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PANCREOSCOPIE ONLINE

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#Data on File

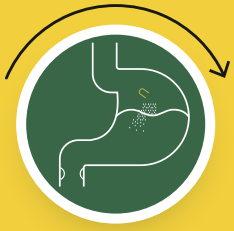
In Pancreatic Exocrine Insufficiency*

Rx

Creon®

Pancreatin Minimicrospheres®Capsules

RIGHT ENZYME | **RIGHT** TIME | **RIGHT** PLACE



RIGHT ENZYME

Adequate lipase, amylase, and protease Additional advantage of Phospholipase A2 and Cholesterolesterase[1]

RIGHT TIME

Gastric acid protection smooth transition to duodenum without dilution in stomach[2]

RIGHT PLACE

Rapid Enzyme release at right pH for maximum lipase availability[2]

AVAILABLE AS

Rx Creon® 10000
Pancreatin Minimicrospheres®Capsules

Rx Creon® 25000
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SCAN THE QR CODE TO VIEW CREON® MMS TECHNOLOGY

*Refer API of Creon | References: 1. Data on file. 2. Shrikhande SV, et al. Drug Design, Development and Therapy. 2021;15:3835.

1. GENERIC NAME AND BRAND NAME: PANCREATIN MINIMICROSPHERE CAPSULESCreon® 10000/ Creon® 25000/ Creon® 40000 2. QUALITATIVE AND QUANTITATIVE COMPOSITION Pancreatin minimicrospheres capsules (Creon® 10000) Each hard gelatin capsule contains: Pancreatin Minimicrospheres equivalent to Pancreatin IP 150 mg Excipients q.s. Colours used in capsule shell: Brilliant Blue FCF, Ponceau 4R, Sunset Yellow FCF, Titanium Dioxide IP Minimicrospheres supplied by Abbott Laboratories GmbH Germany with declared enzyme activity. Amylase 8000 (Ph.Eur.U)/U Lipase 10000 (Ph.Eur.U)/U Protease 600 (Ph.Eur.U)/U Pancreatin minimicrospheres capsules (Creon® 25000) Each hard gelatin capsule contains: Pancreatin Minimicrospheres equivalent to Pancreatin IP 300 mg Excipients q.s. Colours used in capsule shell: Brilliant Blue FCF, Ponceau 4R, Sunset Yellow FCF, Titanium Dioxide IP Minimicrospheres supplied by Abbott Laboratories GmbH Germany with declared enzyme activity. Amylase 18000 (Ph.Eur.U)/U Lipase 25000 (Ph.Eur.U)/U Protease 1000 (Ph.Eur.U)/U Pancreatin minimicrospheres capsules (Creon® 40000) Each hard gelatin capsule contains: Pancreatin Minimicrospheres equivalent to Pancreatin IP 400 mg Excipients q.s. Colours used in capsule shell: Black Oxide of Iron, Red Oxide of Iron, Yellow Oxide of Iron, Titanium Dioxide IP Minimicrospheres supplied by Abbott Laboratories GmbH Germany with declared enzyme activity. Amylase 25000 (Ph.Eur.U)/U Lipase 40000 (Ph.Eur.U)/U Protease 1600 (Ph.Eur.U)/U 3. DOSAGE FORM AND STRENGTH: Refer section 1 and 2 4. CLINICAL PARTICULARS: 4.1 THERAPEUTIC INDICATIONS Treatment of pancreatic exocrine insufficiency. 4.2 POSOLOGY AND METHOD OF ADMINISTRATION Dosage is based on individual needs and severity of the disease and the composition of food. It is recommended to take the enzymes during or immediately after the meals. The capsules should be swallowed intact, without crushing or chewing, with enough fluid during or after each meal or snack. When swallowing of capsules is difficult (e.g. small children or elderly patients), the capsules may be carefully opened and the pellets added to acidic soft food [pH < 5.5] that does not require chewing, or the pellets will be taken with acidic liquid [pH < 5.5]. This could be apple sauce or yogurt or fruit juice with a pH less than 5.5, e.g. apple, orange or pineapple juice. This mixture should not be stored. Crushing and chewing of the pellets or mixing with food or fluid with a pH greater than 5.5 can disrupt the protective enteric coating. This can result in early release of enzymes in the oral cavity and may lead to reduced efficacy and irritation of the mucous membranes. Care should be taken that no product is retained in the mouth. It is important to ensure adequate hydration at all times, especially during periods of increased loss of fluids. Inadequate hydration may aggravate constipation. Any mixture of the pellets with food or liquids should be used immediately and should not be stored. Dosing In Paediatric and Adult Patients With Cystic Fibrosis Based upon a recommendation of the Cystic Fibrosis (CF) Consensus Conference, the US CF Foundation case-control study, and the UK case-control study, the following general dosage recommendation for pancreatic enzyme replacement therapy can be proposed: • Weight-based enzyme dosing should begin with 1000 lipase units/kg/meal for children less than four years of age and with 500 lipase units/kg/meal for those over age four. • Dosage should be adjusted according to the severity of the disease, control of steatorrhea and maintenance of good nutritional status. • Most patients should remain below or should not exceed 10000 lipase units/kg body weight per day or 4000 lipase units/gram fat intake Administration via Gastrostomy Tube Creon® 10000, 25000 and 40000 can be administered via G-tube if medically indicated. Creon® have a pellet/sphere size with a diameter of 0.7-1.6mm. It is important that the appropriateness of the selected syringe and tube is carefully tested. For preparation and administration instructions, see section Special Precautions for Disposal <and other handling>. Dosing In Other Conditions Associated With Exocrine Pancreatic Insufficiency Dosage should be individualized by patients according to the degree of maldigestion and the fat content of the meal. The required dose for a meal ranges from about 25000 to 80000 Ph. Eur.units of lipase and half of the individual dose for snacks. 4.3 CONTRAINDICATIONS Hypersensitivity to active substance or to any of the excipients. 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE Strictures of the ileo-caecum and large bowel (fibrosing colonopathy) have been reported in patients with cystic fibrosis taking high doses of pancreatin preparations. As a precaution, unusual abdominal symptoms or changes in abdominal symptoms should be medically assessed to exclude the possibility of fibrosing colonopathy, especially if the patient is taking in excess of 10,000 units of lipase/kg/day. 4.5 USE IN SPECIAL POPULATION Fertility and pregnancy For pancreatic enzymes no clinical data on exposed pregnancies are available. Animal studies show no evidence for any absorption of porcine pancreatic enzymes. Therefore, no reproductive or developmental toxicity is to be expected. Caution should be exercised when prescribing to pregnant women. Lactation No effects on the suckling child are anticipated since animal studies suggest no systemic exposure of the breastfeeding woman to pancreatic enzymes. Pancreatic enzymes can be used during breastfeeding. If required during pregnancy and lactation Creon® should be used in doses sufficient to provide adequate nutritional status. Paediatric Use The safety and efficacy of pancreatic enzyme products with different formulations consisting of the same active ingredient (lipases, proteases, and amylases) for treatment of children with exocrine pancreatic insufficiency due to cystic fibrosis have been described in the medical literature and through clinical experience. Dosing of pediatric patients should be in accordance with recommended guidance from the Cystic Fibrosis Foundation Consensus Conferences. Doses of other pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with fibrosing colonopathy in children less than 12 years of age. Geriatric Use Clinical studies of CREON did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Creon® has no or negligible influence on the ability to drive and use machines. 4.8 UNDESIRABLE EFFECTS: In clinical trials, more than 1000 patients were exposed to Creon®. The most commonly reported adverse reactions were gastrointestinal disorders and were primarily mild or moderate in severity. The following adverse reactions have been observed during clinical trials with the below indicated frequencies:

