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BLOOD UREA NITROGEN LEVEL: EFFECTIVENESS FOR SEVERITY ASSESSMENT IN ACUTE PANCREATITIS

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SUMMARY

Remarkable efforts have been made to find predictive combinations of clinical and laboratory parameters to identify patients suffering from severe acute pancreatitis early in the course of the disease. Several complex scoring systems have proven to be useful to stratify patients into risk categories. However, frequently encountered limitations to scoring systems remain, including limited availability of the required parameters outside of an intensive care setting and limited predictive value within the first day after admission. Single predictive laboratory parameters have been identified as an alternative, but few are currently available in routine clinical practice because measurement tools are sometimes expensive or not commonly available. A notable exception is blood urea nitrogen (BUN), which has recently been characterized as a valuable single predictor of prognosis in acute pancreatitis. Besides being quantifiable using a widely available and cheap routine measurement, timely monitoring of changes in BUN levels during the first day of admission has been shown to be as exact as complex scoring systems. This makes BUN an attractive candidate parameter for guiding clinical practice during the admission phase, and possibly also during later stages of the disease.

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ACUTE PANCREATITIS

Acute pancreatitis is an acute disease of the pancreas involving an autodigestion and inflammatory reaction of the gland itself, as well as potentially the whole organism (1, 2). The most frequent etiological factors are gallstones and alcohol consumption, and rarely, developmental abnormalities, trauma, endoscopic retrograde cholangiopancreatography (ERCP), drugs and others. In up to 30% of cases, no causal factor can be identified. The clinical course of acute pancreatitis is highly variable, ranging from mild abdominal discomfort to life-threatening complications. About 10-20% of patients with acute pancreatitis suffer from a severe course of the disease (3). The morphological hallmark of pancreatitis is an edema of the pancreas. Depending on severity, various other manifestations can occur, such as effusions and necrosis of the pancreas itself and surrounding tissue and organs.

CLINICAL COURSE OF ACUTE PANCREATITIS

Pancreatitis is diagnosed by definition if at least two of the following occur: abdominal pain, threefold elevation of serum amylase or lipase activity and concordant findings on abdominal ultrasound or cross-sectional imaging (4). The onset of the disease is defined as the time of first symptoms.

Clinical and experimental research has led to the concept that the course of acute pancreatitis can be divided into two pathophysiologically and clinically distinct stages (4). The first is the acute stage, characterized by onset of symptoms and eventually development of systemic complications over approximately 1 week. The severity and prognosis during the first stage of acute pancreatitis mainly depend on the development of a systemic inflammatory response syndrome (SIRS) and organ dysfunction or failure. During the second stage, there is either a gradual recovery or ongoing disease, typically accompanied by necrosis of the pancreas and its complications.

An important step for consensus definitions on the course of acute pancreatitis was the establishment of the Atlanta Classification. The

first version was published in 1992 (5), and the classification is currently subject to a revision (4) in recognition of advances in our understanding of the disease.

NECROSIS

A serious form of acute pancreatitis with a significantly worse outcome is usually characterized by the presence of necrosis of pancreatic and retroperitoneal tissue. It should be noted that peripancreatic necrosis without simultaneous pancreatic parenchymal necrosis is possible, although found in only about 20% of cases of necrotizing pancreatitis. The diagnostic hallmark of tissue necrosis is a non-enhancing area in contrast-enhanced computed tomography (CECT), depicting an area that is not reached by the intravenous contrast agent, e.g., the capillary bloodstream (4). Microcirculatory failure is a key event in the progression from mild to severe acute pancreatitis (6).

Acute pancreatitis with associated necrosis generally has a worse prognosis and outcome (1, 2, 4). On the one hand, persistent areas of necrosis can cause symptoms like impaired oral nutrition by anorexia, nausea or vomiting, as well as abdominal pain or biliary obstruction. On the other hand, necrosis or its liquefied remnants may become infected with bacteria, leading to sepsis and its sequelae.

TREATMENT OF ACUTE PANCREATITIS

The treatment of acute pancreatitis in the uncomplicated course is symptomatic, based on pain therapy, intravenous fluid replacement and early enteral nutrition (1, 2). Prophylactic antibiotics may be given in cases of necrotizing acute pancreatitis, but this is still a matter of debate (7). In biliary pancreatitis, early ERCP is recommended to remove pancreatic ductal obstruction, and cholecystectomy is performed after reconvalescence, if possible during initial hospital stay. An important initial decision is whether admission to the intensive care unit (ICU) is necessary, bearing also significant economic and logistical impact.

