EVIDENCE-BASED MANAGEMENT OF ACUTE PANCREATITIS

PhD Thesis

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2. List of abbreviations

AB: antibiotic
ANC: acute necrotizing collection
ANOVA: analysis of variance
ANP: acute necrotizing pancreatitis
AP: acute pancreatitis
APA: American Pancreatic Association
APFC: acute peripancreatic fluid collection
AUC: area under the curve
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
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
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
OR: odds ratio
PC: pancreatic centre
PCT: procalcitonin
PRSS1: human cationic trypsinogen
RCT: randomized controlled trials
ROC: receiver operation characteristic
SAP: severe acute pancreatitis
SD: standard deviation
SD: surgical department
SIRS: inflammatory response syndrome
SPINK1: serine protease inhibitor Kazal type 1
TIMD: territorial internal medical department
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).

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 (3). Crude incidence of AP proved to be 33.74 cases per 100,000 person-years (95% confidence interval [CI]: 23.33–48.81 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/or the trend of mainly lifestyle-related acquired risk factors (4).

According to the unofficial report of the Hungarian Central Statistical Office, crude incidence of AP can be estimated at 50–55 cases per 100,000 person-years.

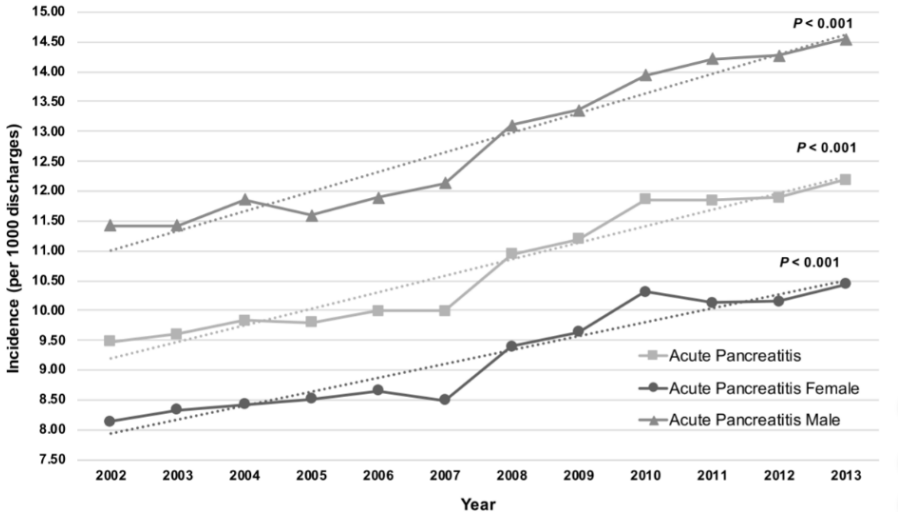

Figure 1. Incidence of acute pancreatitis between 2002 and 2013 in the US. P-values indicate a significant increase in incidence, shown by the dashed trend lines. Reprinted from' *Temporal Trends in Incidence and Outcomes of Acute Pancreatitis in Hospitalized Patients in the United States From 2002 to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

3.2 Pathomechanism and aetiology

In the pathomechanism, we differentiate genetic susceptibility and acquired (mainly environmental) factors. Nevertheless, according to the' multiple hits on multiple targets' theory, the combination of harmful factors ('hits') are required to act on cellular/molecular structures ('targets') to initiate the development of AP (5).

Genetic susceptibility is driven by genes encoding pancreatic proteases or regulators of proteases. In general, mutations of genes (e.g. serine protease inhibitor Kazal type 1 [SPINK1] or human cationic trypsinogen [PRSS1]) lead to premature activation of pancreatic digestive enzymes, causing pancreatic autodigestion (6).

There are numerous environmental or acquired factors which are implicated in the pathomechanism of AP. Biliary pathologies 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 (7). 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 (8). Other aetiological factors include hypertriglyceridaemia, drugs, iatrogenic injury (endoscopic retrograde cholangiopancreatography [ERCP], surgery), trauma, infections, hypoxia and ischaemia, hypercalcaemia and pancreatic malformations. None of the known aetiological factors is identified in 10–30% of the cases, which is termed idiopathic AP (9).