Organ System	Very Common >1/10	Common >1/100 to <1/10	Uncommon >1/1000 to <1/100	Frequency not known
Gastrointestinal disorder	abdominal pain*	Nausea, vomiting, constipation, abdominal distention, diarrhea*		Strictures of ileo-caecum and large bowel (fibrosing colonopathy)
Skin and subcutaneous tissue disorders			rash	pruritus, urticaria
Immune system disorders				hypersensitivity (anaphylactic reactions).

*Gastrointestinal disorders are mainly associated with the underlying disease. Similar or lower incidences compared to placebo were reported for abdominal pain and diarrhea. Strictures of the ileo-caecum and large bowel (fibrosing colonopathy) have been reported in patients with cystic fibrosis taking high doses of pancreatin preparations (See section SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Allergic reactions mainly but not exclusively limited to the skin have been observed and identified as adverse reactions during postapproval use. Because these reactions were reported spontaneously from a population of uncertain size, it is not possible to reliably estimate their frequency. Paediatric population No specific adverse reactions were identified in the pediatric population. Frequency, type and severity of adverse reactions were similar in children with cystic fibrosis as compared to adults.ISSUED ON: 28-09-2023
SOURCE: Prepared based on full prescribing information, Version No. 8.0, dated 27.09.2023
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For full prescribing information, please contact: Medical Sciences Division, Abbott India Limited, Godrej BKC, Plot No. C – 68, BKC, Near MCA Club, Bandra (E), Mumbai – 400 051.

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SUMMARY

EDITORIAL

Dear Reader,

The Pancreoscopie Online editorial team is pleased to present the detailed analysis of articles dealing with pancreas disease management. Pancreas disease can be schematically divided into acute pancreatitis (including necrotizing pancreatitis), chronic pancreatitis and pancreatic cancer. The main causes of acute pancreatitis are gallstone migration and alcohol abuse.

Concerning acute pancreatitis, a systematic review and meta-analysis, published in "Pancreas", analyzed effect of aggressive intravenous fluid resuscitation versus nonaggressive fluid resuscitation. This study demonstrated that aggressive fluid therapy does not improve mortality rates in acute pancreatitis patients and seems associated with the increased the risk of acute renal and respiratory failure.

For severe acute biliary pancreatitis (gallstone migration), a nationwide analysis, published in "J Hepatobiliary Pancreas Sci", suggests that endoscopic retrograde cholangiopancreatography (ERCP) plays an important role in managing patients with acute biliary pancreatitis without cholangitis. Not only, patients who underwent inpatient ERCP appeared to have lower all-cause inpatient mortality than those who did not, but also, earlier ERCP was associated with several benefits in secondary outcomes, including less morbidity and lower hospital charges and costs. However, the APEC trial (Acute biliary Pancreatitis: urgent ERCP with sphincterotomy versus conservative treatment) has shown that patients with predicted severe acute biliary pancreatitis do not benefit from routine urgent ERCP with endoscopic sphincterotomy. A multicentre prospective study (called APEC-2), published recently in "Gut", demonstrated likewise that inpatients with predicted severe acute biliary pancreatitis without cholangitis, urgent ERCP with endoscopic sphincterotomy does not reduce major complications or mortality, even when guided by endoscopic ultrasonography.

Necrotizing pancreatitis is an extreme complication of acute pancreatitis which happens when pancreatitis inflammation is so severe that it causes tissue death (necrosis). A systematic review and meta-analysis, published in "Chinese Journal of Digestive Diseases", made a comparison of early and late intervention for necrotizing pancreatitis. This meta-analysis shows the benefit of late interventions in patients with necrotizing pancreatitis. In details, minimally invasive intervention performed 4 weeks after the onset of disease combined with intensive medical treatment may be associated with lower mortality and fewer procedure-related complications compared to early intervention.

In terms of chronic pancreatitis, a 11-year follow-up study, published in "Journal of Gastroenterology and Hepatology," shows that fully covered self-expandable metal stent may be effective for relieving refractory strictures in symptomatic chronic pancreatitis.

Finally, concerning malignant and benign pathologies in the pancreatic head, a large single-center study, published recently in "Annals of Surgery", suggests that only very few patients (3%) need completion pancreatectomy and that conservative, interventional and pancreas-preserving surgical measures are the mainstay of complication management after pancreatoduodenectomy. An early identification of at-risk patients with laboratory parameters and timely use of CT imaging should help to improve outcomes.

We hope you enjoy reading this detailed analysis of articles dealing with pancreas disease management.

We hope you enjoy reading it.
The Pancreoscopie Online editorial team

THE PANCREOSCOPIE ONLINE EDITORIAL TEAM

1 COMPARISON OF EARLY AND LATE INTERVENTION FOR NECROTIZING PANCREATITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Source : Chen Gu Niu, et al. J Dig Dis. 2023;1–11. DOI: 10.1111/1751-2980.13201

ABSTRACT

OBJECTIVE:

Postponed open necrosectomy or minimally invasive intervention has become the treatment option for necrotizing pancreatitis. Nevertheless, several studies point to the safety and efficacy of early intervention for necrotizing pancreatitis. Therefore, we conducted a systematic review and meta-analysis to compare clinical outcomes of acute necrotizing pancreatitis between early and late intervention.

RESULTS:

Fourteen studies were included in the final analysis. For open necrosectomy intervention, the overall pooled OR of mortality rate with the late intervention compared with early intervention was 7.09 (95% confidence interval [CI] 2.33–21.60; I2 = 54%; P = 0.0006). For minimally invasive intervention, the overall pooled OR of mortality rate with the late intervention compared with early intervention was 1.56 (95% CI 1.11–2.20; I2 = 0%; P = 0.01). The overall pooled OR of pancreatic fistula with the late minimally invasive intervention compared with early intervention was 2.49 (95% CI 1.75–3.52; I2 = 0%; P < 0.00001).

CONCLUSION:

These results showed the benefit of late interventions in patients with necrotizing pancreatitis in both minimally invasive procedures and open necrosectomy. Late intervention is preferred in the management of necrotizing pancreatitis.

