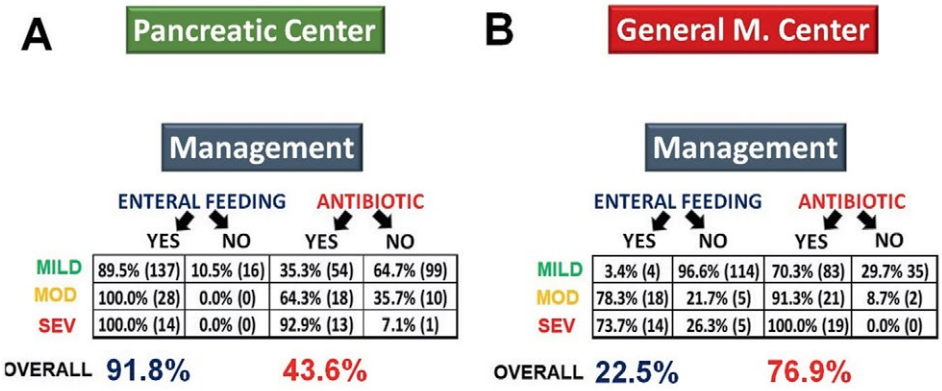
The use of antibiotics also differed; significantly fewer patients were treated with antibiotics in Center A in contrast to Center B (n=85, 43.6% vs. n=123, 76.9%, p<0.001) (Fig. 4 A, B). A detailed analysis of antibiotic use demonstrated a



C

		CENTER A-Pancreatic center		CENTER B-General M. Center		*P* value
COMPLICATION	no	150	76.8%	118	73.8%	0.337
	local	43	22.1%	35	21.8%	0.872
	systemic	21	10.5%	27	16.9%	0.177

Fig. 3. A: The distribution of disease severity, mortality and length of hospitalization (LOH) in the specialized high-volume center; B: The distribution of disease severity, mortality and length of hospitalization (LOH) in the step-up care pathway institution; C: Complications in the two centers. *significant difference; severe (SEV); moderate (MOD); number of cases (n).



C

		CENTER A-Pancreatic center		CENTER B-General M. Center		*P* value
AB THERAPY	total number	85	43.6%	123	76.9%	<0.05*
	mild	54	63.5%	83	67.5%	<0.05*
	moderate	18	21.2%	21	17.1%	0.0236*
	severe	13	15.3%	19	15.4%	0.4242

Fig. 4. A: Managing acute pancreatitis (with antibiotics and enteral nutrition) in the specialized high-volume center; B: Managing acute pancreatitis (with antibiotics and enteral nutrition) in the step-up care pathway institution; C: Antibiotic use in the two centers for different severities of acute pancreatitis. Severe (SEV); moderate (MOD).

significant difference between the two centers with regard to mild and moderate AP (n=54, 63.5%, vs. n=83, 67.5%, p<0.05 and n=18, 21.2%, vs. n=21, 17.1%, p=0.024). There was no difference in antibiotic use between the two centers with regard to severe AP (n=13, 15.3%, vs. n=19, 15.4%, p=0.424). Results are shown on Fig. 4C.

Economic implications

To understand the economic implications of the two different models of AP treatment, the average cost of management for 10 patients was calculated in both groups. The calculated average costs are based on the costs of medication, disposables, procedures and investigations. However, our calculation was limited by costs that could not be estimated, such as the costs of staff and hospital stay (Fig. 5).

The average daily costs in both centers in subgroups of mild, moderate and severe AP are indicated with or without antibiotic treatment. Based on this estimate, the cost of treatment for AP is 25% lower in the specialized care model than in the general medical model.

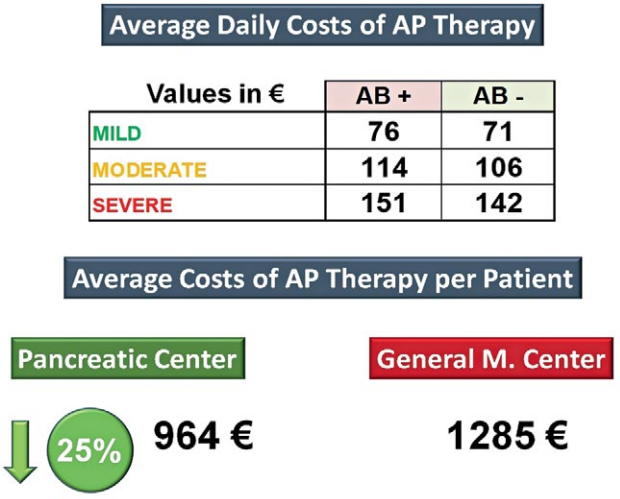


Fig. 5. A: Costs of managing acute pancreatitis (AP) in the specialized, high-volume center; B: Costs of managing acute pancreatitis (AP) in the general medical center. This estimate does not include the costs of staff and hospital bed.

DISCUSSION

We hypothesized that specialized care for AP in high-volume centers is beneficial and measurable in both outcomes and costs. We analyzed comparable cohorts in both centers, without significant differences in their demographics. Both centers are tertiary referral institutions and university hospitals with the same level of medical expertise and skills. Funding for health care services in both centers is identical. The only significant difference in terms of AP is their model of management of AP.

We believe that these prospectively collected data from the two cohorts are nearly as comparable as data from two branches of a randomized controlled trial, and we note that the latter would have been impossible and unethical to organize.

There are multiple reasons we were able to show significantly improved outcomes, management and hospital stay in the specialized center.

In our analysis, we found that lower mortality and shorter hospital stay were associated with significant differences in the practices between the two centers. The specialized center with better outcomes used significantly more often enteral feeding and fewer antibiotics. However, there was no difference in the number of endoscopic or radiological procedures.

Center B followed the guidelines of enteral tube feeding more rigorously than Center A and limited the use of enteral tube feeding to manage patients with severe pancreatitis and predicted severe AP. We acknowledge that Center A used more enteral feeding to treat AP than strict adherence to the guidelines [8] would have suggested. There are many studies with evidence for early feeding in AP, but they compared enteral nutrition or enteral tube feeding vs. nil per os management. We note that there is a lack of clinical trials providing evidence and information on early oral vs. enteral tube feeding.

Petrov et al. [16] reported the benefits of enteral tube feeding in a randomized control trial compared to the nil per os approach and concluded that it leads to less oral food intolerance. Furthermore, our recent meta-analysis by Marta et al. [17] confirmed this. In addition, as a leading pancreatic clinical research unit, Center A is conducting a long-term randomized clinical trial investigating the benefits of early high-energy enteral tube nutrition in AP [14]. Prediction of severe AP is difficult in the early phase of the disease (24–48 hours). Enteral tube feeding may have the potential to prevent severe AP, and this is one of the foci of our research. Patients in Center A started oral feeding once their abdominal pain resolved, and enteral tube feeding often lasted less than one or two days in cases of mild and moderate AP.

Moraes et al. [18] and Larino-Noia et al. [19] showed that early oral re-feeding was safe and well tolerated, but neither study compared it to enteral tube feeding.

Finally, yet importantly, none of the guidelines precludes the option of enteral tube feeding in mild or moderate AP.

In Center A, with high-volume specialized care, patients are reviewed within 24 hours by gastroenterologists with expertise in AP, and patients are looked after by that same team throughout their hospital stay. Therefore, their continuity of care is optimal.

In Center B, patients are admitted to a general internal medicine unit, often without expertise in gastroenterology. We believe that this profound difference results in a significant delay in decision making in the treatment of AP, translated to poorer mortality. Patients transferred between medical teams often receive more fragmented treatment, and this approach increases the possibility of further delays and risks of complications as well.

Other possible factors are suboptimal knowledge and adherence to the AP guidelines among physicians without expertise and low case numbersof AP.

Based on these results, organized specialized care for AP in Hungary could shorten the hospital stay by 1,100 days (2 days/patient) and could save 275 lives (5% more) in a single year. Specialized care could reduce the costs of medications, disposables, procedures and investigations by 25%.

CONCLUSION

Managing AP in a high-volume center can potentially decrease disease severity, reduce the need for medications, improve mortality, shorten hospital stay and reduce costs of care. Therefore, further in-depth analysis would be warranted to establish whether AP should be managed in high-volume specialized centers.

Conflicts of interest: No conflicts to declare.

Authors' contributions: G.S. and H.P. formulated the research questions and designed the study. P.A., G.Z., S.A., G.S. and H.P. interpreted the data. F.N. performed the statistical analysis. G.S., M.A., E.B. and H.P. wrote the manuscript. The other authors contributed to the implementation of the study and the data acquisition. All authors read and approved the final manuscript.

ORCHID numbers of the authors (See Supplementary Material)

Clinical collaborators:

Dezső Kelemen, Róbert Papp (Department of Surgery, University of Pécs School of Medicine, Pécs, Hungary), Nándor Faluhelyi, Krisztián Molnár, Péter Farkas (Department of Radiology, University of Pécs School of Medicine, Pécs, Hungary), Tamás Takács (1st Department of Medicine, University of Szeged, Szeged, Hungary), József Fenyő (Department of Emergency Medicine, St. Rókus Hospital, Baja, Hungary), Előd Papp (Department of Internal Medicine, St. Lukács Hospital, Dombóvár, Hungary), István Késői (Department of Internal Medicine, Komló General Hospital, Komló, Hungary), Balázs Marton (Department of Emergency Medicine, Mohács General Hospital, Mohács, Hungary), Csaba Csizmadia (Department of Internal Medicine, Mohács General Hospital, Mohács, Hungary), János Simon (Department of Emergency Medicine, Balassa János Tolna County Hospital, Szekszárd, Hungary), Ágnes Salamon (Department of Internal Medicine, Balassa János Tolna County Hospital, Szekszárd, Hungary), Éva Szabó (Department of Internal Medicine, Szigetvár General Hospital, Szigetvár, Hungary)

Acknowledgement: The study was supported by a Project Grant (KH125678 to PH), an Economic Development and Innovation Operative Program Grant (GINOP 2.3.2-15-2016-00048 to PH) and a Human Resources Development Operational Program Grant (EFOP-3.6.2-16-2017-00006 to PH) from the National Research, Development and Innovation Office as well as by a Momentum Grant from the Hungarian Academy of Sciences (LP2014-10/2014 to PH) and the ÚNKP-17-3-I. New National Excellence Program, Ministry of Human Capacities (PTE/46539/2017 to KM).

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld.2014.1121.272.pan

REFERENCES

1. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev 2013;(9):CD000197. doi:10.1002/14651858.CD000197.pub3

2. Keller T, Post F, Tzikas S, et al. Improved outcome in acute coronary syndrome by establishing a chest pain unit. Clin Res Cardiol 2010;99:149-155. doi:10.1007/s00392-009-0099-9
3. Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870-947. doi:10.1161/STR.0b013e318284056a
4. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-177. doi:10.1093/eurheartj/ehx393
5. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology 2012;143:1179-1187. e1-3. doi:10.1053/j.gastro.2012.08.002
6. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13(4 Suppl 2):e1-15. doi:10.1016/j.pan.2013.07.063
7. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013;108:1400-1415. doi:10.1038/ajg.2013.218
8. Hritz I, Czako L, Dubravcsik Z, et al. Acute pancreatitis. Evidence-based practice guidelines, prepared by the Hungarian Pancreatic Study Group. Orv Hetil 2015;156:244-261. doi:10.1556/oh.2015.30059
9. Singla A, Simons J, Li Y, et al. Admission volume determines outcome for patients with acute pancreatitis. Gastroenterology 2009;137:1995-2001. doi:10.1053/j.gastro.2009.08.056
10. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102-111. doi:10.1136/gutjnl-2012-302779
11. Dubravcsik Z, Madacsy L, Gyokeres T, et al. Preventive pancreatic stents in the management of acute biliary pancreatitis (PREPAST trial): pre-study protocol for a multicenter, prospective, randomized, interventional, controlled trial. Pancreatology 2015;15:115-123. doi:10.1016/j.pan.2015.02.007
12. Parniczky A, Mosztbacher D, Zsoldos F, Toth A, Lasztity N, Hegyi P. Analysis of Pediatric Pancreatitis (APPLE Trial): Pre-Study Protocol of a Multinational Prospective Clinical Trial. Digestion 2016;93:105-110. doi:10.1159/000441353
13. Zsoldos F, Parniczky A, Mosztbacher D, Toth A, Lasztity N, Hegyi P. Pain in the Early Phase of Pediatric Pancreatitis (PINEAPPLE Trial): Pre-Study Protocol of a Multinational Prospective Clinical Trial. Digestion 2016;93:121-126. doi:10.1159/000441352
14. Marta K, Szabo AN, Pecsi D, et al. High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): protocol of a multicentre randomised double-blind clinical trial. BMJ Open 2017;7:e015874. doi:10.1136/bmjopen-2017-015874
15. Hritz I, Hegyi P. Early Achievable Severity (EASY) index for simple and accurate expedite risk stratification in acute pancreatitis. J Gastrointestin Liver Dis 2015;24:177-182. doi:10.15403/jgld.2014.1121.242.easy
16. Petrov MS, McIlroy K, Grayson L, Phillips AR, Windsor JA. Early nasogastric tube feeding versus nil per os in mild to moderate acute pancreatitis: a randomized controlled trial. Clin Nutr 2013;32:697-703. doi:10.1016/j.clnu.2012.12.011
17. Márta K, Farkas N, Szabó I, et al. Meta-Analysis of Early Nutrition: The Benefits of Enteral Feeding Compared to a Nil Per Os Diet Not Only in Severe, but Also in Mild and Moderate Acute Pancreatitis. Int J Mol Sci 2016;17:1691. doi:10.3390/ijms17101691
18. Moraes JM, Felga GE, Chebli LA, et al. A full solid diet as the initial meal in mild acute pancreatitis is safe and result in a shorter length of hospitalization: results from a prospective, randomized, controlled, double-blind clinical trial. J Clin Gastroenterol 2010;44:517-522. doi:10.1097/MCG.0b013e3181c986b3
19. Lariño-Noia J, Lindkvist B, Iglesias-García J, Seijo-Ríos S, Iglesias-Canle J, Domínguez-Muñoz JE. Early and/or immediately full caloric diet versus standard refeeding in mild acute pancreatitis: a randomized open-label trial. Pancreatology 2014;14:167-173. doi:10.1016/j.pan.2014.02.008

