EDITORIAL

Early prediction and prevention of infected pancreatic necrosis

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Abstract

Approximately 20%-30% of patients with acute necrotizing pancreatitis develop infected pancreatic necrosis (IPN), a highly morbid and potentially lethal complication. Early identification of patients at high risk of IPN may facilitate appropriate preventive measures to improve clinical outcomes. In the past two decades, several markers and predictive tools have been proposed and evaluated for this purpose. Conventional biomarkers like C-reactive protein, procalcitonin, lymphocyte count, interleukin-6, and interleukin-8, and newly developed biomarkers like angiopoietin-2 all showed significant association with IPN. On the other hand, scoring systems like the Acute Physiology and Chronic Health Evaluation II and Pancreatitis Activity Scoring System have also been tested, and the results showed that they may provide better accuracy. For early prevention of IPN, several new therapies were tested, including early enteral nutrition, antibiotics, probiotics, immune enhancement, *etc.*, but the results varied. Taken together, several evidence-supported predictive markers and scoring systems are readily available for predicting IPN. However, effective treatments to reduce the incidence of IPN are still lacking apart from early enteral nutrition. In this editorial, we summarize evidence concerning early prediction and prevention of IPN, providing insights into future practice and study design. A more homogeneous patient population with reliable risk-stratification tools may help find effective treatments to reduce the risk of IPN, thereby achieving individualized treatment.

Key Words: Acute pancreatitis; Infected pancreatic necrosis; Biomarker; Scoring system; Nutrition therapy; Selective digestive decontamination; Probiotics; Antibiotics; Immune enhancement therapy

Core Tip: Several evidence-supported predictive markers and scoring systems are readily available for predicting infected pancreatic necrosis (IPN). However, effective treatments to reduce the incidence of IPN are still lacking apart from early enteral nutrition. In future research and practice, a more homogeneous patient population should be targeted with reliable risk-stratification tools since such a strategy may help find the effective treatment to reduce the risk of IPN, thereby achieving individualized treatment.

INTRODUCTION

Acute pancreatitis (AP) is one of the most common gastrointestinal illnesses worldwide[1]. The majority of AP cases are mild and self-limited, and such patients are discharged without complications. However, approximately 20% of AP patients develop a complex, prolonged clinical course characterized by pancreatic necrosis, especially when infected pancreatic necrosis (IPN) occurs[2,3]. Therefore, it is of clinical value to identify patients at high risk of IPN in the early phase of AP and provide appropriate preventive measures to improve their clinical outcomes.

In the past two decades, several new predictors and predictive tools have been proposed and evaluated, and several new therapies have been tested in trials to prevent IPN. In this editorial, we summarize evidence concerning the early prediction and prevention of IPN (Figure 1), providing insights into future practice and study design.

EARLY PREDICTION OF IPN

Biomarkers

Many classical biomarkers indicating the inflammation and severity of AP, including C-reactive protein (CRP)[3,4], procalcitonin (PCT)[5], interleukins-6 and -8 (IL-6 and IL-8)[6,7], had showed significant association with IPN in individual studies and meta-analysis[8]. Moreover, in a substudy of the PROPATRIA trial, Buddingh *et al*[9] discovered that plasma angiopoietin-2 (Ang-2), which plays an important role in the autocrine regulation of vascular stability and permeability, was a better biomarker than conventional predictors such as CRP, PCT, and the Imrie score with a cut-off value at 4.51 mg/L.

The relationship between immunosuppression and the development of IPN has also been recognized in the past[10], and biomarkers such as interferon-γ[11] and monocyte surface expression of HLA-DR antigens[12,13] have been tested to reflect the severity of immunosuppression. However, most of these markers are not readily available in hospitals. Through a *post-hoc* analysis of the TRACE trial[14], Cai *et al*[15] found that absolute lymphocyte count (ALC), a more readily available clinical measure, can predict the occurrence of IPN. Since ALC is a routine laboratory measurement, it might be of wider clinical use in practice.

Scoring systems

Several clinical scoring systems have been shown to predict IPN with adequate accuracy. The first is the Acute Physiology and Chronic Health Evaluation (APACHE) II. An APACH II score of more than 8 at admission was found to be a risk factor for IPN in patients with severe AP (SAP)[8,16]. Systemic Inflammatory Response Syndrome (SIRS) score was another option since persistent inflammation is involved in the development of IPN[16,17]. An observational study showed that longer SIRS duration was significantly associated with a higher incidence of IPN[18].