IND2321192

DISCUSSION

Acute pancreatitis is a gastrointestinal disorder that may lead to various complications. Necrotizing pancreatitis is associated with significant morbidity and mortality, which afflicts up to 30% of the individuals with acute pancreatitis. In recent years, treatment paradigm for acute necrotizing pancreatitis has evolved from open necrosectomy to a step-up approach with minimally invasive procedures, in which minimally invasive retroperitoneal necrosectomy is recommended when percutaneous or endoscopic drainage fails. Nevertheless, open necrosectomy remains the treatment of choice for complicated pancreatic necrosis. Even if American Gastroenterological Association guidelines advocate postponing all interventions for pancreatic necrosis till at least 4 weeks after the onset of acute pancreatitis, the optimal timing for the intervention of necrotizing pancreatitis remains inconclusive and several studies point out the safety and efficacy of early intervention for necrotizing pancreatitis. Therefore, this systematic review and meta-analysis has been conducted in order to determine whether late intervention was superior to early intervention for the management of necrotizing pancreatitis, encompassing both minimally invasive intervention and open necrosectomy.

Literature search was performed in multiple databases for articles that compared the safety and clinical outcomes of early (<4 weeks from the onset of pancreatitis) versus late intervention (≥4 weeks from the onset of pancreatitis) for necrotizing pancreatitis published up to August 31, 2022. The meta-analysis was performed to determine pooled odds ratio (OR) of mortality rate and procedure-related complications. Patients were classified into two cohorts based on the interventions, ie, open necrosectomy and minimally invasive procedures. The primary outcome was the mortality rate. Odds ratio (OR) for the secondary outcomes including perforation, pancreatic fistula, persistent organ failure, endocrine insufficiency, and bleeding were analyzed, and pooled standardized difference (SD) in the mean length of hospitalization and ICU stay was calculated. A total of 520 studies were collected from MEDLINE (n = 114), EMBASE (n = 55), Web of Science (n = 60), Cochrane Library (n = 105), and Ovid (n = 186) databases, respectively.

For open necrosectomy, the overall pooled OR of mortality rate with the late intervention compared with early intervention was 7.09 (95% CI = [2.33–21.60] ; I2 = 54% ; p = 0.0006). While for minimally invasive intervention, the overall pooled OR of mortality rate with the late intervention compared with early intervention was 1.56 (95% CI = [1.11–2.20] ; I2 = 0% ; p = 0.01). The major complications were mostly reported in studies involving minimally invasive interventions in necrotizing pancreatitis. While for open necrosectomy, the data was insufficient so that the meta-analysis was not performed. The overall pooled OR of pancreatic fistula with late minimally invasive intervention compared with early intervention was 2.49 (95% CI = [1.75–3.52] ; I2 = 0% ; p < 0.00001), showing that pancreatic fistula was more common in patients receiving late minimally invasive intervention. While perforation, persistent organ failure, endocrine insufficiency and bleeding did not differ between the early and late minimally invasive intervention cohorts.

In conclusion, this systematic review and meta-analysis showed the benefit of late interventions in patients with necrotizing pancreatitis. Minimally invasive intervention performed 4 weeks after the onset of disease combined with intensive medical treatment may be associated with lower mortality and fewer procedure-related complications compared to early intervention. Meanwhile, the present study suggests early intensive medical management followed by late open necrosectomy for patients who are not candidates for minimally invasive intervention. This may guide physicians in determining the optimal intervention timing for acute necrotizing pancreatitis.

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THE PANCREOSCOPIE ONLINE EDITORIAL TEAM

2 THE ROLE AND TIMING OF ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY IN ACUTE BILIARY PANCREATITIS WITHOUT CHOLANGITIS: A NATIONWIDE ANALYSIS

Source : Simcha Weissman, et al. J Hepatobiliary Pancreat Sci. 2022 ; 00:1–10. DOI: 10.1002/jhbp.1285

ABSTRACT

OBJECTIVE:

The role and optimal timing of endoscopic retrograde cholangiopancreatography (ERCP) in acute biliary pancreatitis without cholangitis (ABPwoC) remains unclear. Using a large national database, we aimed to examine hospitalization outcomes of patients with ABPwoC as a function of the performance and timing of ERCP.

RESULTS:

Of the 70 030 patients with ABPwoC, 31.37% underwent inpatient ERCP. Performance (aOR: 0.6, $p < .05$), but not timing (aOR: 0.98, $p = .9$), of inpatient ERCP was associated with significantly lower all-cause inpatient mortality. Urgent ERCP (within 24 h) was associated with shorter hospital length of stay, lower charges and cost, and less need for pancreatic drainage procedures, while ERCP within 72 h was associated with less frequent intensive care unit admission (all $p < .05$).

CONCLUSION:

Based on this large, nationwide analysis, inpatient ERCP for ABPwoC is associated with lower all-cause mortality. ERCP within 24 and 72 h, though not associated with lower mortality, are associated with multiple improved clinical outcomes, including lower healthcare charges and costs.

IND2321192

DISCUSSION

Acute pancreatitis is an acute inflammatory disorder of the pancreas responsible for approximately 270 000 United States (US) hospital admissions per year, leading to enormous economic burden and considerable morbidity and mortality. Acute biliary pancreatitis (ABP), that is, gallstone pancreatitis, accounts for up to 60% of all acute pancreatitis cases. Initial management includes fluid resuscitation, pain control, early enteral nutrition, and supportive care for organ failure. In patients with ABP who also have acute cholangitis, urgent (within 24 h) endoscopic retrograde cholangiopancreatography (ERCP) is recommended. In the subset of patients with ABP without cholangitis (ABPwoC), however, the need for and optimal timing of ERCP are unclear. Herein, utilizing a large, nationwide database (National Inpatient Sample [NIS] from 2016–2017), the present retrospective study has been conducted in order to examine the performance and timing of ERCP on hospitalization outcomes in patients with ABPwoC.

Patients who underwent inpatient ERCP were stratified into performance: within 24, 24–48, 48–72, and >72 h of hospital admission. The primary outcome was all-cause inpatient mortality as a function of the performance and timing of ERCP; secondary outcomes, including healthcare utilization, were assessed. Multivariate modeling was used to adjust for potential confounders. Finally, a total of 70 030 adult patients with a diagnosis of ABPwoC were included in the analysis.

Of the 70 030 patients admitted with ABPwoC, 21 970 patients (31.37%) underwent ERCP during hospitalization. Mean time to ERCP was 57.12 h (2.38 days). Performance (aOR = 0.6 ; $p < 0.05$), but not timing (aOR = 0.98 ; $p = 0.9$), of inpatient ERCP was associated with significantly lower all-cause inpatient mortality. Urgent ERCP (within 24 h) was associated with shorter hospital length of stay, lower charges and cost, and less need for pancreatic drainage procedures, while ERCP within 72 h was associated with less frequent intensive care unit admission (all $p < 0.05$).