Pancreatology 19 (2019) 488–499

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

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

Andrea Párniczky [a, b, 1], Tamás Lantos [c, 1], Eszter Margit Tóth [d, e, 1], Zsolt Szakács [a], Szilárd Gódi [f], Roland Hágendorn [g], Dóra Illés [e], Balázs Koncz [e], Katalin Márta [a], Alexandra Mikó [a, h], Dóra Mosztbacher [a, i], Balázs Csaba Németh [e, bk], Dániel Pécsi [a], Anikó Szabó [a], Ákos Szücs [j], Péter Varjú [a], Andrea Szentesi [a, e], Erika Darvasi [e], Bálint Erőss [a], Ferenc Izbéki [k], László Gajdán [k], Adrienn Halász [k], Áron Vincze [f], Imre Szabó [f], Gabriella Pár [f], Judit Bajor [f], Patrícia Sarlós [f], József Czimmer [f], József Hamvas [l], Tamás Takács [e], Zoltán Szepes [e], László Czakó [e], Márta Varga [m], János Novák [d], Barnabás Bod [n], Attila Szepes [o], János Sümegi [p], Mária Papp [q], Csaba Góg [r], Imola Török [s], Wei Huang [t], Qing Xia [t], Ping Xue [u], Weiqin Li [v], Weiwei Chen [w], Natalia V. Shirinskaya [x], Vladimir L. Poluektov [y], Anna V. Shirinskaya [y], Péter Jenő Hegyi [a, z], Marian Bátovský [z], Juan Armando Rodriguez-Oballe [aa], Isabel Miguel Salas [aa], Javier Lopez-Diaz [ab], J. Enrique Dominguez-Munoz [ab], Xavier Molero [ac], Elizabeth Pando [ad], María Lourdes Ruiz-Rebollo [ae], Beatriz Burgueño-Gómez [ae], Yu-Ting Chang [af], Ming-Chu Chang [af], Ajay Sud [ag], Danielle Moore [ag], Robert Sutton [ag], Amir Gougol [ah], Georgios I. Papachristou [ah], Yaroslav Mykhailovych Susak [ai], Illia Olehovych Tiuliukin [ai], António Pedro Gomes [aj], Maria Jesus Oliveira [aj], David João Aparício [aj], Marcel Tantau [ak], Floreta Kurti [al], Mila Kovacheva-Slavova [am], Stephanie-Susanne Stecher [an], Julia Mayerle [an], Goran Poropat [ao], Kshaunish Das [ap], Marco Vito Marino [aq], Gabriele Capurso [ar], Ewa Małecka-Panas [as], Hubert Zatorski [as], Anita Gasiorowska [at], Natalia Fabisiak [at], Piotr Ceranowicz [au], Beata Kuśnierz-Cabala [au], Joana Rita Carvalho [av], Samuel Raimundo Fernandes [av], Jae Hyuck Chang [aw], Eun Kwang Choi [ax], Jimin Han [ay], Sara Bertilsson [az, ba], Hanaz Jumaa [bb], Gabriel Sandblom [bc], Sabite Kacar [bd], Minas Baltatzis [be], Aliaksandr Vladimir Varabei [bf], Vizhynis Yeshy [bg], Serge Chooklin [bh], Andriy Kozachenko [bi], Nikolay Veligotsky [bj], Péter Hegyi [a, e, h, bk, *], on behalf of the Hungarian Pancreatic Study Group

[a] Institute for Translational Medicine, Szentágothai Research Centre, Medical School, University of Pécs, Pécs, Hungary
[b] Heim Pál National Insititute of Pediatrics, Budapest, Hungary
[c] Department of Medical Physics and Informatics, Faculty of Medicine, University of Szeged, Szeged, Hungary
[d] Pándy Kálmán Hospital of Békés County, Gyula, Hungary
[e] First Department of Medicine, Faculty of Medicine, University of Szeged, Szeged, Hungary
[f] Division of Gastroenterology, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary
[g] Intesive Care Unit, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary
[h] Division of Translational Medicine, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary
[i] First Department of Pediatrics, Semmelweis University, Budapest, Hungary
[j] First Department of Surgery, Faculty of Medicine, Semmelweis University, Budapest, Hungary
[k] Szent György University Teaching Hospital of Fejér County, Székesfehérvár, Hungary

* Corresponding author. University of Pécs, Faculty of Medicine Centre for Translational Medicine, Institute for Translational Medicine & Department of Translational Medicine/1st Department of Medicine, 12 Szigeti Street, Pécs, H-7624, Hungary.

URL: http://www.tm-centre.org

https://doi.org/10.1016/j.pan.2019.04.003

[l] Bajcsy-Zsilinszky Hospital, Budapest, Hungary
[m] Dr. Réthy Pál Hospital, Békéscsaba, Hungary
[n] Dr. Bugyi István Hospital, Szentes, Hungary
[o] Bács-Kiskun County Hospital, Kecskemét, Hungary
[p] Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital, Miskolc, Hungary
[q] Department of Internal Medicine, Division of Gastroenterology, University of Debrecen, Debrecen, Hungary
[r] Healthcare Center of County Csongrád, Makó, Hungary
[s] County Emergency Clinical Hospital of Targu Mures Hospital, University of Medicine, Pharmacy, Sciences and Technology of Targu Mures, Targu Mures, Romania
[t] Department of Integrated Traditional Chinese and Western Medicine, Sichuan Provincial Pancreatitis Centre and West China-Liverpool Biomedical Research Centre, West China Hospital of Sichuan University, Chengdu, China
[u] Department of Integrated Traditional Chinese and Western Medicine, Shangjin Hospital, West China Medical School of Sichuan University, Chengdu, China
[v] Surgical Intensive Care Unit (SICU), Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, Nanjing, China
[w] Department of Gastroenterology, Subei People's Hospital of Jiangsu Province, Clinical Medical College of Yangzhou University, Yangzhou, China
[x] Omsk State Medical Information-Analytical Centre, Omsk State Clinical Emergency Hospital #2, Omsk, Russia
[y] Department of Surgery and Urology, Omsk State Medical University, Omsk, Russia
[z] Departement of Gastroenterology Slovak Medical University in Bratislava, Bratislava, Slovakia
[aa] Department of Gastroenterology, University Hospital Santa María - University Hospital Arnau de Vilanova, Lerida, Spain
[ab] Department of Gastroenterology, University Hospital of Santiago de Compostela, Santiago de Compostela, Spain
[ac] Exocrine Pancreas Research Unit, Hospital Universitari Vall d'Hebron - Institut de Recerca, Autonomous University of Barcelona, CIBEREHD, Barcelona, Spain
[ad] Department of Hepato-pancreato-biliary and Transplat Surgery, Hospital Universitari Vall d'Hebron, Barcelona, Spain
[ae] Digestive Diseases Department Clinical University Hospital of Valladolid, Valladolid, Spain
[af] Department of Internal Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan
[ag] Liverpool Pancreatitis Research Group, University of Liverpool and the Royal Liverpool and Broadgreen University Hospital Trust, Liverpool, United Kingdom
[ah] Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[ai] O.O.Bogomolets National Medical University, Kiev, Ukraine
[aj] Department of Surgery, Hospital Prof. Dr. Fernando Fonseca, Amadora, Portugal
[ak] Iuliu Hatieganu" University of Medicine and Pharmacy, Department of Internal Medicine, 3rd Medical Clinic and "Prof. Dr. Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania
[al] Department of Gastroenterology and Hepatology, University Hospital Center "Mother Theresa", Tirana, Albania
[am] University Hospital "Tsaritsa Ioanna - ISUL", Departement of Gastroenterology, Sofia, Bulgaria
[an] Department of Medicine II, University Hospital, LMU Munich, Germany
[ao] Department of Gastroenterology, Clinical Hospital Center Rijeka, Faculty of Medicine, University of Rijeka, Croatia
[ap] Division of Gastroenterology, School of Digestive and Liver Diseases, IPGME &R, Kolkata, India
[aq] Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy
[ar] PancreatoBiliary Endoscopy and EUS Division, Pancreas Translational and Clinical Research Center, IRCCS San Raffaele Scientific Institute, Vita Salute San Raffaele University, Milan, Italy
[as] Department of Digestive Tract Diseases, Medical University of Lodz, Poland
[at] Department of Gastroenterology Medical University of Lodz, Poland
[au] Department of Physiology, Faculty of Medicine, Jagiellonian University Medical College, Krakow, Poland
[av] Department of Gastroenterology and Hepatology, North Lisbon Hospital Center, Hospital Santa Maria, University of Lisbon, Lisbon, Portugal
[aw] Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[ax] Department of Internal Medicine, Jeju National University College of Medicine, Jeju, South Korea
[ay] Department of Internal Medicine, Daegu Catholic University Medical Center, Daegu Catholic University School of Medicine, Daegu, South Korea
[az] Department of Clinical Sciences, Lund University, Lund, Sweden
[ba] Department of Health Sciences, Lund University, Lund, Sweden
[bb] Eskilstuna Hospital, Mälarsjukhuset, Eskilstuna, Sweden
[bc] Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Department of Surgery, Södersjukhuset, Stockholm, Sweden
[bd] Department of Gastroenterology Türkiye Yüksek İhtisas Hospital, Ankara, Turkey
[be] Manchester Royal Infirmary Hospital, Manchester, United Kingdom
[bf] Belarusian Medical Academy of Postgraduate Education, Minsk, Belarus
[bg] Department of Surgery, Belarusian Medical Academy Postgraduate Education, Minsk, Belarus
[bh] Regional Clinical Hospital, Lviv, Ukraine
[bi] Kharkiv Emergency Hospital, Medical Faculty of V. N. Karazin Kharkiv National University, Kharkiv, Ukraine
[bj] Department Thoraco-abdominal Surgery Kharkov Medical Academy Postgraduate Education, Kharkov, Ukraine
[bk] Hungarian Academy of Sciences-University of Szeged, Momentum Gastroenterology Multidisciplinary Research Group, Szeged, Hungary

ARTICLE INFO

Article history:
Received 31 March 2019
Accepted 1 April 2019
Available online 19 April 2019

Keywords:
Acute pancreatitis
Antibiotic
Guideline
Recommendation
Infection

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

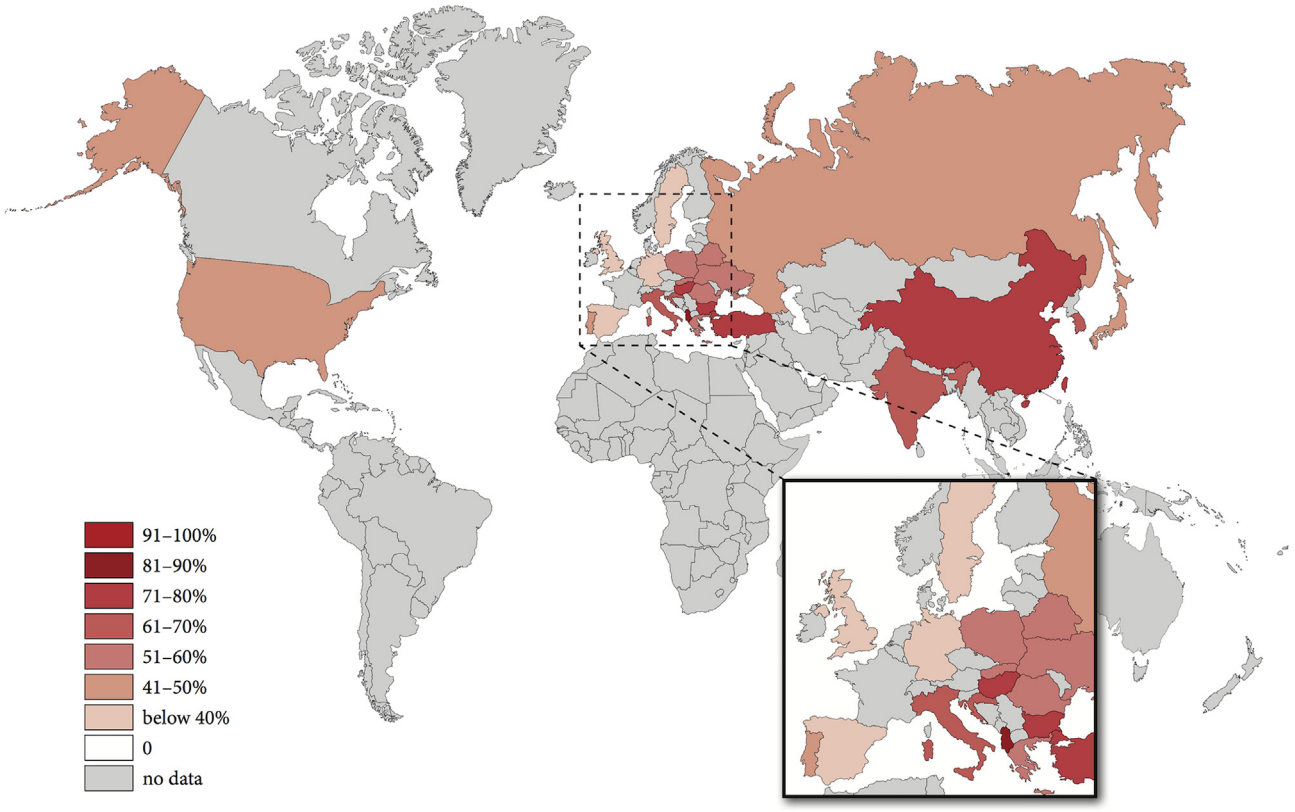


Fig. 1. Map of antibiotic use worldwide. There is a general overuse of AB worldwide (57.2%). The highest rates of AB therapy are in Asia (China 81.4%, Taiwan 80.6%) and Eastern Europe (Albania 78.6%, Bulgaria 78%), whereas the lowest rates are observed in Western Europe (Spain 31.8%, United Kingdom 31.2%).

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).

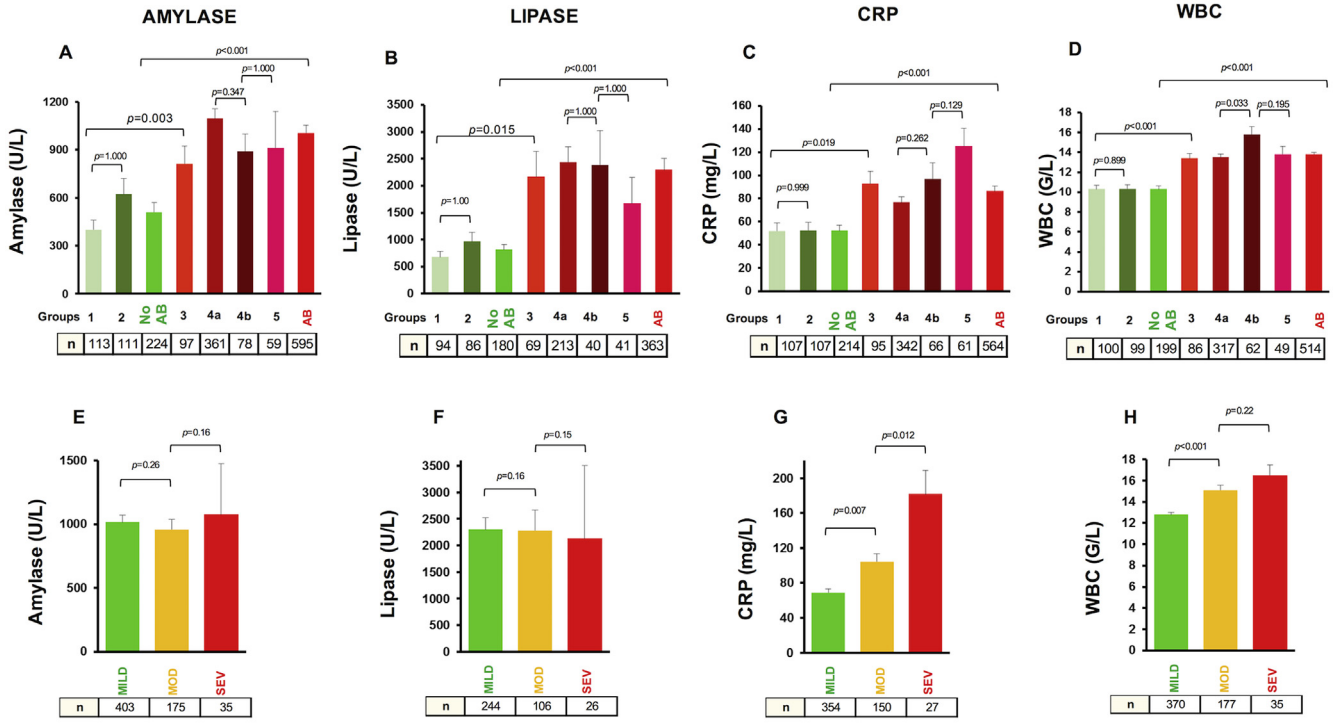


Fig. 3. Most commonly monitored laboratory markers on starting day of AB therapy. Average amylase, lipase, C-reactive protein (CRP) and white blood cells (WBC) were calculated on starting day of AB therapy. In non-AB groups day-matched controls were selected. **A.** Average amylase in non-AB group (510.01 ± 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 $p = 0.22$).