Premature protease activation of any cause leads to injury of pancreatic acinar and ductal cells, by which the mechanisms of cell death are activated. Cell fragments and the released inflammatory mediators activate leukocytes, which produce a large amount of various pro- and anti-inflammatory cytokines, maintaining and aggravating the vicious cycle of cell death and protease activation. 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 to systemic inflammatory response syndrome (SIRS). Since cytokines are vasoactive mediators, the cytokine storm causes distributive vasoplegic shock and multi-organ dysfunction syndrome (MODS) in severe cases (10).

3.3 Diagnostic criteria

The diagnosis of AP requires at least two of the followings (' two out of three criteria') as per the 2012 revised Atlanta Classification (11): **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; **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 can range from mild (almost asymptomatic) cases to the critically-ill cases requiring intensive care. According to the revised Atlanta Classification, severity can be graded based on local and systemic complications (11).

3.4.1 Local complications

Cases can be categorized into acute interstitial oedematous pancreatitis or acute necrotizing pancreatitis (ANP) based on the development of pancreatic and/or peripancreatic necrosis. Other local complications include acute peripancreatic fluid collection (APFC), acute necrotizing collection (ANC), pancreatic pseudocyst and walled-off necrosis (WON). 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, ideally 5–7 days after onset (11, 12). The true incidence of local complications is hard to be estimated due to diagnostic difficulties. ANP might develop in 20–40% and WON in 1–9% of the cases (13); however, a recent prospective study reported a surprisingly high incidence of ANP (81%) and consequent WON (58.7%) based on CECT at 5–7-day, 1-month and 3-month after onset (14). Another study recorded similarly high incidence of APFC (42.7%) and pseudocysts (6.3%) (15). Of note, these numbers should be treated with caution as a lot depends on the study population.

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, should be taken into account. Transient (resolves within 48 hours) and persistent organ failure (lasts longer than 48 hours) should be distinguished. If organ failure affects more than one organ system, it is termed MODS. Any organ failure develops in 5–15% of patients: incidence of respiratory, renal and heart failure was 9, 7 and 4% in a study, respectively (16).

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), its

prognosis is poor with a mortality rate reaching 30% (vs the 13% with sterile necrosis) (17). IPN can be diagnosed with computed tomography- or US-guided fine-needle aspiration biopsy (FNAB), followed by Gram stain/culture. However, strategies based on non-invasive diagnostics are becoming more popular (18).

3.4.4 Severity and mortality

The revised 2012 Atlanta Classification defines disease severity of AP based on the development and duration of organ failure and the development of local complications (11). The classification differentiates mild, moderately severe and severe AP (MAP, MSAP and SAP, respectively; detailed in Table 1. MAP and MSAP are associated with low mortality (<1%) whereas SAP has high mortality approximating 30% (Figure 2) (19). SAP, MSAP and MAP accounted for 8.8, 30.0 and 61.2%, respectively, in our previous study (19). 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% (20, 21): Nevertheless, the tendency is promising: mortality reduced from 1.8 to 1.1% in the US between 2003 and 2012 (4).

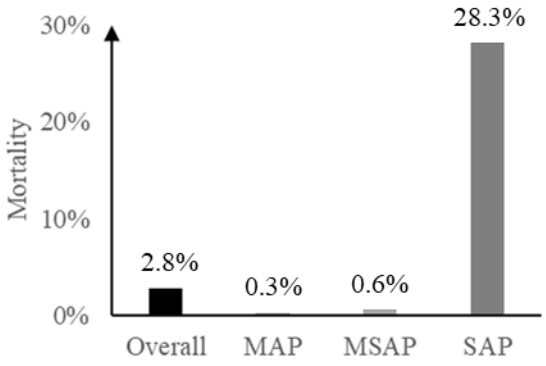

Figure 2. Mortality of acute pancreatitis by severity. MAP: mild acute pancreatitis, MSAP: moderately severe acute pancreatitis, SAP: severe acute pancreatitis. Reprinted and adapted from *'Prospective, Multicentre, Nationwide Clinical Data from 600 Cases of Acute Pancreatitis'* by Párniczky et al., 2016, *PloS One*.