Mean Length of stay (LOS) for all patients admitted with ABPwoC was 5.02 days. Mean LOS for those who underwent ERCP within 24 h and after 24 h of admission were 4.12 and 6.42 days, respectively. Upon multivariate analysis, patients who underwent ERCP within 24 h had a significantly lower LOS compared to those who underwent ERCP at any time point after 24 h of admission (adjusted coefficient: −2.18 days; 95% CI = [−2.48 to −1.89] ; $p < 0.01$). Finally, patients who underwent ERCP within 24 h had significantly lower mean hospitalization charges and costs compared to those who underwent ERCP after 24 h of admission (adjusted coefficient: $-17 330 ; 95% CI = [$-21 754 to $-12 904, $p < 0.01$, and adjusted coefficient: $-3550 ; 95% CI = [$-4416 to $-2684] ; $p < 0.01$, respectively).

In conclusion, these results suggest that ERCP plays an important role in managing ABPwoC. Patients who underwent inpatient ERCP appear to have lower all-cause inpatient mortality than those who did not. In addition, while timing of inpatient ERCP did not impact mortality, earlier ERCP was associated with several benefits in secondary outcomes, including less morbidity and lower hospital charges and costs. Insofar, as high-quality and sizeable RCTs examining the role and timing of ERCP in ABPwoC are unlikely to be conducted, the findings of this large, nationwide study may serve as a useful clinical resource to effectively help guide patient care.

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THE PANCREOSCOPIE ONLINE EDITORIAL TEAM

3 PATIENT SELECTION FOR URGENT ENDOSCOPIC RETROGRADE CHOLANGIO-PANCREATOGRAPHY BY ENDOSCOPIC ULTRASOUND IN PREDICTED SEVERE ACUTE BILIARY PANCREATITIS (APEC-2): A MULTICENTRE PROSPECTIVE STUDY

Source : Nora D Hallensleben, et al. Gut 2023;0:1–9. DOI:10.1136/gutjnl-2022-328258

ABSTRACT

OBJECTIVE:

Routine urgent endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic biliary sphincterotomy (ES) does not improve outcome in patients with predicted severe acute biliary pancreatitis. Improved patient selection for ERCP by means of endoscopic ultrasonography (EUS) for stone/sludge detection may challenge these findings.

RESULTS:

Overall, 83 patients underwent urgent EUS at a median of 21 hours (IQR 17–23) after hospital presentation and at a median of 29 hours (IQR 23–41) after start of symptoms. Gallstones/sludge in the bile ducts were detected by EUS in 48/83 patients (58%), all of whom underwent immediate ERCP with ES. The primary endpoint occurred in 34/83 patients (41%) in the urgent EUS-guided ERCP group. This was not different from the 44% rate (50/113 patients) in the historical conservative treatment group (risk ratio (RR) 0.93, 95% CI 0.67 to 1.29; p=0.65). Sensitivity analysis to correct for baseline differences using a logistic regression model also showed no significant beneficial effect of the intervention on the primary outcome (adjusted OR 1.03, 95% CI 0.56 to 1.90, p=0.92).

CONCLUSION:

In patients with predicted severe acute biliary pancreatitis without cholangitis, urgent EUS-guided ERCP with ES did not reduce the composite endpoint of major complications or mortality, as compared with conservative treatment in a historical control group.

IND2321192

DISCUSSION

The APEC trial (Acute biliary Pancreatitis: urgent ERCP with sphincterotomy versus conservative treatment) has shown that patients with predicted severe acute biliary pancreatitis do not benefit from routine urgent endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES). Biliary decompression using ERCP with ES might be beneficial in a subselection of patients with proven common bile duct stones. Endoscopic ultrasonography (EUS) is one of the most sensitive diagnostic tools to detect bile duct stones and sludge; it prevents an ERCP in patients in whom stones have already passed into the duodenum spontaneously. It is unclear if a targeted approach with EUS-guided ERCP with ES improves outcomes in patients with a predicted severe acute biliary pancreatitis. Therefore, this prospective multicentre cohort study has been conducted in order to assess whether a strategy with urgent EUS followed by urgent ERCP with ES in the case of common bile duct (CBD) stones/sludge reduces major complications or mortality in patients with PSABP (APEC-2).

This cohort study was performed in 15 Dutch hospitals. The outcomes of this study were compared with the outcomes of the conservative treatment group of the APEC trial. The primary endpoint was a composite endpoint of major complications or mortality occurring within 6 months after inclusion. Major complications included: bacteraemia, cholangitis, new onset persistent organ failure (>48 hours or <48 hours and leading to death), pancreatic parenchymal necrosis, pneumonia and pancreatic endocrine or exocrine insufficiency. Secondary endpoints included: the incidence of the individual components of the primary endpoint, occurrence of new onset organ failure (transient=<48 hours or persistent>48 hours, single or multiorgan), ERCP-related complications, length of hospital stay, intensive care unit (ICU) admission, length of ICU stay, number of interventions (i.e. endoscopic, radiological or surgical), readmission for biliary events (i.e. recurrent biliary pancreatitis, cholecystitis, biliary colic, cholangitis and choledocholithiasis) and quality of life. Quality of life was measured using the SF-36 questionnaire. The follow-up of this study was 6 months. Between 15 August 2017 and 21 August 2019, 522 patients with acute biliary pancreatitis were assessed for eligibility.

Cholestasis was present in 53 out of 83 patients (64%) in the urgent EUS group and in 67 out of 113 patients (59%) in the conservative treatment group. Gallstones/sludge in the bile ducts were detected by EUS in 48/83 patients (58%), all of whom underwent immediate ERCP with ES. The primary composite endpoint of major complications or mortality occurred in 34 out of 83 patients (41%) in the urgent EUS group compared with 50 out of 113 patients (44%) in the conservative treatment group (RR = 0.93 ; 95% CI = [0.67-1.29] ; p = 0.65). Apart from a difference in the occurrence of pancreatic exocrine insufficiency, no other differences were found in the individual components of the primary endpoint. Sensitivity analysis to correct for baseline differences using a logistic regression model also showed no significant beneficial effect of the intervention on the primary outcome (adjusted OR = 1.03 ; 95% CI = [0.56-1.90] ; p = 0.92).

In conclusion, the combined results of the current prospective APEC-2 study and the original APEC trial show that inpatients with predicted severe acute biliary pancreatitis without cholangitis, urgent ERCP with ES, even when guided by EUS, does not reduce major complications or mortality. Therefore, a conservative treatment strategy is recommended in patients with predicted severe acute biliary pancreatitis, with an ERCP only in case of concomitant cholangitis (urgent indication) and symptomatic and/or persistent choledocholithiasis (elective indication).

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THE PANCREOSCOPIE ONLINE EDITORIAL TEAM

4 EFFECT OF AGGRESSIVE INTRAVENOUS FLUID RESUSCITATION VERSUS NONAGGRESSIVE FLUID RESUSCITATION IN THE TREATMENT OF ACUTE PANCREATITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Source : Xiaowen Ding, et al. Pancreas. Volume 52, Number 2, February 2023

ABSTRACT

OBJECTIVE:

Despite the need for active fluid therapy, fluid management of most acute pancreatitis (AP) cases is still supportive. The aim of this review is to compare the effect of aggressive versus nonaggressive intravenous (IV) fluid resuscitation in the treatment of acute pancreatitis.