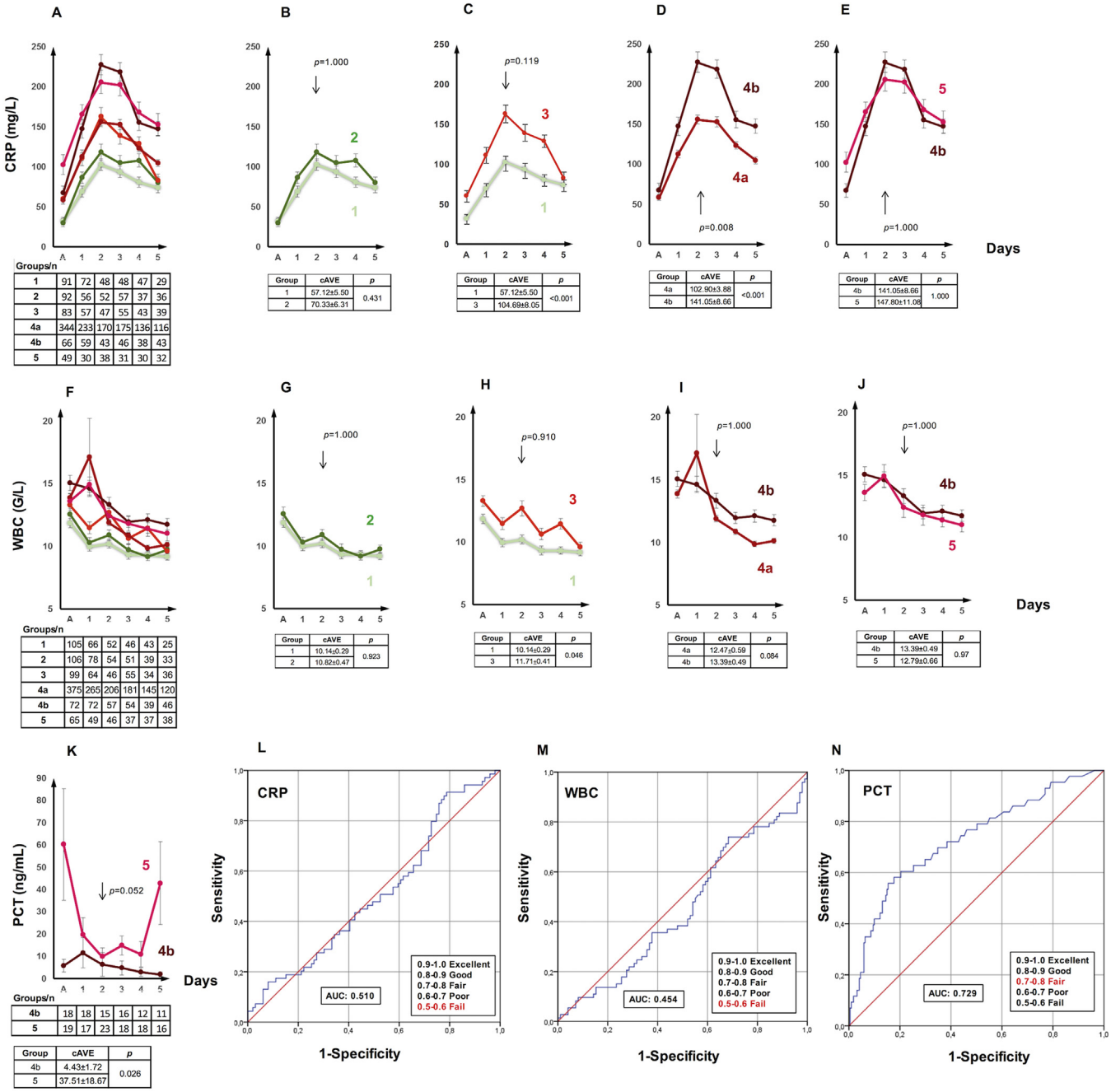


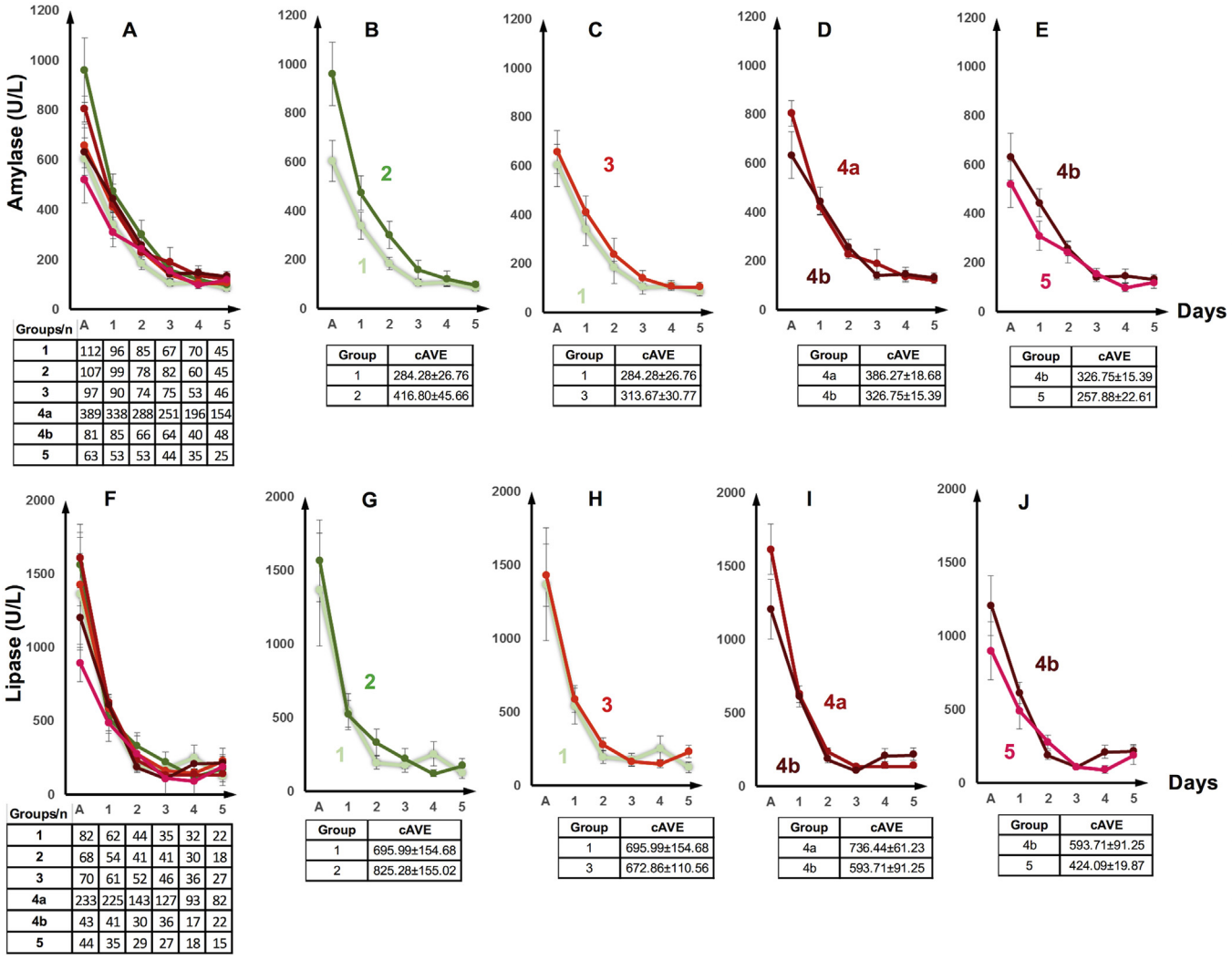
Fig. 4. Trends in the changes of CRP and WBC during the early phase of AP. A. Due to the inflammation of the pancreas, irrespectively from the infection CRP levels rose during the first 3 days. **F.** Non-similar trend can be seen in WBC levels. **B and G.** Suspected infection (Group 2) in AP did not 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

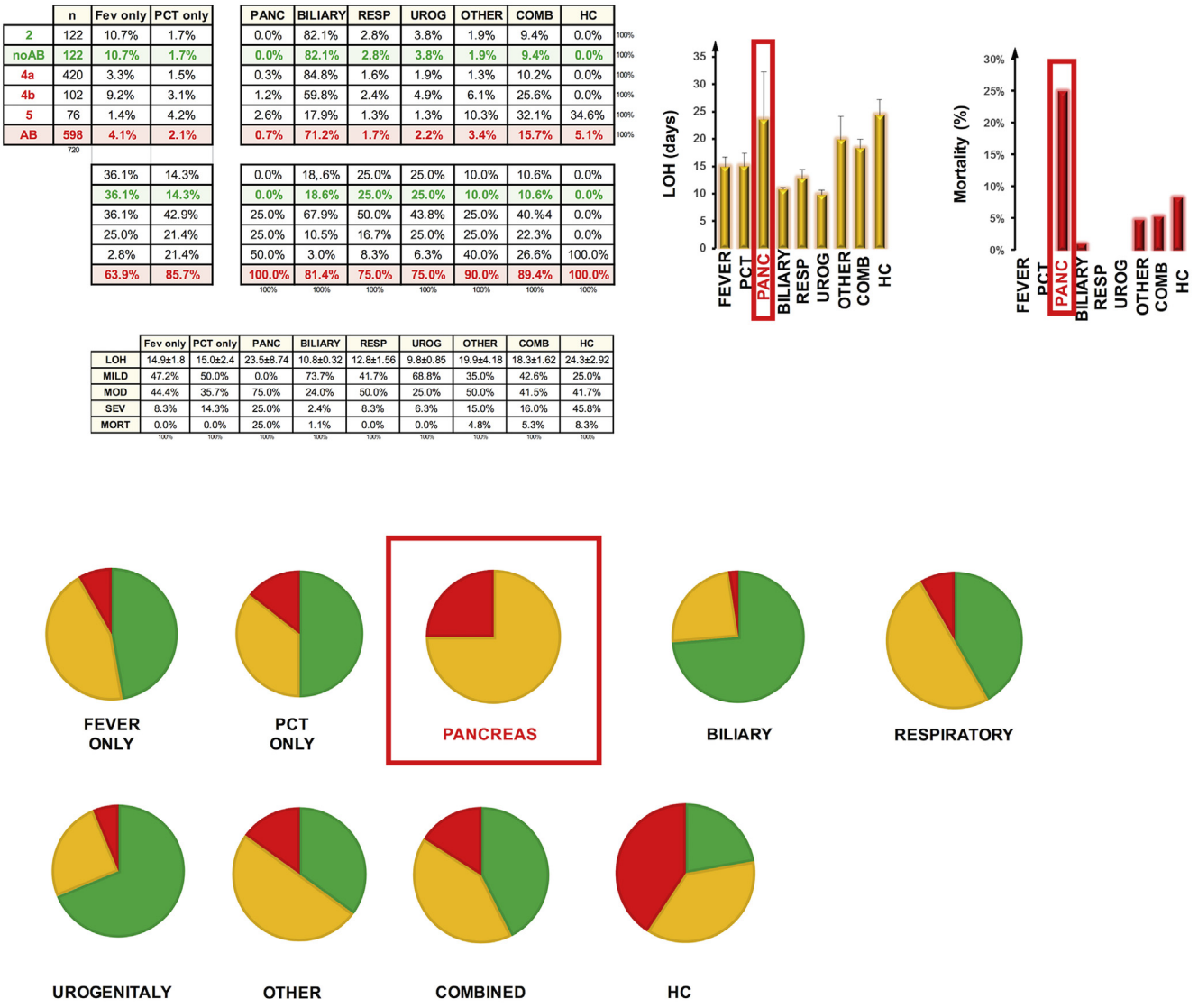


Fig. 6. Source of infection in AP. Infection of the pancreas extended the length of hospitalization (LOH) to 25.55 ± 4.76 days, deteriorated the course of the disease (moderate 25%, severe 75%) and elevated the mortality to 25%. Ple charts represent the distribution of mild (green), moderate (yellow)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

Acknowledgements

The study was supported by Project Grants (KH125678 and K116634 to PH, K120335 to TT), the Economic Development and Innovation Operative Programme Grant (GINOP 2.3.2-15-372 2016-00048 to PH) and Human Resources Development Operational Programme Grant (EFOP-3.6.2-16-2017-00006 to PH) from the National Research Development and Innovation Office, by a Momentum Grant from the Hungarian Academy of Science (LP2014-10/2014 to PH), by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences (to AP) and the ÚNKP-18-4 new national excellence program of the ministry of human capacities (to AP). Data from Liverpool (by AS, DM, RS) were obtained through support from the NIHR Biomedical Research Unit funding scheme.

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.