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

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 (22), which, after update and adaptation, was translated to and published in the Hungarian language by the Hungarian

Pancreatic Study Group (HPSG) in 2015 (23). The guideline panel made recommendations adhering to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system and quantified quality of evidence (as very low, low, moderate or high) and the strength of recommendation (as weak or strong) (24). In addition to the IAP/APA guideline (22), leading evidence-based guidelines were released by the American College of Gastroenterology (2013) (25) and the Japanese Society of Hepato-Biliary-Pancreatic Surgery (2015) (26).

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

Quality of care depends on the case volume treated and the knowledge acquired. 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. 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 both important determinants. For example, 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) (27) or a higher centre and physician volume were found to favourably impact quality indicators of ERCP (28, 29).

Although we have evidence for the beneficial effect of centralization in AP as well, Only the IAP/APA guideline attempts to define specialist units (GRADE 2C, weak agreement) (22):

'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).

3.5.4 Antibiotic use

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 yielded no statistically significant benefit regarding short-term (<3 months) mortality (odds ratio [OR]: 0.81, CI: 0.57–1.15), rate of organ failure, rate of IAP or rate of sepsis based on the data of 17 RCTs in AP. Findings were consistent in ANP and SAP as well. 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 (30). Although the leading guidelines were released earlier than this meta-analysis, their recommendations are mainly in line with its findings: 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).

According to our previous research, 77.1% of patients received ABs during hospital stay. This number is twice as high as expected, considering the estimated incidence of pancreatic and extrapancreatic infections (30–35%). The majority of the patients received ABs for prophylaxis, indicating a significant AB overuse (19). Choosing the population which may benefit from AB treatment is challenging. Many biomarkers used as pervasive indicators of an ongoing infection (white blood cell count [WBC] and acute-phase proteins, e.g. cytokines, C-reactive protein [CRP] and even procalcitonin [PCT]) can change during the natural course of AP, posing difficulty in distinguishing inflammation of sterile and infective origins (31). 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. Our research team analysed the joint effect of ageing and comorbidities in a cohort of AP cases and found that comorbidities are responsible for the increment in mortality in elderly, but both ageing and comorbidities are important regarding severity. 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 (32).

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 (19, 33, 34). Unlike alcoholic and biliary aetiologies which have limited influence on severity and mortality (19, 35, 36). Among lifestyle factors, alcohol intake is considered to be a causative factor of AP (5). 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 (5, 37, 38). Findings from a 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) (39). However, we should take into account that obesity is mostly part of metabolic syndrome (MetS, defined based on five components of which at least two should be met, see Table 2) (40). MetS is a common comorbid condition in AP, its prevalence varies from 18 to 62.8% across studies (41-43). Besides, it was implicated as a potential prognostic factor.

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 (or drug treatment for elevated triglycerides)	>1.7 mmol/L
Reduced HDL-C (or drug treatment for reduced HDL-C)	<1.0 mmol/L for males, <1.3 mmol/L for females
Elevated blood pressure (or antihypertensive drug treatment)	≥130 mm Hg for systolic and/or ≥85 mm Hg for diastolic
Elevated fasting glucose (or drug treatment of elevated glucose)	>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 special 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

We performed three retrospective cohort studies (44-46), where the main source of data was the Hungarian Registry for Pancreatic Patients (in the followings, AP Registry). Besides, we conducted an international survey and a systematic review (as detailed below).

5.1 AP Registry

5.1.1 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 for pancreatic diseases (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.

5.1.2 Recruitment and eligibility

The registry is free to join for all centres providing care for AP patients after claiming local ethical permission for operation. After establishing the diagnosis of AP as per the 2012 Atlanta Classification, patients are offered to participate in the registry.

5.1.3 Data collection and validation

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

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.

5.1.4 Statistical considerations

After choosing the variables for analysis, descriptive statistics are performed. 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. To investigate the diagnostic accuracy of biomarkers, we constructed receiver operation characteristic (ROC) curves and calculated area under the curves (AUC).