RESULTS:

Fourteen trials involving 3423 acute pancreatitis patients were included in the review. We did not observe any differences in the risk of mortality, persistent organ failure, and systemic inflammatory response syndrome in both study groups. However, there was an increased risk of development of pancreatic necrosis, renal failure, and respiratory failure in the aggressive fluid therapy group compared with nonaggressive therapy. The funnel plot showed no publication bias.

CONCLUSION:

Aggressive fluid therapy did not improve mortality rates in acute AP patients and was associated with an increased risk of acute renal failure, and respiratory failure.

IND2321192

DISCUSSION

Acute pancreatitis (AP) is an inflammatory condition that results in severe morbidity with a mortality rate of 5% to 10% among the hospitalized patients. Despite the need for active fluid therapy, fluid management of most acute pancreatitis (AP) cases is still supportive. The American Gastroenterological Association recommended the use of aggressive intravenous (IV) fluid resuscitation in treating AP, but there is limited evidence regarding the type, volume, and rate of fluid resuscitation. However, several studies reported that aggressive IV fluids are associated with increased rates of respiratory and acute renal failure. The aim of this review was to compare the effect of aggressive and nonaggressive IV fluid resuscitation in the treatment of acute pancreatitis.

This review of literature, included parallel arm or cluster randomized controlled trial (RCT), and cohort studies (prospective and retrospective) comparing aggressive IV fluid resuscitation to nonaggressive fluid resuscitation as the treatment option for acute pancreatitis. All publications referred in medical databases, such as Medline, Google Scholar, Science Direct, and Cochrane Central, until April 2022, have been analyzed. The primary outcome was in-hospital mortality. The secondary outcomes chosen were complications pertaining to AP during the disease course (namely SIRS), persistent organ failure, acute kidney injury, respiratory failure (requiring mechanical ventilation), and pancreatic necrosis. All these study outcomes were defined as per the individual study's definitions. In total, 14 trials involving 3423 acute pancreatitis patients were included in the review.

No differences in the risk of mortality (RR =1.28 ; 95% CI = [0.85–1.94]), persistent organ failure (RR = 1.00 ; 95% CI = [0.43–2.32]), and systemic inflammatory response syndrome (RR = 1.02 ; 95% CI = [0.73–1.42]) have been observed in both study groups (aggressive vs. non aggressive resuscitation). However, there was an increased risk of development of pancreatic necrosis (RR = 1.58 ; 95% CI = [1.10–2.25]), renal failure (RR = 2.01 ; 95% CI = [1.56–2.58]), and respiratory failure (RR = 1.69 ; 95% CI = [1.13–2.50]) in the aggressive fluid therapy group compared with the nonaggressive therapy group. The funnel plot showed no publication bias.

In conclusion, this review and meta-analysis shows that aggressive fluid therapy do not improve mortality rates in acute AP patients and seems associated with the increased risk of acute renal and respiratory failure. Further clinical trials evaluating the effectiveness of fluid therapy need to be undertaken to support the use of aggressive therapy over goal directed IV fluid resuscitation.

IND2321192

THE PANCREOSCOPIE ONLINE EDITORIAL TEAM

5 ETIOLOGY AND OUTCOME OF ACUTE RECURRENT PANCREATITIS AND CHRONIC PANCREATITIS

Source : Songpon Getsuwan, et al. Pediatrics International (2022) 64, e15145. DOI: 10.1111/ped.15145

ABSTRACT

OBJECTIVE:

Owing to the lack of data, we aimed to determine the etiology and outcome of acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) in children in Southeast Asia..

RESULTS:

Among 155 patients with pancreatitis, 21 (13.5%) were diagnosed with either ARP (n = 7) or CP (n = 14). Clinical manifestations of CP included chronic abdominal pain (n = 10, 71.4%), steatorrhea (n = 8, 57.1%), and diabetes mellitus (n = 1, 7.1%). Positive radiological findings compatible with CP were detected from an abdominal ultrasound, computed tomography, magnetic resonance cholangiopancreatography in 70%, 90.9%, and 92.9% of patients, respectively. Genetic, metabolic, and pancreaticobiliary causes were the major causes of ARP/CP (23.8% each) and the etiologies were unidentified in one-fifth of the patients. Patients with metabolic diseases who had AP were at-risk of developing ARP (hazards ratio [HR], 4.7, 95% confidence interval [CI]: 1.5–13.9). Children with ARP or CP were younger than those with AP (P = 0.04). Approximately two-thirds of patients with CP had growth faltering and they had more episodes of hospitalization due to acute attacks when compared to patients with ARP (4 [interquartile range [IQR], 3–6] vs. 3 [IQR, 2–3]; P = 0.02).

CONCLUSION:

Genetic, metabolic, and pancreaticobiliary diseases were the common etiologies of ARP and CP among children living in a developing country in Southeast Asia. The burden of CP included malnutrition and frequent hospitalization. The findings emphasize the importance of an early etiological diagnosis and monitoring for pancreatic insufficiency in ARP/CP.

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DISCUSSION

Pediatric pancreatitis can be divided into acute pancreatitis (AP), acute recurrent pancreatitis (ARP), and chronic pancreatitis (CP). While the inflammation in AP is reversible, the pathophysiology of CP is characterized by progressive pancreatic fibroinflammation leading to exocrine and endocrine pancreatic insufficiency (PI). Studies on pediatric ARP and CP in developing countries, particularly from Southeast Asia, are sparse. Therefore, the present retrospective study aimed to determine the etiology and outcome of both conditions in this region. Secondary objectives included finding associated factors among ARP and CP compared to AP, and ARP compared to CP.

Medical records at a university hospital in Bangkok (Thailand) from January 2000 to March 2021 have been retrospectively reviewed. The study enrolled children and adolescents aged 0.5–18 years who were diagnosed with pancreatitis. In total, 155 patients with pancreatitis have been included in the analysis.

Among 155 patients with pancreatitis, 21 (13.5%) were diagnosed with either ARP (n = 7) or CP (n = 14). Clinical manifestations of CP included chronic abdominal pain (n = 10, 71.4%), exocrine PI with steatorrhea (n = 8, 57.1%), and diabetes mellitus (n = 1, 7.1%). Positive radiological findings compatible with CP were detected from abdominal ultrasound (14/20 patients, 70.0%), computed tomography (10/11 patients, 90.9%), and magnetic resonance cholangiopancreatography (MRCP, 13/14 patients, 92.9%). The most common radiological finding in abdominal ultrasound and CT was parenchymal change, while MRCP could define both parenchymal and ductal abnormalities. Genetic, metabolic, and pancreaticobiliary causes were the major causes of ARP/CP (23.8% each) and the etiologies were unidentified in one-fifth of the patients. Patients with metabolic diseases who had AP were at risk of developing ARP (HR = 4.7 ; 95% CI = [1.5–13.9]). Patients with ARP or CP presented at a younger age than patients with AP (p = 0.04). Finally, regarding the association between ARP and CP, patients with CP had a greater number of total episodes of acute attack that required hospitalization compared to patients with ARP (4 vs. 3 times ; p = 0.02). There was no statistical difference between age at onset of the first attack when compared ARP to CP.