The role of surgery in the treatment of severe acute pancreatitis has changed in recent years and strategies to postpone surgical intervention are associated with decreased mortality (8). Typical indications for surgery in acute pancreatitis are infected necrosis and abdominal compartment syndrome (1, 2). Surgical debridement and necrosectomy should be performed as late as possible in the course of the disease, however, as surgical mortality is very high during the first 2 weeks after onset and declines with time. To minimize surgical trauma, a step-up approach employing percutaneous drainage and minimally invasive operations before open surgery has been proposed and confirmed as more efficient in a randomized, controlled trial (9).

PREDICTION OF SEVERITY BY SCORING SYSTEMS

In the Atlanta Classification, which resulted from an international consensus meeting and was published in 1992 (5), acute pancreatitis was divided into mild and severe, the latter being defined by organ failure and/or local complications (virtually synonymous with necrosis). Although it provides an internationally accepted framework for the characterization of acute pancreatitis and its complications, very few studies have validated the classification (10). Furthermore, due to limitations regarding validity of the severity classification and unclear definitions (11), efforts are currently being made to publish a revised version (4, 10). The proposal is to define severe acute pancreatitis by persistent (≥ 48 hours) organ dysfunction or SIRS during the early phase (1-2 weeks) and/or the need for active intervention (due to complications of necrosis) during the late phase.

Regarding the aforementioned typical course of acute pancreatitis, it is clear that early recognition and selection of severe or even life-threatening pancreatitis are desirable. Many studies have been performed to identify predictive parameters that are available early after onset.

One of the first achievements in this sense was the development of Ranson's Criteria (12) over 30 years ago (Table I), for which 11 criteria need to be assessed: 5 on admission and another 6 after 48 hours. A Ranson's score of 3 or more is predictive of severe acute pancreatitis as defined by the Atlanta Classification and mortality increases to 15%. No patient survived when six or more criteria were fulfilled. A simplified version of Ranson's Criteria, using only eight of the original criteria and termed the Glasgow score (13), proved to be equally predictive.

Another risk stratification system for acute pancreatitis is the Acute Physiology And Chronic Health Evaluation (APACHE) II score (14), which incorporates 14 parameters (Table I). Initially developed as a prognostic tool to predict prolonged treatment and mortality in patients treated in the ICU, it proved to be useful for the prediction of acute pancreatitis severity; a score of 8 or more is associated with severe acute pancreatitis, as defined by the Atlanta Classification (4, 15).

The complex Japanese Severity Score (JSS) was established and is still widely used only in Japan (16). In total, 18 parameters are included. The system was useful to stratify patients with severe acute pancreatitis with respect to mortality.

An intriguing recent approach was to employ artificial neural networks (ANNs) for acute pancreatitis severity prediction. In brief, in a first step a set of 10 predictive variables was identified by sensitivity analysis and used as input for ANNs, which were subjected to a mathematical learning procedure aimed at prediction of dichotomous outcome parameters. The resulting ANNs had a significantly higher accuracy in predicting severe acute pancreatitis, multiorgan dysfunction and mortality than the APACHE II and Glasgow scores. The input variables included two measures of response to therapy, namely persistent hypotension or SIRS after 6 hours of therapy. As neither APACHE nor Glasgow scores include such therapy response parameters, it remains unclear whether the superiority of the ANN models can be explained by superior mathematical methodology or better input variable selection.