The Pancreatitis Activity Scoring System (PASS), which is an AP-specific score to reflect the disease severity, was tested in the prediction of IPN. In a retrospective study conducted by Ke *et al*[19], the predictive accuracy of the PASS score at admission was better than the APACHE II score in predicting IPN. However, considering the dominating weight assigned to opioid usage in the PASS, Paragomi *et al*[20] modified the original PASS score by removing or partly reducing the weight of opioid usage (mPASS 1-4). The mPASS could predict SAP with reasonable accuracy and differentiate between patients with different early trajectories in patients with different severities. For the prediction of IPN, Mao *et al* [21] found that the mPASS-4 model outperformed the conventional indices in predicting IPN, thereby increasing the likelihood of clinical usage.

EARLY PREVENTION OF IPN

In the past few decades, multiple attempts have been made to reduce the incidence of IPN, including nutrition therapy, selective digestive decontamination (SDD), antibiotic therapy, and immune enhancement. Unfortunately, most of the studies have not come to a positive conclusion.
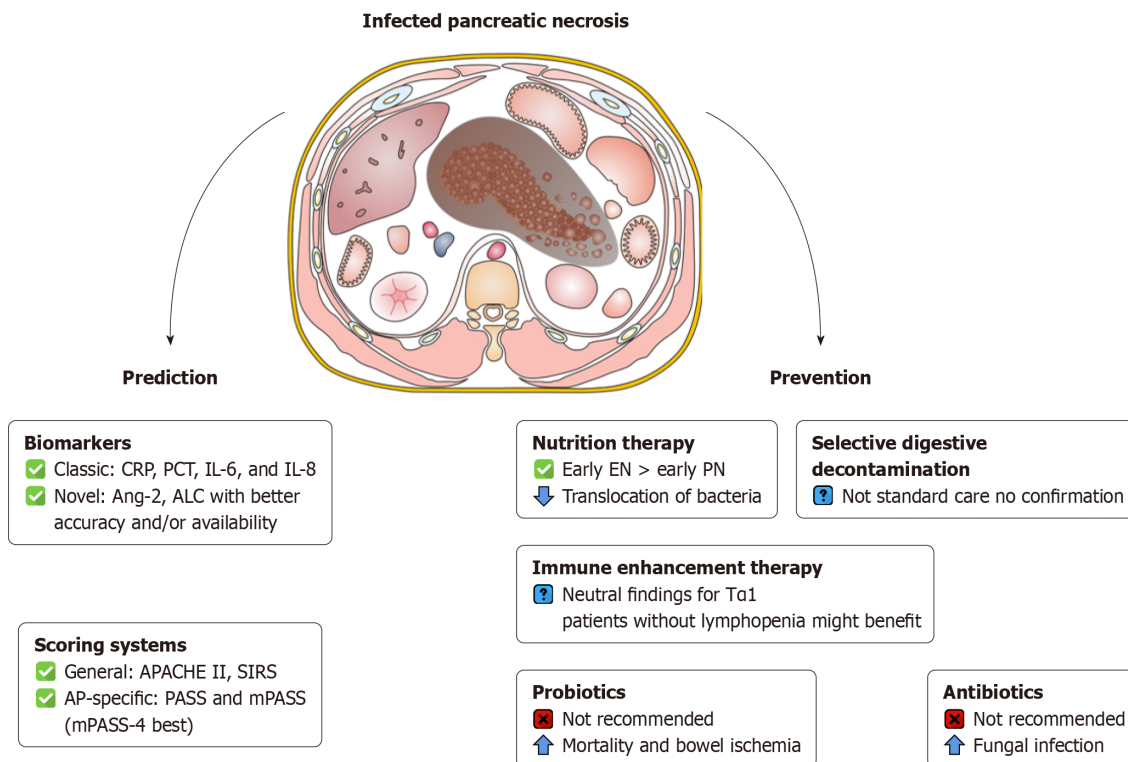
Figure 1 Summary of evidence concerning early prediction and prevention of infected pancreatic necrosis. CRP: C-reactive protein; PCT: Procalcitonin; IL-6 and 8: Interleukins-6 and -8; Ang-2: Angiopoietin-2; ALC: Absolute lymphocyte count; APACHE II: Acute Physiology and Chronic Health Evaluation II; SIRS: systemic inflammatory response syndrome; PASS: Pancreatitis Activity Scoring System; mPASS: Modified Pancreatitis Activity Scoring System; EN: Enteral nutrition; PN: Parenteral nutrition; Tα1: Thymosin alpha 1.