References

[1] Ventola CL. The antibiotic resistance crisis: Part 1: causes and threats. PT 2015;40:277–83.
[2] Ping H, BiRong D, BinYou W, GuanJian L, ChangQuan H, XiaoFang L, et al. Invasive fungal infections in elderly patients receiving antibiotic treatment: an 8-year retrospective study. J Am Geriatr Soc 2009;57:936–7.
[3] Bernatz JT, Safdar N, Hetzel S, Anderson PA. Antibiotic overuse is a major risk factor for clostridium difficile infection in surgical patients. Infect Control Hosp Epidemiol 2017;38:1254–7.
[4] Suda KJ, Hicks LA, Roberts RM, Hunkler RJ, Danziger LH. A national evaluation of antibiotic expenditures by healthcare setting in the United States, 2009. J Antimicrob Chemother 2013;68:715–8.
[5] Report on the consumption of antimicrobials and the spread of antimicrobial resistance in human and veterinary medicine in Germany. 2016.
[6] Meyer E, Gastmeier P, Deja M, Schwab F. Antibiotic consumption and resistance: data from europe and Germany. Int J Med Microbiol 2013;303:388–95.
[7] Summary of the latest data on antibiotic consumption in the European Union. 2017. p. 2017. november.
[8] Antibiotic resistance threats in the United States, 2013. 2013.
[9] World health day. Media fact sheet. 2011.
[10] The bacterial challenge: time to react. A call to narrow the gap between multidrug-resistant bacteria in the eu and the development of new antibacterial agents. 2009.
[11] Fair RJ, Tor Y. Antibiotics and bacterial resistance in the 21st century. Perspect Med Chem 2014;6:25–64.
[12] Sipahi OR. Economics of antibiotic resistance. Expert Rev Anti Infect Ther 2008;6:523–39.
[13] Baltatzis M, Jegatheeswaran S, O'Reilly DA, Siriwardena AK. Antibiotic use in acute pancreatitis: global overview of compliance with international guidelines. Pancreatology 2016;16:189–93.
[14] Hegyi P, Petersen OH. The exocrine pancreas: the acinar-ductal tango in physiology and pathophysiology. Rev Physiol Biochem Pharmacol 2013;165:1–30.
[15] Németh BC, Szücs Á, Hegyi P, Sahin-Tóth M. Novel PRSS1 Mutation p.P17T validates pathogenic relevance of CTRC-mediated processing of the trypsinogen activation peptide in chronic pancreatitis. Am J Gastroenterol. 2017 Dec;112(12):1896–8.
[16] Sah RP, Dawra RK, Saluja AK. New insights into the pathogenesis of pancreatitis. Curr Opin Gastroenterol 2013;29:523–30.
[17] Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis–2012: revision of the atlanta classification and definitions by international consensus. Gut 2013;62:102–11.
[18] Iap/apa evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013;13:e1–15.
[19] Aga institute medical position statement on acute pancreatitis. Gastroenterology 2007;132:2019–21.
[20] Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. Am J Gastroenterol 2006;101:2379–400.
[21] Buchler MW, Klar E. Introduction. Complications of pancreatic surgery and pancreatitis. Dig Surg 2002;19:123–4.
[22] Nesvaderani M, Eslick GD, Faraj S, Vagg D, Cox MR. Study of the early management of acute pancreatitis. ANZ J Surg 2017;87:805–9.
[23] Baltatzis M, Mason JM, Chandrabalan V, Stathakis P, McIntyre B, Jegatheeswaran S, et al. Antibiotic use in acute pancreatitis: an audit of current practice in a tertiary centre. Pancreatology 2016;16:946–51.
[24] Besselink MG, van Santvoort HC, Boermeester MA, Nieuwenhuijs VB, van Goor H, Dejong CH, et al. Timing and impact of infections in acute pancreatitis. Br J Surg 2009;96:267–73.
[25] Parniczky A, Kui B, Szentesi A, Balazs A, Szucs A, Mosztbacher D, et al. Prospective, multicentre, nationwide clinical data from 600 cases of acute pancreatitis. PLoS One 2016;11:e0165309.
[26] Cardoso FS, Ricardo L, Gondar P, Deus JR, Horta D. C-reactive protein may influence decisively the prescription of prophylactic antibiotics in acute pancreatitis: a population-based cohort study. Pancreas 2015;44:404–8.
[27] Greenberg JA, Hsu J, Bawazeer M, Marshall J, Friedrich JO, Nathens A, et al. Compliance with evidence-based guidelines in acute pancreatitis: an audit of practices in university of toronto hospitals. J Gastrointest Surg 2016;20:392–400.
[28] Koutroumpakis E, Slivka A, Furlan A, Dasyam AK, Dudekula A, Greer JB, et al.

Management and outcomes of acute pancreatitis patients over the last decade: a us tertiary-center experience. Pancreatology 2017;17:32–40.
[29] Murata A, Matsuda S, Mayumi T, Yokoe M, Kuwabara K, Ichimiya Y, et al. A descriptive study evaluating the circumstances of medical treatment for acute pancreatitis before publication of the new jpn guidelines based on the Japanese administrative database associated with the diagnosis procedure combination system. J Hepatobiliary Pancreatol Sci 2011;18:678–83.
[30] Hamada S, Masamune A, Shimosegawa T. Transition of early-phase treatment for acute pancreatitis: an analysis of nationwide epidemiological survey. World J Gastroenterol 2017;23:2826–31.
[31] Nakaharai K, Morita K, Jo T, Matsui H, Fushimi K, Yasunaga H. Early prophylactic antibiotics for severe acute pancreatitis: a population-based cohort study using a nationwide database in Japan. J Infect Chemother 2018 Sep;24(9):753–8.
[32] Lankisch PG, Weber-Dany B, Lerch MM. Clinical perspectives in pancreatology: compliance with acute pancreatitis guidelines in Germany. Pancreatology 2005;5:591–3.
[33] Foitzik T, Klar E. (non-)compliance with guidelines for the management of severe acute pancreatitis among German surgeons. Pancreatology 2007;7:80–5.
[34] Sekimoto M, Shikata S, Takada T, Hirata K, Yoshida M, Hirota M, et al. Changes in management of acute pancreatitis before and after the publication of evidence-based practice guidelines in 2003. J Hepatobiliary Pancreatol Sci 2010;17:17–23.
[35] Sun E, Tharakan M, Kapoor S, Chakravarty R, Salhab A, Buscaglia JM, et al. Poor compliance with acg guidelines for nutrition and antibiotics in the management of acute pancreatitis: a north american survey of gastrointestinal specialists and primary care physicians. JOP 2013;14:221–7.
[36] Rebours V, Levy P, Bretagne JF, Bommelaer G, Hammel P, Ruszniewski P. Do guidelines influence medical practice? Changes in management of acute pancreatitis 7 years after the publication of the French guidelines. Eur J Gastroenterol Hepatol 2012;24:143–8.
[37] Lykkegaard J, Andersen MKK, Nexoe J, Hvidt EA. Defensive medicine in primary health care. Scand J Prim Health Care 2018:1–2.
[38] Panella M, Rinaldi C, Leigheb F, Knesse S, Donnarumma C, Kul S, et al. Prevalence and costs of defensive medicine: a national survey of Italian physicians. J Health Serv Res Policy 2017;22:211–7.
[39] Assing Hvidt E, Lykkegaard J, Pedersen LB, Pedersen KM, Munck A, Andersen MK. How is defensive medicine understood and experienced in a primary care setting? A qualitative focus group study among Danish general practitioners. BMJ Open 2017;7:e019851.
[40] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015 statement. Syst Rev 2015;4:1.
[41] von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (strobe) statement: guidelines for reporting observational studies. PLoS Med 2007;4:e296.
[42] Qu R, Ji Y, Ling Y, Ye CY, Yang SM, Liu YY, et al. Procalcitonin is a good tool to guide duration of antibiotic therapy in patients with severe acute pancreatitis. A randomized prospective single-center controlled trial. Saudi Med J 2012;33:382–7.
[43] Barreda L, Targarona J, Milian W, Portugal J, Sequeiros J, Pando E, et al. [is the prophylactic antibiotic therapy with imipenem effective for patients with pancreatic necrosis?]. Acta Gastroenterol Latinoam 2009;39:24–9.
[44] Bassi C, Falconi M, Talamini G, Uomo G, Papaccio G, Dervenis C, et al. Controlled clinical trial of pefloxacin versus imipenem in severe acute pancreatitis. Gastroenterology 1998;115:1513–7.
[45] Craig RM, Dordal E, Myles L, Letter. The use of ampicillin in acute pancreatitis. Ann Intern Med 1975;83:831–2.
[46] Delcenserie R, Yzet T, Ducroix JP. Prophylactic antibiotics in treatment of severe acute alcoholic pancreatitis. Pancreas 1996;13:198–201.
[47] Dellinger EP, Tellado JM, Soto NE, Ashley SW, Barie PS, Dugernier T, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. Ann Surg 2007;245:674–83.
[48] Finch WT, Sawyers JL, Schenker S. A prospective study to determine the efficacy of antibiotics in acute pancreatitis. Ann Surg 1976;183:667–71.
[49] Garcia-Barrasa A, Borobia FG, Pallares R, Jorba R, Poves I, Busquets J, et al. A double-blind, placebo-controlled trial of ciprofloxacin prophylaxis in patients with acute necrotizing pancreatitis. J Gastrointest Surg 2009;13:768–74.
[50] Howes R, Zuidema GD, Cameron JL. Evaluation of prophylactic antibiotics in acute pancreatitis. J Surg Res 1975;18:197–200.
[51] Isenmann R, Runzi M, Kron M, Kahl S, Kraus D, Jung N, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. Gastroenterology 2004;126:997–1004.
[52] Luiten EJ, Hop WC, Lange JF, Bruining HA. Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis. Ann Surg 1995;222:57–65.
[53] Manes G, Rabitti PG, Menchise A, Riccio E, Balzano A, Uomo G. Prophylaxis with meropenem of septic complications in acute pancreatitis: a randomized, controlled trial versus imipenem. Pancreas 2003;27:e79–83.
[54] Manes G, Uomo I, Menchise A, Rabitti PG, Ferrara EC, Uomo G. Timing of antibiotic prophylaxis in acute pancreatitis: a controlled randomized study with meropenem. Am J Gastroenterol 2006;101:1348–53.
[55] Nordback I, Sand J, Saaristo R, Paajanen H. Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis–a single-center randomized study. J Gastrointest Surg 2001;5:113–8. discussion 118-120.
[56] Pederzoli P, Bassi C, Vesentini S, Campedelli A. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. Surg Gynecol Obstet 1993;176:480–3.
[57] Rokke O, Harbitz TB, Liljedal J, Pettersen T, Fetvedt T, Heen LO, et al. Early treatment of severe pancreatitis with imipenem: a prospective randomized clinical trial. Scand J Gastroenterol 2007;42:771–6.
[58] Schwarz M, Isenmann R, Meyer H, Beger HG. [antibiotic use in necrotizing pancreatitis. Results of a controlled study]. Dtsch Med Wochenschr 1997;122:356–61.
[59] Xue P, Deng LH, Zhang ZD, Yang XN, Wan MH, Song B, et al. Effect of antibiotic prophylaxis on acute necrotizing pancreatitis: results of a randomized controlled trial. J Gastroenterol Hepatol 2009;24:736–42.
[60] Yang XN, Deng LH, Xue P, Zhao L, Jin T, Wan MH, et al. [non-preventive use of antibiotics in patients with severe acute pancreatitis treated with integrated traditional Chinese and western medicine therapy: a randomized controlled trial]. Zhong Xi Yi Jie He Xue Bao 2009;7:330–3.
[61] Maravi-Poma E, Gener J, Alvarez-Lerma F, Olaechea P, Blanco A, Dominguez-Munoz JE. Early antibiotic treatment (prophylaxis) of septic complications in severe acute necrotizing pancreatitis: a prospective, randomized, multicenter study comparing two regimens with imipenem-cilastatin. Intensive Care Med 2003;29:1974–80.
[62] Špičák J, Hubaczová M, Antoš F. Antibiotics in the treatment of acute pancreatitis - findings from a randomized multi-centre prospective study. Ceská Slov Gastroenterol Hepatol 2002;56:183–9.
[63] Špičák J, Hejtmánková S, Hubaczová M. Antibiotic prophylaxis of infectious complications of acute pancreatitis - the results of randomised study by meropenem. Ceská Slov Gastroenterol Hepatol 2003;57:222–7.
[64] Powell JJ, Campbell E, Johnson CD, Siriwardena AK. Survey of antibiotic prophylaxis in acute pancreatitis in the UK and Ireland. Br J Surg 1999;86:320–2.
[65] King NK, Siriwardena AK. European survey of surgical strategies for the management of severe acute pancreatitis. Am J Gastroenterol 2004;99:719–28.
[66] Mayumi T, Ura H, Arata S, Kitamura N, Kiriyama I, Shibuya K, et al. Evidence-based clinical practice guidelines for acute pancreatitis: Proposals. J Hepatobiliary Pancreatol Surg 2002;9:413–22.
[67] Takeda K, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, et al. Jpn guidelines for the management of acute pancreatitis: medical management of acute pancreatitis. J Hepatobiliary Pancreatol Surg 2006;13:42–7.
[68] Werge M, Novovic S, Schmidt PN, Gluud LL. Infection increases mortality in necrotizing pancreatitis: a systematic review and meta-analysis. Pancreatology 2016;16:698–707.
[69] Guo Q, Li A, Xia Q, Liu X, Tian B, Mai G, et al. The role of organ failure and infection in necrotizing pancreatitis: a prospective study. Ann Surg 2014;259:1201–7.
[70] Schepers NJ, Bakker OJ, Besselink MG, Ahmed Ali U, Bollen TL, Gooszen HG, et al. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. Gut 2018;0:1–8. https://doi.org/10.1136/gutjnl-2017-314657 (PMID: 29950344).
[71] de Vries AC, Besselink MG, Buskens E, Ridwan BU, Schipper M, van Erpecum KJ, et al. Randomized controlled trials of antibiotic prophylaxis in severe acute pancreatitis: relationship between methodological quality and outcome. Pancreatology 2007;7:531–8.
[72] Moggia E, Koti R, Belgaumkar AP, Fazio F, Pereira SP, Davidson BR, et al. Pharmacological interventions for acute pancreatitis. Cochrane Database Syst Rev 2017;4:CD011384.
[73] Stirling AD, Moran NR, Kelly ME, Ridgway PF, Conlon KC. The predictive value of c-reactive protein (crp) in acute pancreatitis - is interval change in crp an additional indicator of severity? HPB (Oxford) 2017;19:874–80.
[74] Puolakkainen P, Valtonen V, Paananen A, Schroder T. C-reactive protein (crp) and serum phospholipase a2 in the assessment of the severity of acute pancreatitis. Gut 1987;28:764–71.
[75] Panek J, Kusnierz-Cabala B, Dolecki M, Pietron J. Serum proinflammatory cytokine levels and white blood cell differential count in patients with different degrees of severity of acute alcoholic pancreatitis. Pol Przegl Chir 2012;84:230–7.
[76] Bierma MJ, Coffey MJ, Nightingale S, van Rheenen PF, Ooi CY. Predicting severe acute pancreatitis in children based on serum lipase and calcium: a multicentre retrospective cohort study. Pancreatology 2016;16:529–34.
[77] Kumaravel A, Stevens T, Papachristou GI, Muddana V, Bhatt A, Lee PJ, et al. A model to predict the severity of acute pancreatitis based on serum level of amylase and body mass index. Clin Gastroenterol Hepatol 2015;13:1496–501.
[78] Fabre A, Boulogne O, Gaudart J, Mas E, Olives JP, Sarles J. Evaluation of serum lipase as predictor of severity of acute pancreatitis in children. J Pediatr Gastroenterol Nutr 2014;58:e41–2.
[79] Devanath A, Kumari J, Joe J, Peter S, Rajan S, Sabu L, et al. Usefulness of lipase/amylase ratio in acute pancreatitis in south indian population. Indian J Clin Biochem 2009;24:361–5.

frontiers in Physiology

ORIGINAL RESEARCH
published: 20 September 2019
doi: 10.3389/fphys.2019.01202

Multiple Hits in Acute Pancreatitis: Components of Metabolic Syndrome Synergize Each Other's Deteriorating Effects

Andrea Szentesi[1,2,3], Andrea Párniczky[1,4], Áron Vincze[5], Judit Bajor[5], Szilárd Gódi[6], Patricia Sarlós[5], Noémi Gede[1], Ferenc Izbéki[7], Adrienn Halász[7], Katalin Márta[1], Dalma Dobszai[1,3], Imola Török[8], Hunor Farkas[8], Mária Papp[9], Márta Varga[10], József Hamvas[11], János Novák[12], Artautas Mickevicius[13,14], Elena Ramirez Maldonado[15], Ville Sallinen[16], Dóra Illés[2], Balázs Kui[2], Bálint Erőss[1], László Czakó[2] Tamás Takács[2] and Péter Hegyi[1,2,6,17] on behalf of the Hungarian Pancreatic Study Group*