5.1.5 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.

5.2 International survey

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. 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.

5.3 Systematic review

5.3.1 Background and objectives

Systematic reviews aim to deliver reliable information, the essentials of knowledge in a quickly and easily digestible format. 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.

5.3.2 Data sources and eligibility

We searched three medical databases (MEDLINE via PubMed, Embase and CENTRAL) systematically up to July 2018 with a query 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.

5.3.3 Selection, data collection and risk of bias assessment

After the removal of duplicates, 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. 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, risk of bias assessment could not be carried out with the tool dedicated to assessing RCTs.

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 3. 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).

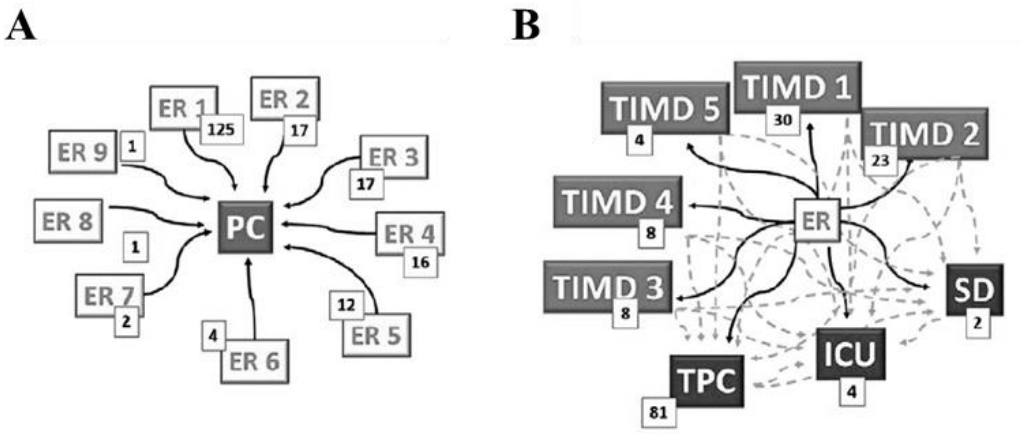

Figure 3. The models of centralized (A) and non-centralized care (B) of acute pancreatitis. The arrows with solid line represent the direction of regular patient referral; those with dash line occasionally represent referrals. The number of patients in each unit is shown in squares. ER: emergency unit, 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 4). 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).

6.1.3 Therapeutic approach and interventions

The proportion of ERCPs, necrosectomy or guided drainage did not differ between groups. 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 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.