There have also been efforts to predict acute pancreatitis severity by morphological parameters assessed by CECT. Numerous scores have been developed, among which the Balthazar score (17) is the

Table I. *Overview of selected classic and simplified scoring systems for risk stratification in acute pancreatitis.*

Score	Ref.	Time point	Parameters
Ranson	12	Admission After 48 hours	Age, WBC, GOT, LDH, GLC Volume deficit, BUN, BE, paO_2, Ca, HCT
APACHE II	14	Daily	Temperature, MAP, HR, RR, paO_2, FiO_2, pH or BIC, Na, K, Crea, HCT, WBC, GCS, chronic organ failure (liver cirrhosis, COPD, NYHA IV, CRF, immunosuppression)
BALI	20	Admission	On admission: **B**UN, **A**ge, **L**DH, **I**L-6
SPS	21	Admission	On admission: BUN, LDH, CECT
POP	19	During 24 hours after admission	pH, age, BUN, MAP, paO_2, FiO_2, Ca
BISAP	22	Admission	**B**UN, **I**mpaired mental status, **S**IRS, **A**ge, **P**leural effusion
CART	23	Admission	SIRS, BUN, Ca, pleural effusion

WBC, white blood cell count; GOT, serum glutamate-ornithine transferase; LDH, serum lactate dehydrogenase; GLC, blood glucose; BUN, blood urea nitrogen; BE, base excess; paO_2, arterial partial pressure of oxygen; Ca, serum calcium; HCT, hematocrit; MAP, mean arterial pressure; HR, heart rate; RR, respiratory rate; FiO_2, fractional inspiratory concentration of oxygen; BIC, serum bicarbonate; Na, serum natrium; K, serum potassium; Crea, serum creatinine; GCS, Glasgow Coma Scale; COPD, chronic obstructive pulmonary disease; NYHA IV, heart failure New York Heart Association grade IV; CRF, chronic renal failure; IL, interleukin; CECT, contrast-enhanced computed tomography; SIRS, systemic inflammatory response syndrome.

most well known. However, a large recent study showed that on admission, none of seven radiological scoring systems was better than the clinical APACHE II or bedside index for severity in acute pancretatitis (BISAP) scores. Therefore, the use of CECT on admission cannot be recommended in general (18).

SIMPLIFIED SCORING SYSTEMS

The aforementioned classical Ranson, Glasgow, APACHE II and JSS scoring systems share the disadvantage that they are only completely assessable after 48 hours or more. In clinical reality, however, the first important decisions on treatment are made upon admission. Furthermore, complex multiparametric scoring systems are not likely to be applied to the general clinical practice. Predictive simple scores for mortality that are available during the first 24 hours are therefore needed. Four recent studies concentrated on prediction of mortality within the first 24 hours after admission by simplified scoring systems.

A large-scale study from the U.K. (19) used data obtained from over 2,400 patients with severe pancreatitis to develop the sophisticated Pancreatitis Outcome Prediction (POP) Score to predict mortality within the first 24 hours of ICU admission. The model includes six variables and was able to predict mortality even more precisely than the APACHE II score within the first 24 hours (Table I). A drawback is that the variables employed are usually only available in the intensive care setting.

The BALI score (20) included serum interleukin-6 (IL-6) levels and performed comparably to the Ranson/Glasgow and APACHE II scores (Table I). The simple prognostic score (SPS) from Japan (21) employs only three parameters assessed on admission and compares equally to Ranson/Glasgow and APACHE II scores concerning mortality prediction in severe acute pancreatitis. However, necrosis seen on CECT is one included parameter that is of questionable utility during the first week, as demarcation of necrotic areas is usually not present in the early phase (Table I).

Finally, a recent large population-based study aimed to develop a simple clinical score for risk stratification concerning mortality in acute pancreatitis during the first 24 hours after hospitalization. The resulting BISAP score (22) proved to be equally predictive as the APACHE II score (Table I). In contrast to the aforementioned BALI, SPS and POP, the BISAP score was developed based on population and the results are therefore not restricted to patients with severe acute pancreatitis.

Another simple yet valid prediction model was developed by classification and regression tree analysis (CART) (23), which yields a decision tree instead of a score. The model predicted the occurrence of severe acute pancreatitis by the use of four variables (Table I) and proved to be significantly more accurate than the APACHE II score on admission. An advantage for clinical use is the simplicity of the decision tree, a slight drawback is that assessment of SIRS in fact includes more laboratory and clinical parameters (1).

PREDICTION OF SEVERITY BY SINGLE LABORATORY PARAMETERS

To simplify the effort of predicting the course of acute pancreatitis, an armamentarium of single laboratory parameters has been evaluated. Of note, serum activity levels of amylase or lipase, while necessary for diagnosis, are not predictive of the severity of acute pancreatitis (4, 24).