[1] Institute for Translational Medicine, Szentágothai Research Centre, Medical School, University of Pécs, Pécs, Hungary, [2] First Department of Medicine, University of Szeged, Szeged, Hungary, [3] Doctoral School of Clinical Medicine, University of Szeged, Szeged, Hungary, [4] Heim Pál National Institute of Pediatrics, Budapest, Hungary, [5] Division of Gastroenterology, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary, [6] Division of Translational Medicine, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary, [7] Szent György Teaching Hospital of Fejér County, Székesfehérvár, Hungary, [8] County Emergency Clinical Hospital – Gastroenterology and University of Medicine, Pharmacy, Sciences and Technology, Târgu Mureş, Romania, [9] Division of Gastroenterology, Department of Internal Medicine, University of Debrecen, Debrecen, Hungary, [10] Dr. Réthy Pál Hospital of Békés County, Békéscsaba, Hungary, [11] Bajcsy-Zsilinszky Hospital, Budapest, Hungary, [12] Department of Gastroenterology, Pándy Kálmán Hospital of Békés County, Gyula, Hungary, [13] Vilnius University Hospital Santaros Clinics, Vilnius, Lithuania, [14] Clinics of Abdominal Surgery, Nephrourology and Gastroenterology, Faculty of Medicine, Vilnius University, Vilnius, Lithuania, [15] Consorci Sanitari del Garraf, Sant Pere de Ribes, Barcelona, Spain, [16] Department of Transplantation and Liver Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland, [17] Hungarian Academy of Sciences – University of Szeged, Momentum Gastroenterology Multidisciplinary Research Group, Szeged, Hungary

OPEN ACCESS

Edited by:
Richard T. Waldron,
Cedars-Sinai Medical Center,
United States

Reviewed by:
Juan Sastre,
University of Valencia, Spain
Savio George Barreto,
Medanta – The Medicity, India

***Correspondence:**
Péter Hegyi
hegyi2009@gmail.com

Specialty section:
This article was submitted to Gastrointestinal Sciences, a section of the journal Frontiers in Physiology

Received: 04 May 2019
Accepted: 03 September 2019
Published: 20 September 2019

Citation:
Szentesi A, Párniczky A, Vincze Á, Bajor J, Gódi S, Sarlós P, Gede N, Izbéki F, Halász A, Márta K, Dobszai D, Török I, Farkas H, Papp M, Varga M, Hamvas J, Novák J, Mickevicius A, Maldonado ER, Sallinen V, Illés D, Kui B, Erőss B, Czakó L, Takács T and Hegyi P (2019) Multiple Hits in Acute Pancreatitis: Components of Metabolic Syndrome Synergize Each Other's Deteriorating Effects. Front. Physiol. 10:1202. doi: 10.3389/fphys.2019.01202

Introduction: The incidence of acute pancreatitis (AP) and the prevalence of metabolic syndrome (MetS) are growing worldwide. Several studies have confirmed that obesity (OB), hyperlipidemia (HL), or diabetes mellitus (DM) can increase severity, mortality, and complications in AP. However, there is no comprehensive information on the independent or joint effect of MetS components on the outcome of AP. Our aims were (1) to understand whether the components of MetS have an independent effect on the outcome of AP and (2) to examine the joint effect of their combinations.

Methods: From 2012 to 2017, 1435 AP cases from 28 centers were included in the prospective AP Registry. Patient groups were formed retrospectively based on the presence of OB, HL, DM, and hypertension (HT). The primary endpoints were mortality, severity, complications of AP, and length of hospital stay. Odds ratio (OR) with 95% confidence intervals (CIs) were calculated.

Results: 1257 patients (55.7 ± 17.0 years) were included in the analysis. The presence of OB was an independent predictive factor for renal failure [OR: 2.98 (CI: 1.33–6.66)] and obese patients spent a longer time in hospital compared to non-obese patients (12.1 vs. 10.4 days, $p = 0.008$). HT increased the risk of severe AP [OR: 3.41 (CI: 1.39–8.37)], renal failure [OR: 7.46 (CI: 1.61–34.49)], and the length of hospitalization

(11.8 vs. 10.5 days, $p = 0.020$). HL increased the risk of local complications [OR: 1.51 (CI: 1.10–2.07)], renal failure [OR: 6.4 (CI: 1.93–21.17)], and the incidence of newly diagnosed DM [OR: 2.55 (CI: 1.26–5.19)]. No relation was found between the presence of DM and the outcome of AP. 906 cases (mean age ± *SD*: 56.9 ± 16.7 years) had data on all four components of MetS available. The presence of two, three, or four MetS factors increased the incidence of an unfavorable outcome compared to patients with no MetS factors.

Conclusion: OB, HT, and HL are independent risk factors for a number of complications. HT is an independent risk factor for severity as well. Components of MetS strongly synergize each other's detrimental effect. It is important to search for and follow up on the components of MetS in AP.

Keywords: acute pancreatitis, metabolic syndrome, obesity, diabetes mellitus, hypertension, hyperlipidemia, severity, mortality

INTRODUCTION

Acute pancreatitis is a severe inflammatory condition with increasing incidence and hospitalization worldwide (Forsmark et al., 2016; Garg et al., 2019). AP has a variable severity ranging from mild and self-limited to severe and fatal. The mortality of the disease ranges approximately from 2 to 5% and depends on the development of organ failure and local complications, which are summarized in the revised Atlanta classification (Banks et al., 2013). The major etiological factors are gallstones and alcohol consumption (Forsmark et al., 2016), but hypertriglyceridemia (HTG) and intake of certain medications may also be in the background.

The severity and outcome of AP are influenced by the metabolic comorbidities of the host (Working Group Iap/Apa Acute Pancreatitis Guidelines, 2013; Goodger et al., 2016). Metabolic syndrome is characterized by the clustering of abdominal OB, HTG, low levels of high-density lipoprotein (HDL), elevations in blood pressure and fasting glucose, or diabetes (Alberti et al., 2009). MetS is associated with an increased risk of development of and death from cardiovascular disease and chronic kidney disease (Isomaa et al., 2001). The presence of MetS was previously shown to be associated with a higher risk of severe AP, higher mortality rate, and longer duration of stay in the intensive care unit (Mikolasevic et al., 2016). However, in another study, MetS did not affect the severity of AP (Sawalhi et al., 2014). OB was previously shown to be independently associated with the severity of AP (Sawalhi et al., 2014) and the development of organ failure but not with mortality in AP (Smeets et al., 2019). DM was associated with a higher risk of AP (Yang et al., 2013) and negatively influenced the outcome of AP by raising the incidence of renal failure, intensive care unit admission, and length of hospital stay (LOS) (Miko et al., 2018). The presence of HTG increased severity, complication rate, and mortality in AP (Kiss et al., 2018).

However, there is no data regarding a link between the outcome of AP and the presence of arterial HT. Furthermore, there is a lack of data on how the components of MetS, namely, OB, DM, HT, and HL, influence the outcome of AP individually or in combination. Therefore, in this study, we aimed to analyze how the components of MetS influence the outcome of AP (1) individually and (2) in combination.

Abbreviations: AP, acute pancreatitis; APR, Acute Pancreatitis Registry; BMI, body mass index; CI, 95% confidence interval; DM, diabetes mellitus; HL, hyperlipidemia; HPSG, Hungarian Pancreatic Study Group; HT, hypertension; LOS, length of hospital stay; MetS, metabolic syndrome; OB, obesity; OR, odds ratio; SD, standard deviation.

MATERIALS AND METHODS

Patient Population and Study Design

The APR launched in 2011 by the Hungarian Pancreatic Study Group is an international prospective registry for patients suffering from AP. Besides pancreatic registries, HPSG has already organized five registered clinical trials to investigate AP with the acronyms PREPAST (Dubravcsik et al., 2015), APPLE (Parniczky et al., 2016), PINEAPPLE (Zsoldos et al., 2016), GOULASH (Marta et al., 2017), and EASY (Hritz and Hegyi, 2015) and has submitted three further pre-study protocols: GOULASH PLUS (follow-up to the GOULASH study), EMILY (endoscopic sphincterotomy for delaying cholecystectomy in mild acute biliary pancreatitis), and LIFESPAN (lifestyle, prevention, and risk of AP).

From June 2012 to September 2017, 1435 adult patients with AP from 28 community and university hospitals were prospectively enrolled (**Supplementary Appendix S1**). Demographic and anthropometric data; history of HL, HT, and DM; previous medical therapy and etiology; severity; local and systemic complications; and mortality of AP were collected.

In this study, we aimed to maximize the number of cases for each individual effect analysis. We had information concerning OB from 1257 cases, HT from 1127 cases, DM from 1257 cases, and HL from 1036 cases. Patients were grouped based on the World Health Organization (WHO) classification of BMI ($\geq$30 or $<$30 kg/m^2) and the presence or absence of three other components, HT, HL, and DM. However, in the "joint effect analysis," we only included cases where data from all four components of

MetS, OB, HL, HT, and DM were available (906 cases). We conducted an additional analysis to confirm that the cohorts noted above represent the total cohort of 1435 cases. Importantly, there were no significant differences in demographics or the main outcome parameters between the cohorts (**Supplementary Appendix S2**).

Data were collected by treating physicians with the help of trained and experienced study administrators on the basis of a standardized case report form and protocol in the prospective APR. Accuracy of data recorded is secured by a four-level quality check system involving both medical administrative personnel and gastroenterologists. Data quality is presented in **Supplementary Appendix S3**. The study protocol was approved by the Scientific and Research Ethics Committee of the Medical Research Council (22254-1/2012/EKU). All patients provided written informed consent to participate in the registry.

Definitions

Diagnosis of AP was made according to the recommendations in the IAP/APA guidelines. At least two criteria of the following three were present: upper abdominal pain, pancreatic enzyme levels exceeding more than three times the upper normal level, and features of pancreatitis on imaging (Working Group Iap/Apa Acute Pancreatitis Guidelines, 2013). Severity and complications of AP were determined according to the revised Atlanta classification (Banks et al., 2013). OB was determined if BMI was $\geq$30 kg/m^2 (Jensen et al., 2014). HT was determined if blood pressure was $\geq$140/90 mmHg or if the patient was on anti-hypertensive medication. HL was defined by the presence of either hypercholesterolemia or a low level of HDL or HTG. The condition was regarded as HL when fasting cholesterol level >200 mg/dL (5.2 mmol/L), HDL < 44 mg/dL (1.15 mmol/L; female) or <35 mg/dL (0.9 mmol/L; male), triglyceride level exceeded 150 mg/dL (1.7 mmol/L), or the patient was receiving drug therapy for HL. The diagnosis of DM was made in accordance with the American Diabetes Association Criteria (American Diabetes Association, 2010) or if the patient was receiving drug therapy for hyperglycemia.

The primary endpoints were mortality, severity, and complications of AP and LOS.

Statistical Analyses

Case numbers and percentages were calculated for categorical variables, mean with *SD*, and medians with 25 and 75% quartiles (Q1 and Q3, respectively) and ranges were computed for numerical variables in descriptive analysis.

The *t*-test was used for normally distributed data and the Mann–Whitney *U*-test for non-normally distributed data to compare two groups of independent samples. The relation between categorical variables was inspected by the Chi-square test and *Z*-test with the Bonferroni correction and ORs with 95% CIs.

Logistic regression was used to define the independent effect of the MetS factors and age. A two-sided *p*-value of <0.05 was regarded as statistically significant. The available-case analysis was used for missing data. Statistical analyses were performed with SPSS 25.0 software (IBM Corporation).

RESULTS

Individual Effect Analysis

A total of 1257 patients (mean age ± *SD*: 55.7 ± 17.0 years, males vs. females: 57.1 vs. 42.9%) were recruited for the "individual effect analysis." 371 patients (29.5%) had OB, 676 (60.0%) had HT, 349 (33.7%) had HL, and 206 (16.4%) had DM (**Table 1**).

The major etiologies of AP were biliary stones in 37.8% of the cases of the total cohort, alcohol in 18.5%, and HL in 3.7%. OB increased the risk of biliary etiology [OR: 2.06 (CI: 1.61–2.64)]. Meanwhile, HTG-induced AP was more frequent in the presence of HL (12.9 vs. 0.1%, $p < 0.001$) compared to the non-HL group and in the presence of DM compared to the non-DM patient group [OR: 2.34 (CI: 1.39–4.00)], respectively (**Table 1**).

Obesity (Figure 1)

Obesity was less common in males [OR: 0.75 (CI: 0.58–0.95)]. There was no difference between the ages of the OB and non-OB groups (56.3 ± 15.2 vs. 55.4 ± 17.7, $p = 0.398$), although the age distribution showed a larger proportion of obese patients in the older age groups.

Obesity increased the risk of severe AP [OR: 2.15 (CI: 1.31–3.54)] but showed no relation to the mortality rate [OR: 1.39 (CI: 0.66–2.96)]. OB did not influence the incidence of local complications (**Figure 2F**) but increased the risk of systemic complications [OR: 1.99 (CI: 1.30–3.05)], and respiratory [OR: 2.15 (CI: 1.26–3.65)] and renal [OR: 4.56 (CI: 2.23–9.32)] failure in AP. Obese patients spent a longer time in the hospital (12.1 vs. 10.4 days, $p = 0.008$) (**Figure 2G**).

Independent effect

Logistic regression revealed that OB was an independent predictive factor for renal failure [OR: 2.98 (CI: 1.33–6.66)] (**Table 2**).

Hypertension (Figure 2)

Patients with HT were 17.6 years older on average (63.8 ± 14.1 vs. 46.2 ± 15.2, $p < 0.001$). Male gender was associated with a lower risk of HT [OR: 0.66 (CI: 0.52–0.84)].

Hypertension increased the risks of severe AP [OR: 2.39 (CI: 1.30–4.38)], systemic complications [OR: 2.83 (CI: 1.64–4.88)], and respiratory [OR: 3.14 (CI: 1.51–6.52)], heart [OR: 3.82 (CI: 1.11–13.11)], and renal failure [OR: 6.40 (CI: 1.93–21.17)]. HT was also associated with longer hospitalization (11.8 vs. 10.5 days, $p = 0.020$) (**Figure 3E**).

Independent effect

Logistic regression revealed that HT was a predictive factor for severity [OR: 3.41 (CI: 1.39–8.37)], systemic complications [OR: 2.64 (CI: 1.27–5.51)], and renal failure [OR: 7.46 (CI: 1.61–34.49)] as well (**Table 2**).

Hyperlipidemia (Figure 3)

Contrary to OB and HT, HL was associated with younger age (54.0 ± 14.5 vs. 56.4 ± 17.8, $p = 0.032$) and a higher rate among male patients [OR: 1.47 (CI: 1.12–1.92)].

For patients with HL, the chance of having mild AP was lower [OR: 0.64 (CI: 0.49–0.85)], but HL had no significant effect

TABLE 1 | Individual effect analysis.