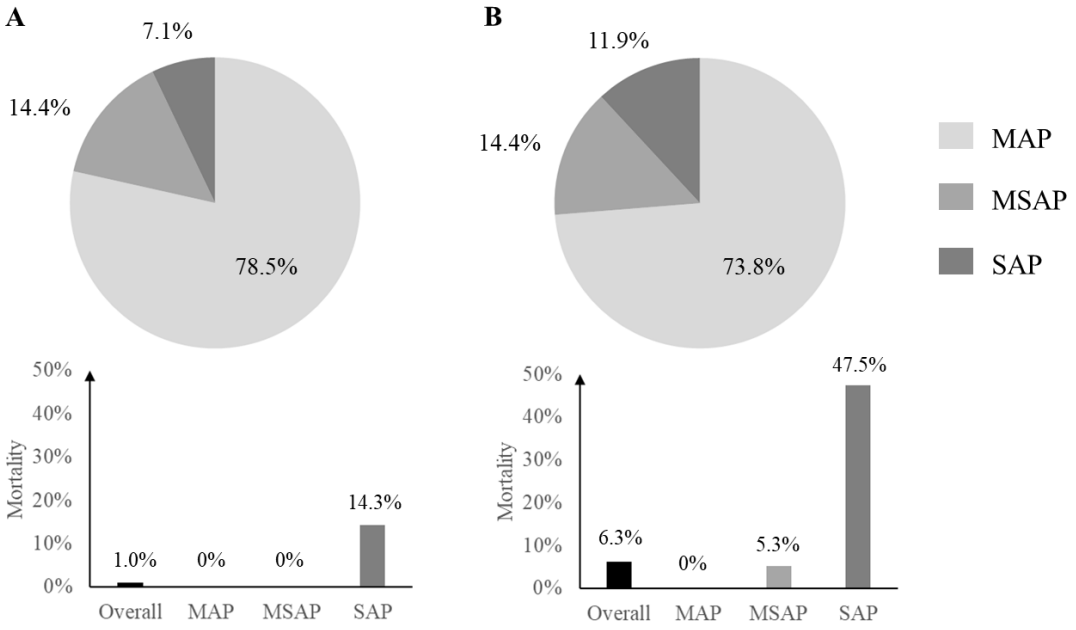

Figure 4. Severity and mortality in Healthcare Model A (providing centralized care) and Healthcare Model B (providing non-centralized care). Pie charts show the distribution of severity; bar charts show overall and severity-stratified mortality. Severity was graded by the 2012 Atlanta Classification. 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

6.1.4 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 only RCT investigating the guidance of AB therapy was a two-arm study in SAP. While the clinical efficacy of the strategies was found to be equal, the PCT-guided treatment proved to be more cost-effective vs standard treatment (24,401±2,631 vs 27,813±2,529 US dollars for the PCT-guided vs control groups, respectively; $p<0.001$) (47).

In the remaining 22 studies testing the efficacy of AB treatment vs various control groups, the definitions for pancreatic infection was substantially heterogeneous. 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

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%.

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 5.

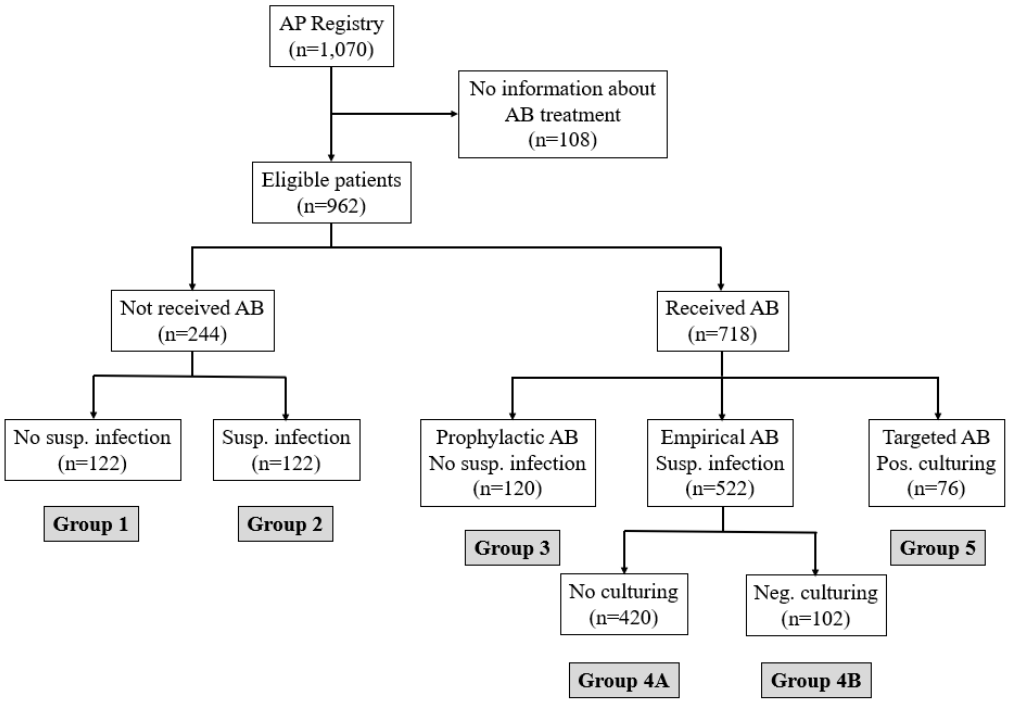

Figure 5. Study subgroups. Groups 1 and 2 did not, whereas Groups 1, 2 and 3 did receive antibiotics. Infection was suspected based on clinical signs and symptoms. Prophylactic (Group 3), empirical (Group 4) and targeted (Group 5) antibiotic treatment were defined if no infection was suspected, infection 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. The leading aetiology was the biliary origin (42.1%), followed by idiopathic AP (21.5%) and alcoholic AP (18.8%).