In conclusion, genetic, metabolic, and pancreaticobiliary diseases remained the common etiology of ARP and CP in children living in a developing country in Southeast Asia. An etiology in one-fifth of patients remained unidentified. Monitoring for PI is important in patients with ARP and CP, whose burdens could include frequent hospitalization and malnutrition. Several improvements could be made for early etiological diagnosis and management of treatable causes of ARP to prevent the development of CP, a condition that could lead to significant morbidities, frequent hospitalization, and mortality.

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THE PANCREOSCOPIE ONLINE EDITORIAL TEAM

6 COMPLETION PANCREATECTOMY AFTER PANCREATODUODENECTOMY: WHO NEEDS IT?

Source : Martin Loos, et al. Annals of Surgery, Volume 278, Number 1, July 2023. DOI: 10.1097/SLA.0000000000005494

ABSTRACT

BACKGROUND:

The objective of this study was to identify the indications for and report the outcomes of completion pancreatectomy (CPLP) in the postoperative course after pancreatoduodenectomy (PD). Background CPLP may be considered or even inevitable for damage control after PD.

RESULTS:

A total of 3953 consecutive patients underwent PD during the observation period. CPLP was performed in 120 patients (3%) after a median of 10 days following PD. The main indications for CPLP included postpancreatectomy acute necrotizing pancreatitis [n=47 (39%)] and postoperative pancreatic fistula complicated by hemorrhage [n=41 (34%)] or associated with uncontrollable leakage of the pancreatoenteric anastomosis [n=23 (19%)]. The overall 90-day mortality rate of all 3953 patients was 3.5% and 37% for patients undergoing CPLP.

CONCLUSION:

Our finding that only very few patients (3%) need CPLP suggests that conservative, interventional, and organ-preserving surgical measures are the mainstay of complication management after PD. Postpancreatectomy acute necrotizing pancreatitis, uncontrollable postoperative pancreatic fistula, and fistula-associated hemorrhage are highly dangerous and represent the main indications for CPLP after PD.

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DISCUSSION

Pancreatoduodenectomy (PD) is the standard procedure for malignant and benign pathologies in the pancreatic head. Advances in surgical technique along with improvements in perioperative care and better complication management have led to a decrease in mortality to <5% in high-volume centers. However, postoperative morbidity rates remain high. Severe complications such as postoperative pancreatic fistula (POPF), postpancreatectomy acute (and even necrotizing) pancreatitis (PPAP), postpancreatectomy hemorrhage (PPH), or abdominal sepsis are feared complications associated with increased postoperative mortality of up to > 50%. Although several pancreas-preserving surgical strategies such as necrosectomy and drainage, redo of the pancreatic anastomosis, and external wirsungostomy have been reported in the literature, completion pancreatectomy (CPLP) is the only therapeutic approach enabling the eradication of the underlying cause of morbidity in case of severe POPF or necrotizing PPAP. The aim of this retrospective analysis was to identify indications for CPLP and to assess outcomes of CPLP in complication management after PD.

The prospectively maintained pancreas database of the Department of General, Visceral and Transplantation Surgery was searched for all patients who had undergone PD at the Heidelberg University Hospital, Germany, between October 1, 2001, and December 31, 2019. Those patients in whom CPLP was necessary in the postoperative course after PD were identified and included in the analysis. Baseline characteristics, perioperative details, and outcomes of CPLP patients were analyzed and specific indications for CPLP were identified. A total of 3953 consecutive patients underwent PD during the observation period. CPLP was performed in 120 patients (3%) after a median of 10 days following PD.

The median reoperation time was 165 minutes and the median blood loss during CPLP was 1450 mL. Ninety-four patients (78%) needed an intraoperative blood transfusion and the median number of packed red blood cells was 3. Intraoperative findings that required CPLP included acute necrotizing pancreatitis (n = 47, 39%), PPH (n = 41, 34%), and uncontrollable leakage of the pancreaticojejunostomy (n = 23, 19%). The overall 90-day mortality rate of all 3953 patients was 3.5% and 37% for patients undergoing CPLP. Stratified by indication for CPLP, patients undergoing CPLP for PPH (n = 41) had the highest 90-day mortality rate (46%) and all but 1 of these 41 patients had POPF (98%) and 82% had PPAP. The 90-day mortality rate of patients undergoing CPLP for necrotizing PPAP was 28%. The vast majority of patients with acute necrotizing pancreatitis also had POPF (83%). Uncontrollable leakage of the pancreaticojejunostomy as the main indication for CPLP was associated with a 90-day mortality rate of 39%. Of the 102 patients with POPF, 91 patients also had PPAP (89%).

In conclusion, this large single-center study suggests that only very few patients (3%) need CPLP and that conservative, interventional and pancreas-preserving surgical measures are the mainstay of complication management after PD. The sequelae of adverse postoperative events requiring CPLP seem to evolve mostly from the combination of postpancreatectomy acute (necrotizing) pancreatitis with POPF. Early identification of these patients with laboratory parameters and timely use of CT imaging may help to improve outcomes of this subgroup of patients. Post-operative serum amylase levels are highly elevated in patients with postpancreatectomy acute necrotizing pancreatitis and could therefore be useful to identify those patients. However, further studies are needed to better understand the role of PPAP in patients with adverse short-term outcomes after PD, especially in those patients with simultaneous POPF.

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THE PANCREOSCOPIE ONLINE EDITORIAL TEAM

7 LONG-TERM CLINICAL OUTCOMES OF A FULLY COVERED SELF-EXPANDABLE METAL STENT FOR REFRACTORY PANCREATIC STRICTURES IN SYMPTOMATIC CHRONIC PANCREATITIS: AN 11-YEAR FOLLOW-UP STUDY

Source : Sung Woo Ko, et al. Journal of Gastroenterology and Hepatology. January 8, 2023. DOI: 10.1111/jgh.16105

ABSTRACT

BACKGROUND:

A fully covered self-expandable metal stent (FCSEMS) has recently been applied in the management of chronic pancreatitis patients with pancreatic strictures. However, related long-term effects remain unclear. This study aimed to evaluate the long-term outcomes of FCSEMS placement in chronic pancreatitis patients with refractory strictures.

RESULTS:

A total of 35 patients were included. Technical success was achieved in all patients. The median FCSEMS indwelling time was 3.2 months (interquartile range [IQR], 3.0–4.9 months). Radiological success was achieved in all patients (complete, n = 2; partial, n = 33). Clinical success was achieved in 29 patients (82.9%; complete analgesic cessation, n = 19; analgesic reduction >50%, n = 11). During the median follow-up of 136 months, (IQR, 85.8–145.5 months), eight patients (22.9%) experienced recurrence. The median interval from stent removal to recurrence was 24.9 months (IQR, 11.3–30.3 months). Biliary obstruction, an early adverse event, occurred in two patients (5.7%); the late adverse event stent-induced de novo stricture was observed in 17 patients (48.6%).