	Total cohort	Obesity (*n* = 1257)		Hypertension (*n* = 1127)		Hyperlipidemia (*n* = 1036)		Diabetes mellitus (*n* = 1257)	
		Non-OB	OB	Non-HT	HT	Non-HL	HL	Non-DM	DM
n	1257	886	371	451	676	687	349	1051	206
% within groups		70.5	29.5	40.0	60.0	66.3	33.7	83.6	16.4
Age, sex, CCI									
Average age	55.7	55.4	56.3	**46.2**	**63.8***	**56.4**	**54.0***	**54.5**	**61.7***
SD (average age)	17.0	17.7	15.2	15.2	14.1	17.8	14.5	17.3	13.9
Male (%)	57.1	59.3	52.0	61.9	51.8	**55.6**	**64.8***	56.4	60.7
Female (%)	42.9	**40.7**	**48.0***	**38.1**	**48.2***	44.4	35.2	43.6	39.3
Average CCI	1.4	1.3	1.6	0.9	1.7	1.3	1.7	1.0	2.9
SD (CCI)	1.6	1.6	1.7	1.4	1.7	1.6	1.8	1.4	1.7
Etiology (%)									
Biliary	37.8	**33.6**	**47.7***	31.3	44.1	41.3	26.4	38.2	35.9
Alcoholic	18.5	21.1	12.1	20.2	12.4	21.4	17.2	19.0	15.5
HTG-induced	3.7	3.0	5.4	3.3	3.7	**0.1**	**12.9***	**2.8**	**8.7***
Alcoholic + HTG-induced	1.8	1.9	1.6	1.6	1.9	0.0	6.6	1.8	1.9
Post-ERCP	2.6	3.0	1.6	3.1	2.8	2.9	0.9	2.6	2.9
Combined	8.0	7.1	10.0	11.1	7.0	7.7	7.2	7.9	8.3
Idiopathic	20.5	22.0	17.0	21.5	20.7	18.8	23.8	20.6	20.4
Other	7.1	8.1	4.6	8.0	7.4	7.7	5.2	7.2	6.3
Severity, mortality, LOS									
Mild (%)	69.6	69.9	69.0	70.1	69.5	**73.5**	**64.2***	69.7	68.9
Moderate (%)	25.1	26.1	22.6	26.8	23.4	22.1	29.5	24.9	25.7
Severe (%)	5.3	**4.1**	**8.4***	**3.1**	**7.1***	4.4	6.3	5.3	5.3
Mortality (%)	2.4	2.1	3.0	1.3	3.1	2.3	1.4	2.5	1.9
Average LOS	10.9	**10.4**	**12.1***	**10.5**	**11.8***	10.5	11.4	10.7	11.8
SD (LOS)	9.3	8.6	10.6	7.9	10.1	9.0	10.3	9.0	10.6
Complications (%)									
Local complications	29.0	28.6	30.2	29.5	28.3	**25.3**	**34.7***	29.1	28.6
Fluid collection	25.0	24.7	26.7	23.9	25.3	**22.1**	**29.8***	24.9	27.2
Pseudocyst	7.6	7.8	7.3	6.9	9.3	**6.0**	**10.6***	7.6	7.8
Necrosis	8.0	7.1	10.2	7.8	8.0	8.2	8.9	8.3	6.8
New onset diabetes	3.8	3.5	4.6	2.7	4.1	3.6	5.2	4.6	N/A
Systemic complications	7.6	**6.0**	**11.3***	**3.8**	**10.1***	6.6	9.5	7.0	10.2
Respiratory failure	4.6	**3.5**	**7.3***	**2.0**	**6.1***	4.5	4.9	4.1	7.3
Heart failure	1.8	1.4	3.0	**0.7**	**2.5***	1.9	2.0	1.9	1.5
Renal failure	2.7	**1.4**	**5.9***	**0.7**	**4.1***	**2.2**	**4.6***	2.8	2.4

Description of the study population. Demography, etiology, and outcome of AP. Significantly different values are marked in bold digits with an asterisk. Statistical analysis is summarized in ***Supplementary Appendix S4****.*

on mortality. HL increased the risk of local complications [OR: 1.55 (CI: 1.17–2.05)], and, within local complications, acute fluid collections and pseudocyst formation were more frequent [OR: 1.48 (CI: 1.11–1.99); OR: 1.81 (CI: 1.14–2.88), respectively]. HL also increased the risk of renal failure [OR: 2.17 (CI: 1.06–4.43)].

Independent effect

Logistic regression revealed that HL was an independent predictive factor for local complications [OR: 1.51 (CI: 1.10–2.07)] and for a new diagnosis of DM [OR: 2.55 (CI: 1.26–5.19)] (**Table 2**).

Diabetes Mellitus (Figure 4)

Patients with DM were older (61.7 ± 13.9 vs. 54.5 ± 17.3, $p < 0.001$), while there was no difference in the gender ratio between the DM and non-DM groups [OR: 1.19 (CI: 0.88–1.62)] (**Supplementary Appendix S4**). Statistical analyses demonstrated no significant relation between DM and the severity, mortality, and complications of AP.

Joint Effect Analysis

A total of 906 patients in our cohort (mean age ± *SD*: 56.9 ± 16.7 years, males vs. females: 57.3 vs. 42.7%) were eligible for the "joint effect analysis." 189 patients (20.9%) had no components of MetS, 294 (32.5%) had OB, 560 (61.8%) had HT, 316 (34.9%) had HL, and 162 (17.9%) had DM. We formed groups of patients according to the factor combinations they had and compared the outcome parameters between the different factor combinations and the group of no MetS factors

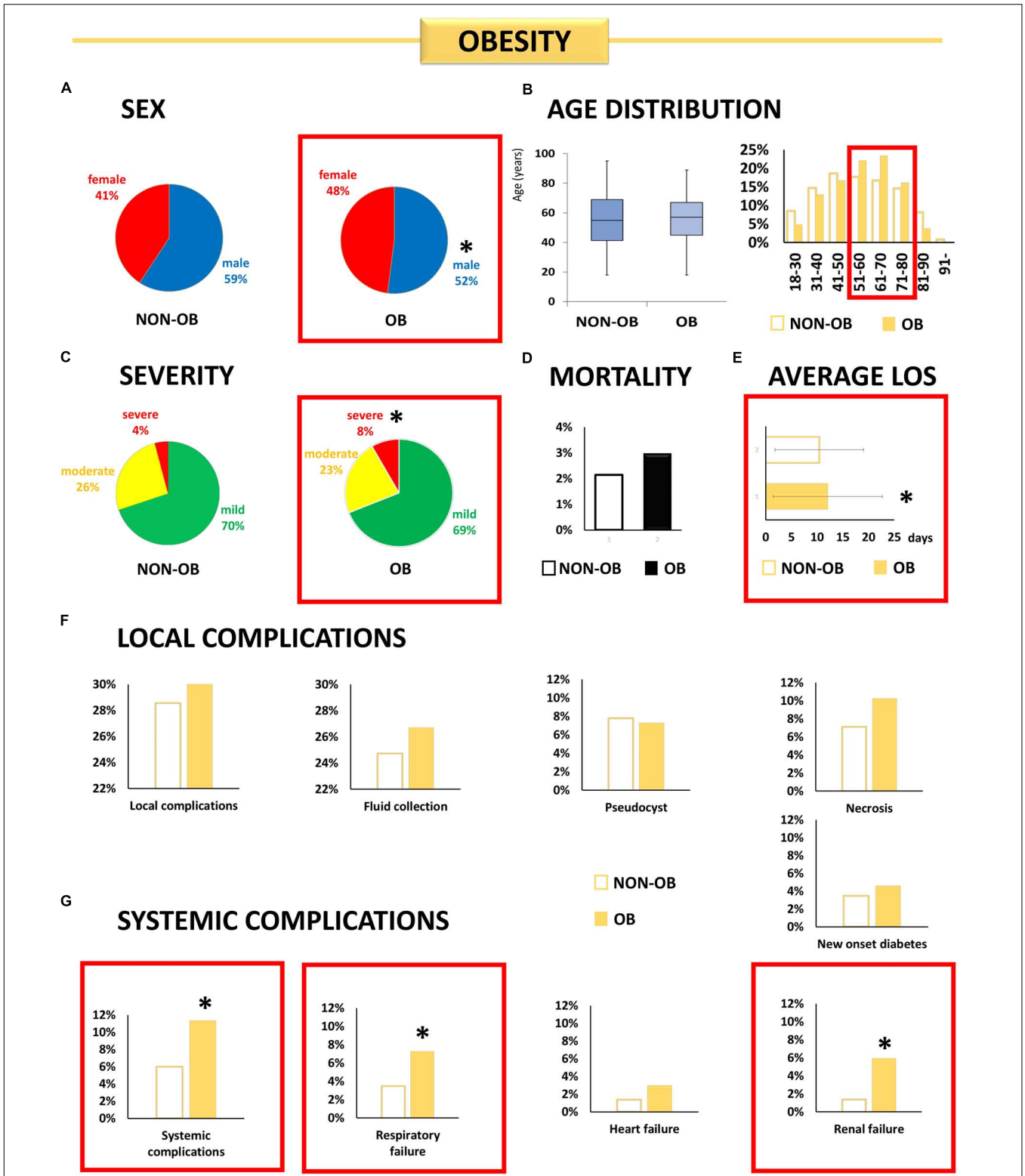


FIGURE 1 | Individual effect analysis. OB and the outcome of AP. **(A)** The share of male patients was lower in the OB group [*OR: 0.75 (CI: 0.58–0.95)]. **(B)** There is no difference in the average age between the OB and non-OB groups ($p = 0.398$). **(C)** Obese patients have more than double the risk of severe AP [*OR: 2.15 (CI: 1.31–3.54)]. **(D)** Obese patients did not have a higher risk of mortality. **(E)** Obese patients spent more time in the hospital (*$p = 0.008$). **(F)** More local complications were observed in the OB group, although the difference was not significant. **(G)** Obese patients had a higher risk of systemic complications [*OR: 1.99 (CI: 1.30–3.05)], respiratory failure [*OR: 2.15 (CI: 1.26–3.65)], and renal failure [*OR: 4.56 (CI: 2.23–9.32)].

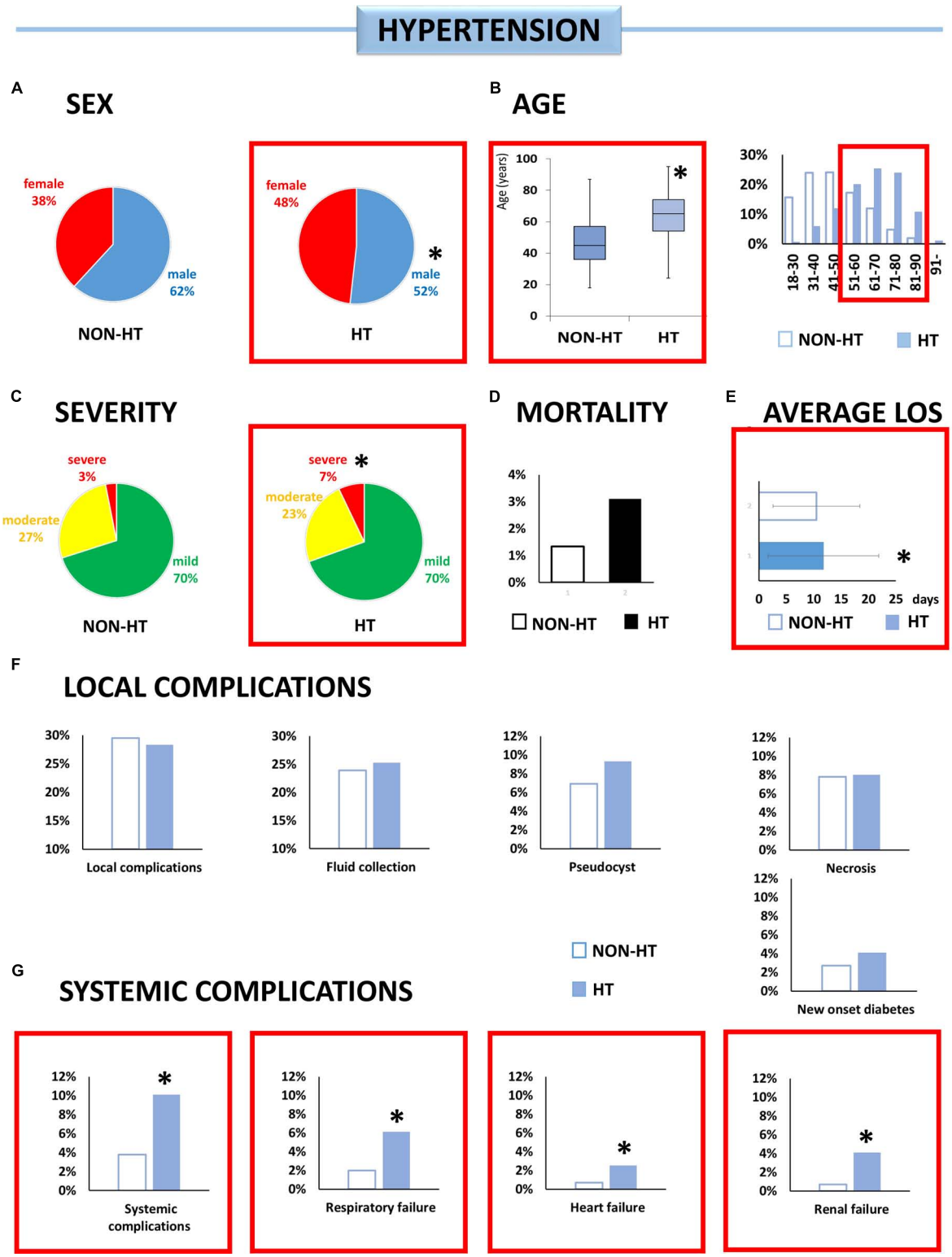


FIGURE 2 | Individual effect analysis. HT and the outcome of AP. **(A)** There are fewer male patients with HT [*OR: 0.66 (CI: 0.52–0.84)]. **(B)** Patients with HT are older than patients without it (*$p < 0.001$). **(C)** Hypertensive patients have more than double the risk of the severe form of AP [*OR: 2.39 (CI: 1.30–4.38)]. **(D)** The risk of mortality was not higher in the HT group. **(E)** Patients with HT spent more time in the hospital (*$p = 0.020$). **(F)** There was a higher incidence of fluid collection, pseudocysts, and new onset diabetes, although the difference was not significant. **(G)** Hypertensive patients have a higher risk of systemic complications [*OR: 2.83 (CI: 1.64–4.88)], respiratory failure [*OR: 3.14 (CI: 1.51–6.52)], heart failure [*OR: 3.82 CI: (1.11–13.11)], and renal failure [*OR: 6.40 (CI: 1.93–21.17)].

TABLE 2A | Independent effect of components of MetS, including age, in the logistic regression.

MetS component	Outcome parameter	OR	95% CI
	Severity	1.38	0.73–2.58
	Mortality	1.06	0.38–2.96
	Local complications	0.99	0.72–1.37
	Fluid collection	1.05	0.75–1.48
	Pseudocyst	0.85	0.50–1.44
OB	Necrosis	1.48	0.89–2.45
	New onset of diabetes	1.52	0.73–3.14
	Systemic complication	1.35	0.79–2.30
	Respiratory failure	1.52	0.77–3.02
	Heart failure	2.45	0.88–6.78
	Renal failure	**2.98**	**1.33–6.66**
	Severity	**3.41**	**1.39–8.37**
	Mortality	4.50	0.91–22.20
	Local complications	1.22	0.85–1.75
	Fluid collection	1.42	0.97–2.08
	Pseudocyst	1.55	0.85–2.81
HT	Necrosis	1.36	0.76–2.43
	New onset of diabetes	1.56	0.66–3.65
	Systemic complication	**2.64**	**1.27–5.51**
	Respiratory failure	1.59	0.63–4.00
	Heart failure	1.41	0.36–5.54
	Renal failure	**7.46**	**1.61–34.49**
	Severity	1.40	0.73–2.67
	Mortality	0.61	0.19–2.00
	Local complications	**1.51**	**1.10–2.07**
	Fluid collection	1.32	0.94–1.84
	Pseudocyst	1.58	0.95–2.61
HL	Necrosis	1.06	0.63–1.78
	New onset of diabetes	**2.55**	**1.26–5.19**
	Systemic complication	1.34	0.77–2.32
	Respiratory failure	0.90	0.43–1.90
	Heart failure	1.59	0.54–4.67
	Renal failure	1.93	0.85–4.38
	Severity	0.48	0.20–1.16
	Mortality	0.46	0.10–2.14
	Local complications	0.84	0.56–1.28
	Fluid collection	1.02	0.67–1.56
	Pseudocyst	1.01	0.53–1.91
DM	Necrosis	0.53	0.24–1.14
	New onset of diabetes	N/A	N/A
	Systemic complication	0.92	0.48–1.74
	Respiratory failure	1.48	0.68–3.20
	Heart failure	0.32	0.07–1.53
	Renal failure	0.43	0.15–1.22

OB is an independent predictive factor for renal failure; HT for severity; and systemic complications, renal failure, and hyperlipidemia for local complications and for a new diagnosis of diabetes mellitus. OR, odds ratio; CI, confidence interval. Statistically significant values (ORs with CIs) are marked in bold digits.

one by one (**Supplementary Appendix S5**). The presence of two, three, or four MetS factors significantly increased the rate of worse outcome parameters by 9.5, 24.1, and 66.7%, respectively (**Figure 5**).