The best-known example of a valid and applicable single laboratory parameter in acute pancreatitis is C-reactive protein (CRP) (25). A cutoff of 150 mg/L during the first 48 hours can be used as a marker for necrotizing acute pancreatitis. Newly available laboratory parameters, such as the cytokines IL-6, IL-8 and TNF-α (26), as well as urinary trypsinogen activation peptide (TAP) (27), neutrophil elastase (28), procalcitonin (PCT) (29) and matrix metalloproteinase (MMP) (30), have been demonstrated to be of predictive value, but cannot be considered to be generally available. Furthermore, their predictive values are not significantly better than that of CRP, which

is therefore today considered the gold standard of single laboratory parameters in acute pancreatitis. The two simple laboratory parameters already included in the Ranson's Criteria, blood glucose level and hematocrit (24), also have a relatively high sensitivity and specificity for necrotizing acute pancreatitis when applied as single markers. Importantly, these two markers have a higher predictive value on admission than after 48 hours.

BLOOD UREA NITROGEN (BUN) FOR PREDICTION OF PROGNOSIS

In the continued search for markers of the severity of acute pancreatitis, BUN has recently emerged as a valid parameter. Urea is a small organic molecule with a high solubility in water. In human metabolism, urea is part of the urea cycle and is derived from oxidation of amino acids (as an alternative energy source) or synthesized from ammonia (to excrete excess ammonia). The principal sites of urea production and excretion are the liver and kidneys, respectively. BUN is the measure for urea content in blood, and elevated levels are found when renal excretion is impaired or protein catabolism is increased.

By multivariable analysis of 44 patients with severe necrotizing acute pancreatitis treated at the surgical ICU of our institution (31), we found that the BUN levels on admission and in the course of the disease were significant predictors of mortality and the only independent predictor of prolonged ICU stay (see Fig. 1). At a cutoff of 33 mg/dL BUN on admission, mortality could be ruled out correctly in 82% (negative predictive value) of cases. More importantly, however, BUN levels during the course of the disease had a 92% negative predictive value regarding mortality. These findings suggest that monitoring BUN level as part of the physiological response to therapy may serve as a single and cheap laboratory parameter to guide the management of patients with severe necrotizing acute pancreatitis.

Wu et al. (3) tested the utility of BUN in a retrospective study including over 5,800 patients with acute pancreatitis. The first finding was that increased BUN on admission was predictive of mortality (odds ratio of 2.9 for each increase of 5 mg/dL over the median). This confirms earlier reports where BUN is included in scoring systems: the Ranson, Glasgow, JSS, BALI, POP and BISAP scores.

Importantly, changes in BUN levels during the first 24 hours of admission also reflected the risk of death independently from admission BUN levels: a rise of BUN by 5 mg/dL was associated with an increase in mortality (odds ratio 2.2). In time-specific analysis, the predictive capacity of BUN levels increased significantly during the first 24 hours, but not thereafter. The combination of admission BUN and changes in BUN level during the first 24 hours after admission achieved the highest predictive capacity (AUC = 0.91). Inclusion of other laboratory parameters known from other scoring systems (cal-