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 5 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 5. Mortality, severity and length of hospital stay across groups.

Group	Mortality (%)	Severity (%)	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 5.

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, and 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).

6.2.3.4 Biomarkers and the initiation of antibiotic treatment

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 an (Group 1).

6.2.3.5 Changes in biomarkers during the disease course

Figure 6 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 6D). 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.

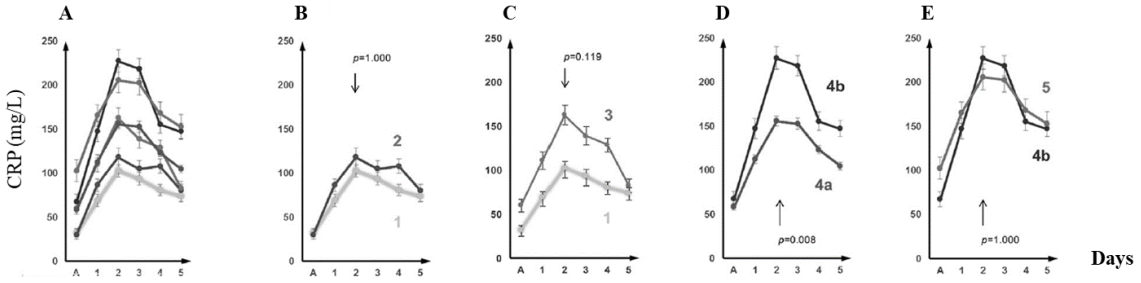

Figure 6. Changes in biomarkers during disease course across groups by antibiotic treatment and status of infection. (A) All groups (for illustrative purpose only), **(B)** Groups 1 vs 2, **(C)** Groups 1 vs 3, **(D)** Groups 4a vs 4b and **(E)** Groups 4b vs 5 with the corresponding p-values embedded in the figures. Group are indicated with numbers in the figures, for the definitions of groups, see Figure 5. The horizontal axis represents the days of hospital stay (A: admission). CRP: C-reactive protein, Adapted and reprinted from' Antibiotic Therapy in Acute Pancreatitis: From Global Overuse to Evidence Based Recommendations' by Párniczky et al., 2019, Pancreatology.

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 7B).

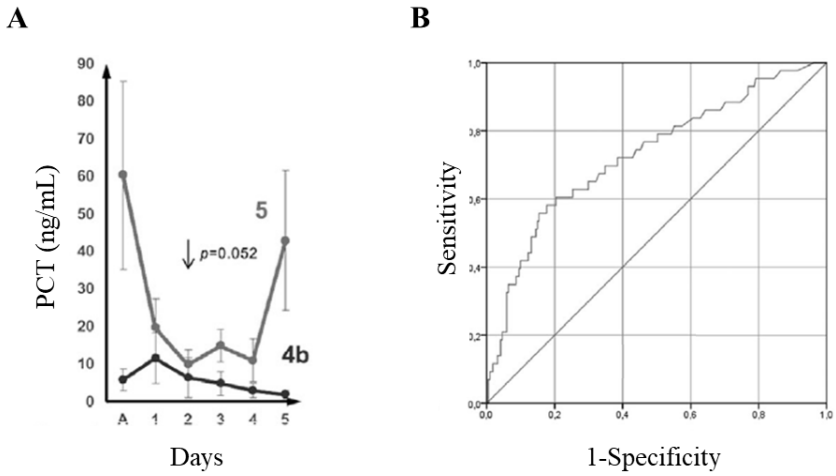

Figure 7. Procalcitonin and infections in acute pancreatitis. (A) Changes of procalcitonin level during disease course in Groups 4b vs 5 with the corresponding p-value embedded in the figure. **(B)** Diagnostic accuracy of procalcitonin in discriminating pancreatic infections: area under the curve was 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. 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. Obesity, hypertension, hyperlipidaemia and diabetes mellitus accounted for 29.5, 60.0, 33.6 and 16.4% of the cases.