TABLE 2B | Logistic regression.

	Severity	1.01	0.99–1.03
	Mortality	1.02	0.98–1.05
	Local complications	0.99	0.98–1.00
	Fluid collection	0.99	0.98–1.00
	Pseudocyst	1.00	0.98–1.01
Age	Necrosis	0.99	0.97–1.00
	New onset of diabetes	1.01	0.99–1.04
	Systemic complication	1.01	0.99–1.03
	Respiratory failure	**1.03**	**1.01–1.06**
	Heart failure	**1.05**	**1.01–1.09**
	Renal failure	1.00	0.97–1.03

Older age was demonstrated to be independently associated with respiratory and heart failure in our study. Statistically significant values (ORs with CIs) are marked in bold digits.

DISCUSSION

Summary of Findings

Our results demonstrated in a large database of prospectively collected cases that the components of MetS deteriorate the outcome of AP. OB was shown to be an independent risk factor for renal failure and was associated with a longer hospital stay. HT was proved to be an independent risk factor for severity of AP and increased the risk of renal failure, while patients with HT spent a longer time in hospital. HL increased the risk of local complications, renal failure, and the new diagnosis of DM. Preexisting DM did not change the outcome of AP. Our study demonstrated that the more components of MetS the patients had, the higher the rate of worse outcome parameters was observed.

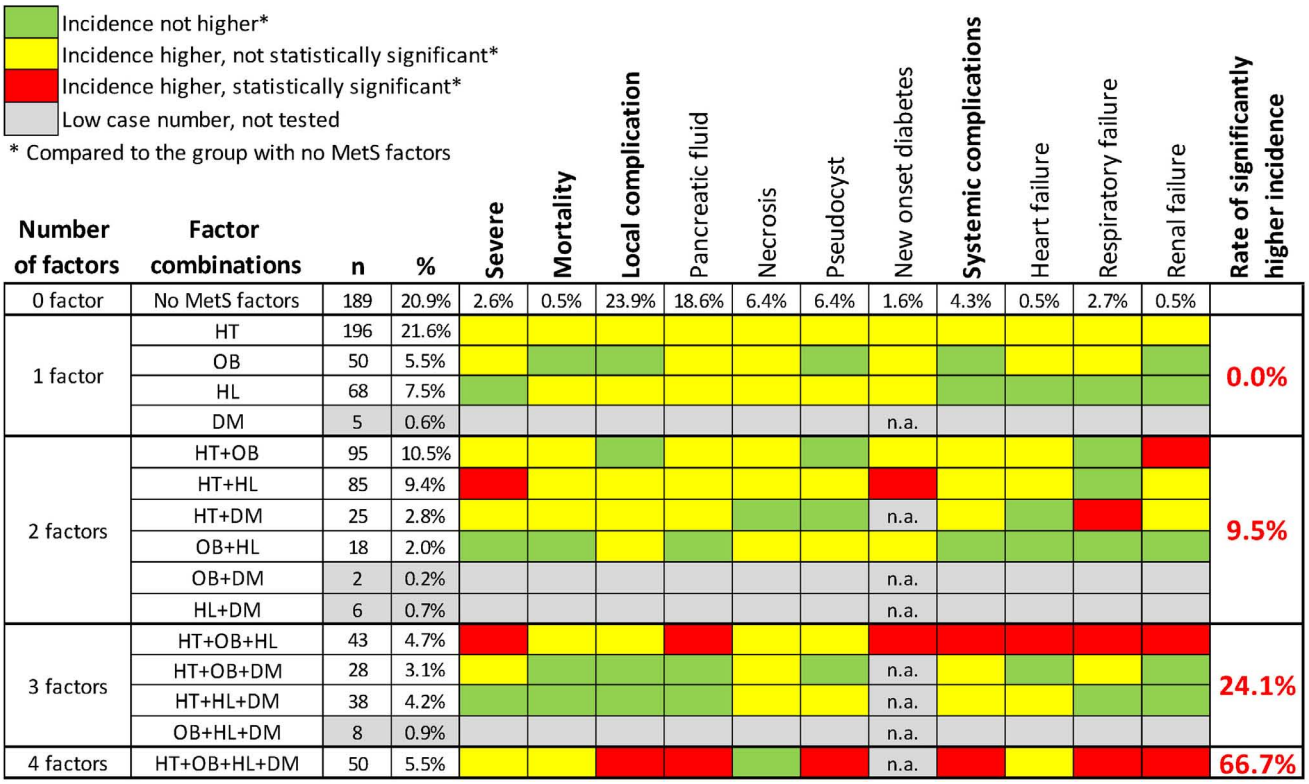
The incidence of AP is increasing, and this is partly due to the rising prevalence of OB, which stimulates gallstone formation and increases HL, both causing AP (Yadav and Lowenfels, 2013; Bonfrate et al., 2014). Indeed, biliary AP was more frequent in obese patients compared to the total cohort in our study.

To date, several cohort studies and a systematic review have reported that OB increases the severity, mortality, and occurrence of local and systemic complications in AP. However, these results are conflicting on the link between OB and outcomes in AP (Dobszai et al., 2019). The reason behind this conflict may be that most of the included studies reported unadjusted analysis; therefore, it cannot be clarified whether OB is an independent prognostic factor in AP or not (Dobszai et al., 2019). In a recent individual patient data meta-analysis, where confounders were adjusted, OB was independently associated with the development of organ failure and multiple organ failure in AP; however, there was no relation between OB and mortality, necrosis, and intervention (Premkumar et al., 2015). These data are in agreement with our results, where OB was demonstrated to be an independent predictive factor for renal failure but did not modify the mortality rate (**Table 2**).

A possible mechanism by which OB is associated with a higher risk of renal failure is lipotoxicity.

FIGURE 3 | Individual effect analysis. HL and the outcome of AP. **(A)** There are more male patients with HL [*OR: 1.47 (CI: 1.12–1.92)]. **(B)** Patients with HL are younger than patients without it (*$p < 0.001$). **(C)** Hyperlipidemic patients have a lower chance of having mild AP [*OR: 0.65 (CI: 0.49–0.85)]. **(D)** Patients with HL did not have a higher risk of mortality. **(E)** Patients with HL spent more time in the hospital (*$p = 0.053$). **(F)** HL increases the risk of local complications [*OR: 1.55 (CI: 1.17–2.05)], acute fluid collection [*OR 1.48 (CI: 1.11–1.99)], and pseudocysts [*OR 1.81 (CI: 1.14–2.88)]. **(G)** Hyperlipidemic patients have a higher risk of renal failure [*OR 2.17 (CI: 1.51–4.43)].

FIGURE 4 | Individual effect analysis. DM and the outcome of AP. **(A)** There is no significant difference in sex between the two groups. **(B)** Patients with diabetes are older than patients without it (*$p < 0.001$). **(C,D)** Diabetic patients did not have a higher risk of moderately severe or severe AP or mortality in our cohort. **(E)** There is no difference in LOS between the two groups ($p = 0.139$). **(F,G)** As regards local or systemic complications, there are no differences between diabetic and non-diabetic patients in our cohort.



Number of factors	Factor combinations	n	%	Severe	Mortality	Local complication	Pancreatic fluid	Necrosis	Pseudocyst	New onset diabetes	Systemic complications	Heart failure	Respiratory failure	Renal failure	Rate of significantly higher incidence
0 factor	No MetS factors	189	20.9%	2.6%	0.5%	23.9%	18.6%	6.4%	6.4%	1.6%	4.3%	0.5%	2.7%	0.5%	
1 factor	HT	196	21.6%												0.0%
	OB	50	5.5%												
	HL	68	7.5%												
	DM	5	0.6%							n.a.					
2 factors	HT+OB	95	10.5%												9.5%
	HT+HL	85	9.4%												
	HT+DM	25	2.8%							n.a.					
	OB+HL	18	2.0%												
	OB+DM	2	0.2%							n.a.					
	HL+DM	6	0.7%							n.a.					
3 factors	HT+OB+HL	43	4.7%												24.1%
	HT+OB+DM	28	3.1%							n.a.					
	HT+HL+DM	38	4.2%							n.a.					
	OB+HL+DM	8	0.9%							n.a.					
4 factors	HT+OB+HL+DM	50	5.5%							n.a.					66.7%

FIGURE 5 | Joint effect analysis. The effect of MetS factor combinations on the outcome of AP. The more MetS factors are present, the more significantly higher incidence of the different outcome parameters can be observed. Statistical analysis is summarized in **Supplementary Appendix S5**.

Obesity is associated with elevated levels of intrapancreatic fat and with elevated visceral fat surrounding the pancreas (Smeets et al., 2019). This hypothesis is also supported by experimental data. A long-term high-fat diet caused acinar cell injury and pancreatic fibrosis via fat accumulation in pancreatic acinar cells (Matsuda et al., 2014). It has also been suggested that intrapancreatic fat, which may cause metabolic and inflammatory processes, is associated with OB (Majumder et al., 2017). In addition, in the presence of intrapancreatic fat, pancreatic lipases are released in AP digest adipocytes, resulting in an outflow of unsaturated fatty acids into the circulation; they are toxic and can act as proinflammatory mediators and are implicated in the development of systemic inflammation and organ failure (Navina et al., 2011).

Hypertension was independently associated with the severity of AP and the rate of renal failure in our study. To the best of our knowledge, no study has ever analyzed the effect of arterial HT on the outcome of AP. The underlying mechanisms by which HT deteriorates the outcome of AP is unclear. It has been suggested that the sympathetic nervous system may act as an amplifier of the blood pressure elevation and may be involved in the development of HT-related complications. Sympathetic activation favors the development and progression of vascular hypertrophy and remodeling and contributes to impairing arterial distensibility and vascular compliance (Seravalle et al., 2014). The presence of a hyperadrenergic state and microvascular and macrovascular structural changes in the arteries may be responsible for the deteriorative effects of HT (Smits and van Geenen, 2011).

Preexisting HL was shown to be independently associated with local complications and renal failure in our study. Our results are in line with those of a recent meta-analysis, which reported that the presence of HTG significantly elevated the risk of renal failure but did not increase the risk of mortality in AP (Kiss et al., 2018). However, HTG also significantly elevated the risk of severe AP in this meta-analysis (Kiss et al., 2018), while HL did not increase the risk of severe AP in our study. This discrepancy can be explained by the fact that (1) most of the studies included in the meta-analysis reported an unadjusted analysis, and, therefore, the independent effect of HTG in AP cannot be elucidated; and (2) the HL group in our study included patients with either hypercholesterinemia and/or HTG, while patients with HTG only were included in the meta-analysis. One possible mechanism by which HL increases local and systemic complications in AP is the formation and toxic effect of unsaturated fatty acid by pancreatic lipases. In addition, in the case of HTG, the chylomicron concentration is elevated. As a result, blood viscosity increases, thus impairing blood flow and causing pancreatic ischemia and acidosis (Pedersen et al., 2016).

There is a special relationship between the exocrine and endocrine pancreas. Experimental data suggest that insulin has

a local protective effect on acinar cells during pancreatitis. Pancreatitis evoked by L-arginine causes severe acinar cell necrosis in most of the territory of the exocrine pancreas. However, acinar cells located around the islets of Langerhans remain totally intact (Hegyi et al., 1997). In addition, we also confirmed that if the beta cells are destroyed by streptozotocin treatment prior to the induction of AP, this locally visible protective effect disappears irrespectively of exogenous insulin administration (Takacs et al., 2001). Unfortunately, in our registry analysis, we could not investigate the local effects of insulin. Here we showed that preexisting DM does not significantly influence severity, mortality, or rate of complications in AP in our cohort. We hypothesized that our cohort was not sufficiently large to determine a significant difference. We have recently published a meta-analysis in which DM significantly elevated both local and systemic complications when an analysis was conducted of 354,880 cases (Miko et al., 2018). However, it is clearly impossible to collect this number of patients in a single cohort. Furthermore, intensive care unit mortality only grew significantly with higher mean blood glucose concentration in non-DM patients but not in DM patients (Egi et al., 2008; Pedersen et al., 2016). In agreement with our results, critically ill patients with DM did not have higher mortality compared to non-DM patients (Whitcomb et al., 2005).

Older age was demonstrated to be independently associated with pulmonary and heart failure in our study (**Table 2B**). Older age has been investigated extensively as a marker of severity and mortality in AP and is included in the APACHE II score, Ranson score, Bedside Index of Severity in AP (BISAP) score, and Japanese Severity Score (JSS) as a marker of severity (Graham et al., 2010). However, after adjusting for comorbid disease, only the very extreme age (>85 years old) was associated with 30-day in-patient mortality and persistent organ failure in a recent prospective, multicenter study (Mounzer et al., 2012). Our results are in line with a recent cohort analysis that found that elderly patients had a significantly higher risk of developing systemic complications, while high mortality in this group is due to the effect of severe comorbidities (Szakacs et al., 2018).

Patients with AP often develop diabetes during and after the attack of AP (Moran et al., 2018); however, the risk of DM was not fully evaluated. The severity of AP, its etiology, and individuals' age and sex had a minimal effect on the development of newly diagnosed diabetes in AP (Moran et al., 2018). We showed that HL is an independent risk factor for the development of newly diagnosed DM in AP. High cholesterol and triglyceride levels increase the risk of DM, a finding supported by earlier studies (von Eckardstein and Sibler, 2011; Das et al., 2014). We can hypothesize that the predisposition to DM caused by dyslipidemia was manifested during AP. This finding emphasizes the need for a thorough screening for DM in AP patients with HL. Moreover, all AP patients should be followed and screened for DM as hyperglycemia stimulates the proliferation of pancreatic stellate cells and collagen secretion, while hypoinsulinemia inhibits acinar cell growth and synthesis of pancreatic enzymes and therefore facilitates fibrosis of the pancreas and might cause chronic pancreatitis (Czako et al., 2009).

Strengths and Limitations

The main strength of the present study is that it has a large sample size of prospectively collected cases from hospitals in multiple countries, including tertiary and non-tertiary centers. Furthermore, a logistic regression analysis was applied to control confounding variables, and the independent prognostic factors of the components of MetS were analyzed for AP. Finally, our study is the first to report the relation between the outcome of AP and the presence of arterial HT and to analyze the influence of the combined presence of the components of MetS on the outcome of AP.