Nutrition therapy

Two different randomized controlled trials[22,23] conducted in patients with SAP demonstrated that early total enteral nutrition, compared with total parenteral nutrition, could reduce the incidence of IPN, thereby reducing organ failure and mortality. On the one hand, the lack of enteral feeding results in atrophy of the gastrointestinal mucosa, bacterial overgrowth, and increased intestinal permeability[24]. On the other hand, parenteral nutrition (enteric starvation) was associated with rapid and severe atrophy of lymphoid tissue associated with the gut[25-27]. As a result, early enteral nutrition may alleviate the translocation of bacteria or bacterial products into the circulation[28-31].

SDD

In the 1980s, investigations into the source of infection in SAP patients found that Gram-negative aerobic bacteria originating from the digestive tract are predominantly isolated from IPN samples[32,33]. Accordingly, SDD has gained broad interest among the research community. The results of a more recent randomized trial[34] with a relatively small sample size of 102 SAP patients showed that SDD could significantly reduce the incidence of IPN, which was associated with improved morbidity and mortality. However, these results have not been confirmed by a large, multicenter trial, and therefore, SDD has not become a standard of care in current guidelines[35].

Probiotics

In experimental and small clinical studies, certain strains of probiotic bacteria might prevent infectious complications by reducing small-bowel bacterial overgrowth, restoring gastrointestinal barrier function, and modulating the immune system[36,37]. To confirm the clinical significance of probiotics in SAP patients, Besselink *et al*[38] conducted a large, randomized, double-blind, controlled trial testing the effect of probiotic therapy on the incidence of infectious complications. Unfortunately, the results showed no beneficial effect of probiotic prophylaxis on multiple infectious complications. On the contrary, mortality in the probiotics group was about twice as high as in the placebo group, which might be attributed to an increased incidence of bowel ischemia. The administration of probiotic bacteria daily as an adjunct to enteral nutrition might increase local oxygen demand, with a combined deleterious effect on the already compromised blood flow. Another possible explanation could be that the presence of probiotics caused local inflammation at the mucosal level. Experimental studies have shown that gut epithelial cells under metabolic stress react to commensal bacteria with an inflammatory response[39]. Recently, in addition to Gram-negative bacteria, infections associated with Gram-positive bacteria and yeasts were observed with an increasing incidence[40-42]. Therefore, research interests in the source of bacteria in IPN patients have been raised again, and the corresponding preventive measures need to be further studied.

Antibiotics

Systemic antibiotic prophylaxis has long been considered effective in preventing secondary infection in AP[43]. The results from a randomized controlled trial testing prophylactic meropenem suggest that although early antibiotic treatment might reduce the occurrence of septic complications and improve the prognosis of AP, it does not prevent the occurrence of IPN[44]. However, another randomized, double-blind trial conducted in patients with sterile necrotizing pancreatitis demonstrated similar rates of infection, operation, and death between the groups receiving meropenem or placebo[45]. In addition, imipenem-cilastatin was also tested in patients with ANP. However, it did not reduce the incidence of IPN and increased the risk of fungal infections[46].

In summary, current evidence does not support the use of prophylactic antibiotics in patients with necrotizing pancreatitis since it is ineffective in reducing IPN and may be associated with potential risks.

Immune enhancement therapy

Given that there is evidence of immunosuppression in the early phase of SAP and its association with infectious complications[10,47-49], the Chinese Acute Pancreatitis Clinical Trials Group (CAPCTG) conducted serial trials to test the effects of immune enhancement by subcutaneous injection of thymosin alpha 1 (Tα1) on the incidence of IPN[14]. In the pilot trial, it was found that the 28-d positive blood culture rate was almost half in the thymosin α1 group than in the control group (16.6% *vs* 41.7%, $P = 0.012$), and the rate of IPN decreased from 29.4% to 8.3% ($P = 0.036$) after the treatment of thymosin α1. However, the phase III confirmatory trial found that the immune-enhancing Tα1 treatment did not significantly reduce the incidence of IPN compared with placebo in patients with predicted severe ANP. This was followed by a *post-hoc* analysis of the trial[50], which found that patients with predicted severe ANP and no lymphopenia (baseline ALC ≥ 0.8×10^9/L) may benefit from Tα1. However, due to the *post-hoc* design, new trials are needed to confirm the findings before any formal recommendation can be made.

CONCLUSION

In conclusion, several evidence-supported predictive markers and scoring systems are readily available for predicting IPN. However, effective treatments to reduce the incidence of IPN are still lacking apart from early enteral nutrition. In future research, a more homogeneous group of patients should be selected with reliable risk-stratification tools since such a strategy may help find the effective treatment to reduce the risk of IPN, thereby achieving individualized treatment.

FOOTNOTES

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