6.3.2 The association of components of metabolic syndrome with disease outcomes

Table 6 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.

Table 6. Disease outcomes

	Total	**Obesity**		**Hypertension**		**Hyper-lipidaemia**		**Diabetes mellitus**	
		No	Yes	No	Yes	No	Yes	No	Yes
Number of cases	1,257	886	371	451	676	687	349	1,051	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.

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.

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 (44). 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 (45). In the third study, MetS and its components predisposed patients to develop a more severe disease course (46).

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 (48-52). 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 3). 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 a multiple low volume centres.

Four studies provided evidence that a higher hospital volume has a favourable impact on mortality of AP (for an example, see Figure 8) (48-50, 52), the fifth found no benefit (51). Length of hospital stay consistently reduced in four studies (48-51). Cost of care was reduced in one study (50); however, another one reported no change (51). 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.

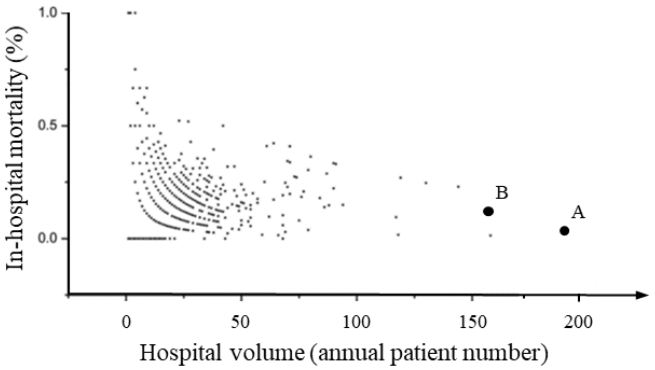

Figure 8. The association between hospital volume and in-hospital mortality. The higher the hospital volume, the lower the in-hospital mortality. In our study, in-hospital mortality was 1 and 6.3% with annual case numbers 195 and 160 in Healthcare Models A and B, respectively (represented by the larger 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.*

Providing care of AP in special units is supported by several arguments:

1) 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.
3) Adherence to evidence-based guidelines is better in specialist units as treating physicians are motivated to keep pace with changes in recommendations.
4) Special units contribute to research activity to a considerable extent, which provides further financial and infrastructural access and promote guideline adherence (53).

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.

7.2.2 Antibiotic use

In 1975, two RCTs were published which investigated the efficacy of prophylactic AB use in AP (54, 55), writing the first pages of the saga of ABs in AP. Although now we consider prophylactic AB use ineffective (30), defining the population which benefits from ABs has remained an open debate.

In line with our preliminary publication (19), 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. 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 (44).

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 (56). 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 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 (57)). 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 (58). In contrast, AUC for on-admission PCT was measured only 0.729 in our cohort of patients (shown by Figure 7B) while on-admission CRP had an even worse poor diagnostic performance.

Biomarker-guided initiation of AB therapy is an enticing possibility. 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 (47). Further research is awaited.

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 and 19.7% had a BMI>30 kg/m^2 in 2017. In contrast, prevalence of obesity was almost 30% in our study. 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. (59)). In line with other reports (41-43), 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 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.

Guideline adherence may differ across centres, so does diagnostic and therapeutic approaches, both having the potential to modify disease outcomes. Access to interventions may affect outcomes as well: centres cannot adhere to the step-up approach if endoscopic or percutaneous interventions are not available (60). Incidence of local complications is probably underestimated, affecting the categorization of disease severity. Besides, transient and permanent organ failure are sometimes hard to be distinguished.

The high total case number (>1,000 cases) allows a detailed analysis of rare conditions as well. Although data quality for disease outcomes and certain baseline 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.

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 in AP. PCT shows fair diagnostic performance in detecting infections.**
   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 warrants further investigation.
3. **Components of MetS are independent predictors of various outcomes in AP. 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. Prognostic scores might benefit from incorporating MetS or items of MetS.

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