The present study has limitations. First, since APR is a multicenter prospective registry and not an observational trial, our findings are affected by confounding factors or selection bias. Second, our study design is cross-sectional, thus precluding any causal interferences about the directionality of the relations observed in our study; therefore, long-term clinical outcomes could not be evaluated. Accordingly, long-term prospective trials are needed in the future. Third, our study assessed the effect of HL, not HTG, thus not fully suiting the definition of MetS. Fourth, peripancreatic fluid accumulations could not always be adequately defined according to the modified Atlanta classification. Acute fluid collection and acute necrotic fluid collection, pseudocysts, and walled-off pancreatic necrosis could not always be differentiated because abdominal CT was not performed in all cases. Therefore, peripancreatic fluid collections without a definitive wall were named as acute fluid collections and with a wall as pseudocysts.

CONCLUSION

In conclusion, the components of MetS deteriorate the outcome of AP. OB, HT, and HL are independent risk factors for a number of complications. HT is an independent risk factor for severity as well. The more elements of MetS are present, the higher the risk for complications. It is important to search for and follow up on the components of MetS in AP.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the **Supplementary Files**.

ETHICS STATEMENT

The study protocol was approved by the Scientific and Research Ethics Committee of the Medical Research Council (22254-1/2012/EKU). All patients provided written informed consent to participate in the study.

AUTHOR CONTRIBUTIONS

AS, AP, and PH contributed to the design of the research. AP, ÁV, JB, SG, PS, FI, AH, IT, HF, MP, MV, JH, JN, AM, EM, VS, LC,

and TT collected the data. AP, KM, DD, DI, and BK assessed the data quality. NG and AS processed the data and conducted the analysis. AS and PH designed the figures. AS, LC, and BE drafted the manuscript. PH supervised and coordinated the work. All the authors discussed the results and commented on the manuscript.

FUNDING

The study was funded by the Project Grants (KH125678 and K116634 to PH, K120335 to TT, and K128222 to LC); the Economic Development and Innovation Operational Programme Grant (GINOP 2.3.2-15-2016-00048 to PH); the Human Resources Development Operational Programme Grant (EFOP-3.6.2-16-2017-00006 to PH) from the National Research, Development and Innovation Office; and a Momentum Grant from the Hungarian Academy of Sciences (LP2014-10/2014 to PH).

ACKNOWLEDGMENTS

We would like to thank the contributing investigators not meeting the authorship policy. These centers are the Joint Saint Istvan and Saint Laszlo Hospitals (Budapest, Hungary), the Institute of Surgery, University of Debrecen (Debrecen, Hungary), the Bács-Kiskun County Hospital (Kecskemét, Hungary), the Healthcare Center of County Csongrád (Makó, Hungary), the Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital (Miskolc, Hungary), the Second Department of Medicine, University of Szeged (Szeged), the Department of Emergency, University of Szeged (Szeged, Hungary), the Department of Surgery, University of Szeged (Szeged, Hungary), the Department of Gastroenterology, Dr. Bugyi István Hospital (Szentes, Hungary), the Markusovszky University Teaching Hospital (Szombathely, Hungary), the Hospital of Bezmialem Vakif University, School of Medicine (Istanbul, Turkey), the Saint Luke Clinical Hospital (St. Petersburg, Russia), the Department of Gastroenterology, Vítkovická Nemocnice (Ostrava-Vítkovice, Czechia), the Gomel Regional Clinical Hospital (Gomel, Belarus), the Pauls Stradins Clinical University Hospital (Riga, Latvia), the Bogomolets National Medical University (Kiev, Ukraine), and the Keio University (Tokyo, Japan).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2019.01202/full#supplementary-material

APPENDIX S1 | Center distribution.

APPENDIX S2 | Demography and representativeness of study populations.

APPENDIX S3 | Data quality.

APPENDIX S4 | Statistics of individual effect analysis.

APPENDIX S5 | Joint effect analysis. **(A)** Description of demography and incidences of the different outcomes. **(B)** Statistics.

APPENDIX S6 | Database of the analysis.

REFERENCES

Alberti, K. G., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., et al. (2009). Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; american heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. *Circulation* 120, 1640–1645. doi: 10.1161/CIRCULATIONAHA.109.192644

American Diabetes Association (2010). Diagnosis and classification of diabetes mellitus. *Diabetes Care* 33(Suppl. 1), S62–S69. doi: 10.2337/dc10-S062

Banks, P. A., Bollen, T. L., Dervenis, C., Gooszen, H. G., Johnson, C. D., Sarr, M. G., et al. (2013). Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 62, 102–111. doi: 10.1136/gutjnl-2012-302779

Bonfrate, L., Wang, D. Q., Garruti, G., and Portincasa, P. (2014). Obesity and the risk and prognosis of gallstone disease and pancreatitis. *Best Pract. Res. Clin. Gastroenterol.* 28, 623–635. doi: 10.1016/j.bpg.2014.07.013

Czako, L., Hegyi, P., Rakonczay, Z. Jr., Wittmann, T., and Otsuki, M. (2009). Interactions between the endocrine and exocrine pancreas and their clinical relevance. *Pancreatology* 9, 351–359. doi: 10.1159/000181169

Das, S. L., Singh, P. P., Phillips, A. R., Murphy, R., Windsor, J. A., and Petrov, M. S. (2014). Newly diagnosed diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis. *Gut* 63, 818–831. doi: 10.1136/gutjnl-2013-305062

Dobszai, D., Matrai, P., Gyongyi, Z., Csupor, D., Bajor, J., Eross, B., et al. (2019). Body-mass index correlates with severity and mortality in acute pancreatitis: a meta-analysis. *World J. Gastroenterol.* 25, 729–743. doi: 10.3748/wjg.v25.i6.729

Dubravcsik, Z., Madacsy, L., Gyokeres, T., Vincze, A., Szepes, Z., Hegyi, P., et al. (2015). Preventive pancreatic stents in the management of acute biliary pancreatitis (PREPAST trial): pre-study protocol for a multicenter, prospective, randomized, interventional, controlled trial. *Pancreatology* 15, 115–123. doi: 10.1016/j.pan.2015.02.007

Egi, M., Bellomo, R., Stachowski, E., French, C. J., Hart, G. K., Hegarty, C., et al. (2008). Blood glucose concentration and outcome of critical illness: the impact of diabetes. *Crit. Care Med.* 36, 2249–2255. doi: 10.1097/CCM.0b013e318181039a

Forsmark, C. E., Vege, S. S., and Wilcox, C. M. (2016). Acute pancreatitis. *N. Engl. J. Med.* 375, 1972–1981. doi: 10.1056/NEJMra1505202

Garg, S. K., Sarvepalli, S., Campbell, J. P., Obaitan, I., Singh, D., Bazerbachi, F., et al. (2019). Incidence, admission rates, and predictors, and economic burden of adult emergency visits for acute pancreatitis: data from the national emergency department sample, 2006 to 2012. *J Clin Gastroenterol* 53, 220–225. doi: 10.1097/MCG.0000000000001030

Goodger, R. L., Asrani, V. M., Windsor, J. A., and Petrov, M. S. (2016). Impact of metabolic comorbidities on outcomes of patients with acute pancreatitis: a scoping review. *Panminerva Med.* 58, 86–93.

Graham, B. B., Keniston, A., Gajic, O., Trillo Alvarez, C. A., Medvedev, S., and Douglas, I. S. (2010). Diabetes mellitus does not adversely affect outcomes from a critical illness. *Crit. Care Med.* 38, 16–24. doi: 10.1097/CCM.0b013e3181b9eaa5

Hegyi, P., Takacs, T., Jarmay, K., Nagy, I., Czako, L., and Lonovics, J. (1997). Spontaneous and cholecystokinin-octapeptide-promoted regeneration of the pancreas following L-arginine-induced pancreatitis in rat. *Int. J. Pancreatol.* 22, 193–200. doi: 10.1007/BF02788384

Hritz, I., and Hegyi, P. (2015). Early achievable severity (EASY) index for simple and accurate expedite risk stratification in acute pancreatitis. *J. Gastrointestin. Liver Dis.* 24, 177–182. doi: 10.15403/jgld.2014.1121.242.easy

Isomaa, B., Almgren, P., Tuomi, T., Forsen, B., Lahti, K., Nissen, M., et al. (2001). Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24, 683–689.

Jensen, M. D., Ryan, D. H., Apovian, C. M., Ard, J. D., Comuzzie, A. G., Donato, K. A., et al. (2014). 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J. Am. Coll. Cardiol.* 63(25 Pt B), 2985–3023. doi: 10.1016/j.jacc.2013.11.004

Kiss, L., Fur, G., Matrai, P., Hegyi, P., Ivany, E., Cazacu, I. M., et al. (2018). The effect of serum triglyceride concentration on the outcome of acute pancreatitis: systematic review and meta-analysis. *Sci. Rep.* 8:14096. doi: 10.1038/s41598-018-32337-x

Majumder, S., Philip, N. A., Takahashi, N., Levy, M. J., Singh, V. P., and Chari, S. T. (2017). Fatty pancreas: should we be concerned? *Pancreas* 46, 1251–1258. doi: 10.1097/MPA.0000000000000941

Marta, K., Szabo, A. N., Pecsi, D., Varju, P., Bajor, J., Godi, S., et al. (2017). High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): protocol of a multicentre randomised double-blind clinical trial. *BMJ Open* 7:e015874. doi: 10.1136/bmjopen-2017-015874

Matsuda, A., Makino, N., Tozawa, T., Shirahata, N., Honda, T., Ikeda, Y., et al. (2014). Pancreatic fat accumulation, fibrosis, and acinar cell injury in the Zucker diabetic fatty rat fed a chronic high-fat diet. *Pancreas* 43, 735–743. doi: 10.1097/MPA.0000000000000129

Miko, A., Farkas, N., Garami, A., Szabo, I., Vincze, A., Veres, G., et al. (2018). Preexisting diabetes elevates risk of local and systemic complications in acute pancreatitis: systematic review and meta-analysis. *Pancreas* 47, 917–923. doi: 10.1097/MPA.0000000000001122

Mikolasevic, I., Milic, S., Orlic, L., Poropat, G., Jakopcic, I., Franjic, N., et al. (2016). Metabolic syndrome and acute pancreatitis. *Eur. J. Intern. Med.* 32, 79–83. doi: 10.1016/j.ejim.2016.04.004

Moran, R. A., Garcia-Rayado, G., de la Iglesia-Garcia, D., Martinez-Moneo, E., Fort-Martorell, E., Lauret-Brana, E., et al. (2018). Influence of age, body mass index and comorbidity on major outcomes in acute pancreatitis, a prospective nation-wide multicentre study. *United European Gastroenterol. J.* 6, 1508–1518. doi: 10.1177/2050640618798155

Mounzer, R., Langmead, C. J., Wu, B. U., Evans, A. C., Bishehsari, F., Muddana, V., et al. (2012). Comparison of existing clinical scoring systems to predict persistent organ failure in patients with acute pancreatitis. *Gastroenterology* 142, 1476–1482. doi: 10.1053/j.gastro.2012.03.005

Navina, S., Acharya, C., DeLany, J. P., Orlichenko, L. S., Baty, C. J., Shiva, S. S., et al. (2011). Lipotoxicity causes multisystem organ failure and exacerbates acute pancreatitis in obesity. *Sci. Transl. Med.* 3:107ra110. doi: 10.1126/scitranslmed.3002573

Parniczky, A., Mosztbacher, D., Zsoldos, F., Toth, A., Lasztity, N., Hegyi, P., et al. (2016). Analysis of pediatric pancreatitis (APPLE Trial): pre-study protocol of a multinational prospective clinical trial. *Digestion* 93, 105–110. doi: 10.1159/000441353

Pedersen, S. B., Langsted, A., and Nordestgaard, B. G. (2016). Nonfasting mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis. *JAMA Intern Med* 176, 1834–1842. doi: 10.1001/jamainternmed.2016.6875

Premkumar, R., Phillips, A. R., Petrov, M. S., and Windsor, J. A. (2015). The clinical relevance of obesity in acute pancreatitis: targeted systematic reviews. *Pancreatology* 15, 25–33. doi: 10.1016/j.pan.2014.10.007

Sawalhi, S., Al-Maramhy, H., Abdelrahman, A. I., Allah, S. E., and Al-Jubori, S. (2014). Does the presence of obesity and/or metabolic syndrome affect the course of acute pancreatitis: a prospective study. *Pancreas* 43, 565–570. doi: 10.1097/MPA.0000000000000028

Seravalle, G., Mancia, G., and Grassi, G. (2014). Role of the sympathetic nervous system in hypertension and hypertension-related cardiovascular disease. *High Blood Press. Cardiovasc. Prev.* 21, 89–105. doi: 10.1007/s40292-014-0056-1

Smeets, X., Knoester, I., Grooteman, K. V., Singh, V. K., Banks, P. A., Papachristou, G. I., et al. (2019). The association between obesity and outcomes in acute pancreatitis: an individual patient data meta-analysis. *Eur. J. Gastroenterol. Hepatol.* 31, 316–322. doi: 10.1097/MEG.0000000000001300

Smits, M. M., and van Geenen, E. J. (2011). The clinical significance of pancreatic steatosis. *Nat. Rev. Gastroenterol. Hepatol.* 8, 169–177. doi: 10.1038/nrgastro.2011.4

Szakacs, Z., Gede, N., Pecsi, D., Izbeki, F., Papp, M., Kovacs, G., et al. (2018). Aging and comorbidities in acute pancreatitis II.: a cohort-analysis of 1203 prospectively collected cases. *Front. Physiol.* 9:1776. doi: 10.3389/fphys.2018.01776

Takacs, T., Hegyi, P., Jarmay, K., Czako, L., Gog, C., Rakonczay, Z. Jr., et al. (2001). Cholecystokinin fails to promote pancreatic regeneration in diabetic rats following the induction of experimental pancreatitis. *Pharmacol. Res.* 44, 363–372. doi: 10.1006/phrs.2001.0843

von Eckardstein, A., and Sibler, R. A. (2011). Possible contributions of lipoproteins and cholesterol to the pathogenesis of diabetes mellitus type 2. *Curr. Opin. Lipidol.* 22, 26–32. doi: 10.1097/MOL.0b013e3283412279

Whitcomb, B. W., Pradhan, E. K., Pittas, A. G., Roghmann, M. C., and Perencevich, E. N. (2005). Impact of admission hyperglycemia on hospital mortality in various intensive care unit populations. *Crit. Care Med.* 33, 2772–2777.

Working Group Iap/Apa Acute Pancreatitis Guidelines (2013). IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 13(4 Suppl. 2), e1–e15. doi: 10.1016/j.pan.2013.07.063

Yadav, D., and Lowenfels, A. B. (2013). The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* 144, 1252–1261. doi: 10.1053/j.gastro.2013.01.068

Yang, L., He, Z., Tang, X., and Liu, J. (2013). Type 2 diabetes mellitus and the risk of acute pancreatitis: a meta-analysis. *Eur. J. Gastroenterol. Hepatol.* 25, 225–231. doi: 10.1097/MEG.0b013e32835af154

Zsoldos, F., Parniczky, A., Mosztbacher, D., Toth, A., Lasztity, N., Hegyi, P., et al. (2016). Pain in the early phase of pediatric pancreatitis (PINEAPPLE Trial): pre-study protocol of a multinational prospective clinical trial. *Digestion* 93, 121–126. doi: 10.1159/000441352

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.