CONCLUSION:

Our findings suggest that an FCSEMS is effective for relieving refractory strictures in chronic pancreatitis. However, FCSEMSs were associated with stent-induced de novo strictures in nearly half of the patients. Prospective studies are required to further evaluate the long-term efficacy and safety of FCSEMSs in chronic pancreatitis.

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DISCUSSION

An endoscopic placement of single plastic stent has been recommended for the management of symptomatic chronic pancreatitis with main pancreatic duct (MPD) stricture. Current guidelines recommend the application of multiple side-by-side plastic stents in the management of refractory pancreatic strictures. Fully covered self-expandable metal stent (FCSEMS) placement has been utilized as an alternative treatment option for symptomatic refractory pancreatic strictures in patients with chronic pancreatitis. Albeit several studies have focused on the clinical efficacy and safety of FCSEMS in such patients, this has not been sufficiently examined in the long term. Therefore, the present retrospective study has been conducted in order to evaluate the long-term clinical outcomes of FCSEMS placement for refractory symptomatic strictures in patients with chronic pancreatitis.

A total of 35 patients (29 men; median age = 47 years) undergoing FCSEMS placement for refractory pancreatic strictures between September 2008 and December 2010 have been included in the analysis. The main outcomes were technical, radiological, and clinical success, as well as recurrence and adverse events.

Technical success was achieved in all patients. In terms of radiological outcomes, success was achieved in all patients, with complete radiological success in 2 (5.7%) and partial radiological success in 33 (94.3%). Clinical success was achieved in 29 of 35 patients (82.9% 95% ; CI = [65.7–92.8%]) ; among them, 18 patients (51.4%) were able to stop treatment with analgesics, and 11 (31.4%) experienced ≥50% decreases in analgesic doses after FCSEMS insertion.

The median indwelling time of placed FCSEMSs was 3.2 months (IQR = [3–4.9]). During FCSEMS placement, stent migration was not observed in any patient. In terms of long-term clinical outcomes, median follow-up period was 136 months (IQR, 85.8–145.5 months). During follow-up, 8 patients (22.9%) experienced recurrence, with a median interval from stent removal to recurrence of 24.9 months (IQR = [11.3–30.3]). Biliary obstruction, an early adverse event, occurred in 2 patients (5.7%) ; the late adverse event stent-induced de novo stricture was observed in 17 patients (48.6%).

In conclusion, FCSEMS may be effective for relieving refractory strictures in symptomatic chronic pancreatitis. Although it has not been observed FCSEMS migration, stent-induced de novo strictures were associated with FCSEMSs in approximately 48% of patients during follow-up. Long-term prospective studies with a sufficient number of cases are needed to investigate and validate the clinical efficacy and safety of placing newly developed FCSEMS to treat refractory pancreatic stricture in chronic pancreatitis patients.

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THE PANCREOSCOPIE ONLINE EDITORIAL TEAM

8 CLINICAL PRACTICE GUIDELINES FOR PANCREATIC CANCER 2022 FROM THE JAPAN PANCREAS SOCIETY: A SYNOPSIS

Source : Takuji Okusaka, et al. International Journal of Clinical Oncology. February 14, 2023. DOI: 10.1007/s10147-023-02317-x

ABSTRACT

OBJECTIVES:

Clinical Practice Guidelines for Pancreatic Cancer was first published in 2006 by the Japan Pancreas Society, and revised in 2009, 2013, 2016, and 2019. In July 2022, Clinical Practice Guidelines for Pancreatic Cancer was newly revised in Japanese.

RESULTS:

The guideline includes algorithms for diagnosis, treatment, chemotherapy, and precision medicine of pancreatic cancer, and addresses 7 subjects: diagnosis, surgical therapy, adjuvant therapy, radiation therapy, chemotherapy, stent therapy, and supportive & palliative medical care. It includes 73 clinical questions and 112 statements. The statements correspond to the clinical questions, evidence levels, recommendation strengths, and agreement rates.

CONCLUSION:

This guideline represents the most standard clinical and practical management guideline available until date in Japan. This is the English synopsis of the Clinical Practice Guidelines for Pancreatic Cancer 2022 in Japanese, and is an attempt to disseminate the Japanese guideline worldwide to introduce the Japanese approach to the clinical management of pancreatic cancer.

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DISCUSSION

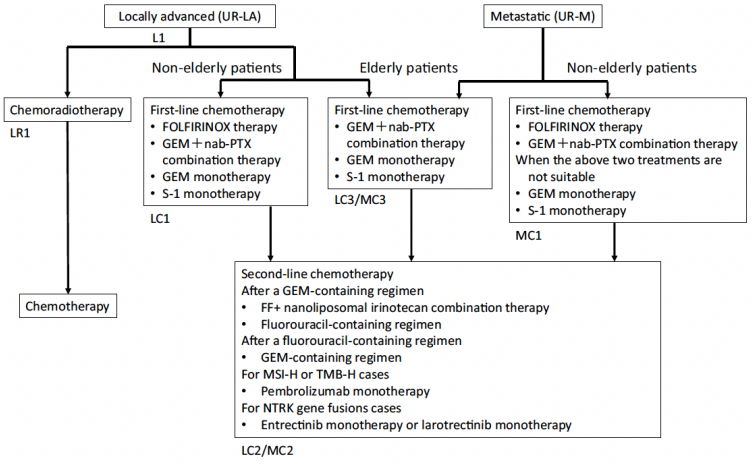
The Clinical Practice Guidelines for Pancreatic Cancer based on Evidence-Based Medicine 2006 was first published by the Japan Pancreas Society (JPS), and has undergone repeated revision: in July 2009, October 2013, October 2016, and July 2019, with the last new revision published in July 2022.

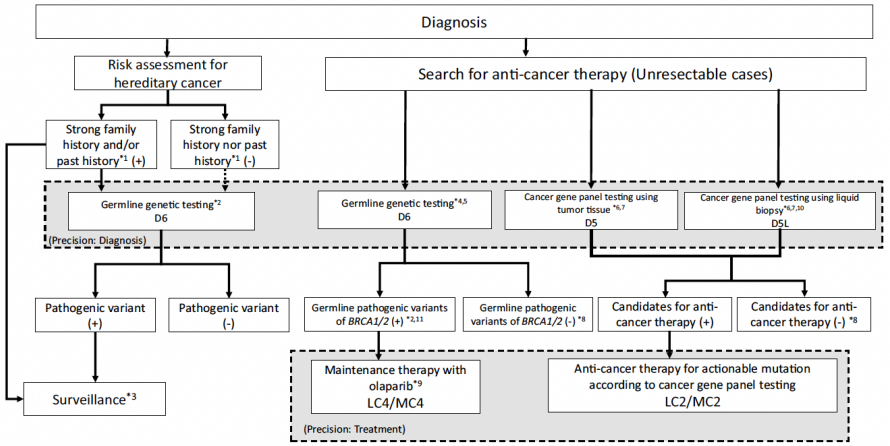
For this latest revision, entirely new guidelines according to the Minds Manual for Guideline Development 2020 have been developed, which include the concepts of GRADE (Grading Recommendations Assessment, Development, and Evaluation). There were changes in the composition of the committee members for this revision, and more specialists from a wide variety of fields were included to avoid biases in the recommendations. Patients and the public have been actively involved in both the guideline development and implementation, with the organization for this revision of "the patient and public group" including four representatives for patients and/or members of the public and four health professionals.