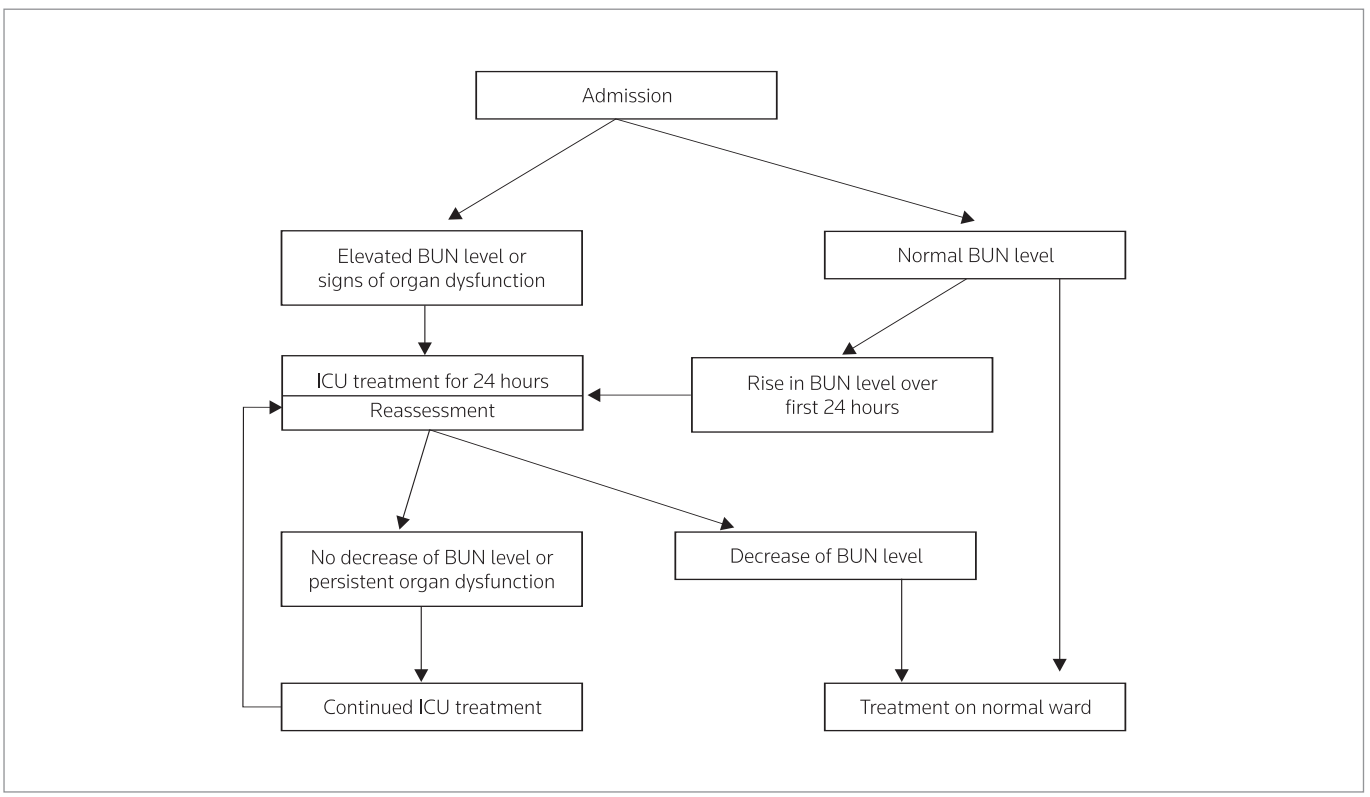

Figure 1. Hypothetical flow scheme for treatment of acute pancreatitis guided by blood urea nitrogen (BUN) levels. ICU, intensive care unit.

cium, white blood cell count, creatinine and hemoglobin) in a time-specific multivariable prediction model for mortality revealed that at 24 hours and later, BUN was the only independent predictor.

These findings have recently been validated in an international validation study (32). Of note, BUN level as a single parameter during the first 24 hours was equally predictive in terms of mortality as the complex APACHE II score.

SUMMARY AND PERSPECTIVE

Efforts have been made to identify predictive combinations of clinical and laboratory parameters to identify patients suffering from severe acute pancreatitis. Complex scoring systems are capable of stratifying patients into risk categories. However, important limitations remain, i.e., the limited availability of the required parameters outside of an ICU setting, as well as the limited predictive value within the admission phase. Single predictive laboratory parameters have also been identified, but few are currently available in routine clinical practice.

BUN has recently been recognized as a valuable single predictor of prognosis in acute pancreatitis. Besides being quantifiable via a widely available and cheap routine measurement, monitoring temporal changes in BUN levels during the first day of admission is as exact as complex scoring systems. Limited data also suggest a role for BUN in guiding therapy during the later stages of ICU treatment.

Some recent studies focus on the evaluation of early treatment response (33-37). From the still limited data, however, it seems clear that the dynamic nature of organ failure in pancreatitis is an important indicator of severity that has previously not been adequately appreciated. In fact, BUN changes during the first day may be representative of response to therapy, which explains their high predictive value.

A goal-directed approach is desirable to guide the treatment of pancreatitis. In light of the aforementioned findings, BUN appears to be an attractive parameter for guiding clinical practice during early admission, as well as the later ICU treatment phase. However, this approach remains to be evaluated in a prospective manner in clinical practice.

DISCLOSURES

The authors state no conflicts of interest.

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