The analyzed algorithms present the flows for the diagnosis, treatment, chemotherapy, and precision medicine of pancreatic cancer. So, the guidelines include these algorithms and address 7 subjects: diagnosis, surgical therapy, adjuvant therapy, radiation therapy, chemotherapy, stent therapy, and supportive & palliative medical care. It includes 73 clinical questions and 112 statements. The statements correspond to the clinical questions, evidence levels, recommendation strengths, and agreement rates.

These guidelines represent the most standard guidelines for clinical and practical care of patients with pancreatic cancer available at this time. However, they should not be inflexibly used for the practical management of individual patients. Finally, the English synopsis of the Japanese Clinical Practice Guidelines for Pancreatic Cancer 2022 is an attempt to disseminate the Japanese guidelines worldwide to introduce the Japanese approach to the clinical management of pancreatic cancer.

Figure: Algorithm for chemotherapy of pancreatic cancer.
GEM: gemcitabine; nab-PTX: nab-paclitaxel;
FF: fluorouracil + calcium folinate; MSI-H: microsatellite instability-high;
TMB-H: tumor mutational burden-high





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This statement is derived from reference no. 2 and 3.

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1. GENERIC NAME AND BRAND NAME: PANCREATIN MINIMICROSPHERE CAPSULESCreon® 10000/ Creon® 25000/ Creon® 40000 2. QUALITATIVE AND QUANTITATIVE COMPOSITION Pancreatin minimicrospheres capsules (Creon® 10000) Each hard gelatin capsule contains: Pancreatin Minimicrospheres equivalent to Pancreatin IP 150 mg Excipients q.s. Colours used in capsule shell: Brilliant Blue FCF, Ponceau 4R, Sunset Yellow FCF, Titanium Dioxide IP Minimicrospheres supplied by Abbott Laboratories GmbH Germany with declared enzyme activity. Amylase 8000 (Ph.Eur.U)/U Lipase 10000 (Ph.Eur.U)/U Protease 600 (Ph.Eur.U)/U Pancreatin minimicrospheres capsules (Creon® 25000) Each hard gelatin capsule contains: Pancreatin Minimicrospheres equivalent to Pancreatin IP 300 mg Excipients q.s. Colours used in capsule shell: Brilliant Blue FCF, Ponceau 4R, Sunset Yellow FCF, Titanium Dioxide IP Minimicrospheres supplied by Abbott Laboratories GmbH Germany with declared enzyme activity. Amylase 18000 (Ph.Eur.U)/U Lipase 25000 (Ph.Eur.U)/U Protease 1000 (Ph.Eur.U)/U Pancreatin minimicrospheres capsules (Creon® 40000) Each hard gelatin capsule contains: Pancreatin Minimicrospheres equivalent to Pancreatin IP 400 mg Excipients q.s. Colours used in capsule shell: Black Oxide of Iron, Red Oxide of Iron, Yellow Oxide of Iron, Titanium Dioxide IP Minimicrospheres supplied by Abbott Laboratories GmbH Germany with declared enzyme activity. Amylase 25000 (Ph.Eur.U)/U Lipase 40000 (Ph.Eur.U)/U Protease 1600 (Ph.Eur.U)/U 3. DOSAGE FORM AND STRENGTH: Refer section 1 and 2 4. CLINICAL PARTICULARS: 4.1 THERAPEUTIC INDICATIONS Treatment of pancreatic exocrine insufficiency. 4.2 POSOLOGY AND METHOD OF ADMINISTRATION Dosage is based on individual needs and severity of the disease and the composition of food. It is recommended to take the enzymes during or immediately after the meals. The capsules should be swallowed intact, without crushing or chewing, with enough fluid during or after each meal or snack. When swallowing of capsules is difficult (e.g. small children or elderly patients), the capsules may be carefully opened and the pellets added to acidic soft food [pH < 5.5] that does not require chewing, or the pellets will be taken with acidic liquid [pH < 5.5]. This could be apple sauce or yogurt or fruit juice with a pH less than 5.5, e.g. apple, orange or pineapple juice. This mixture should not be stored. Crushing and chewing of the pellets or mixing with food or fluid with a pH greater than 5.5 can disrupt the protective enteric coating. This can result in early release of enzymes in the oral cavity and may lead to reduced efficacy and irritation of the mucous membranes. Care should be taken that no product is retained in the mouth. It is important to ensure adequate hydration at all times, especially during periods of increased loss of fluids. Inadequate hydration may aggravate constipation. Any mixture of the pellets with food or liquids should be used immediately and should not be stored. Dosing In Paediatric and Adult Patients With Cystic Fibrosis Based upon a recommendation of the Cystic Fibrosis (CF) Consensus Conference, the US CF Foundation case-control study, and the UK case-control study, the following general dosage recommendation for pancreatic enzyme replacement therapy can be proposed: • Weight-based enzyme dosing should begin with 1000 lipase units/kg/meal for children less than four years of age and with 500 lipase units/kg/meal for those over age four. • Dosage should be adjusted according to the severity of the disease, control of steatorrhea and maintenance of good nutritional status. • Most patients should remain below or should not exceed 10000 lipase units/kg body weight per day or 4000 lipase units/gram fat intake Administration via Gastrostomy Tube Creon® 10000, 25000 and 40000 can be administered via G-tube if medically indicated. Creon® have a pellet/sphere size with a diameter of 0.7-1.6mm. It is important that the appropriateness of the selected syringe and tube is carefully tested. For preparation and administration instructions, see section Special Precautions for Disposal <and other handling>. Dosing In Other Conditions Associated With Exocrine Pancreatic Insufficiency Dosage should be individualized by patients according to the degree of maldigestion and the fat content of the meal. The required dose for a meal ranges from about 25000 to 80000 Ph. Eur.units of lipase and half of the individual dose for snacks. 4.3 CONTRAINDICATIONS Hypersensitivity to active substance or to any of the excipients. 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE Strictures of the ileo-caecum and large bowel (fibrosing colonopathy) have been reported in patients with cystic fibrosis taking high doses of pancreatin preparations. As a precaution, unusual abdominal symptoms or changes in abdominal symptoms should be medically assessed to exclude the possibility of fibrosing colonopathy, especially if the patient is taking in excess of 10,000 units of lipase/kg/day. 4.5 USE IN SPECIAL POPULATION Fertility and pregnancy For pancreatic enzymes no clinical data on exposed pregnancies are available. Animal studies show no evidence for any absorption of porcine pancreatic enzymes. Therefore, no reproductive or developmental toxicity is to be expected. Caution should be exercised when prescribing to pregnant women. Lactation No effects on the suckling child are anticipated since animal studies suggest no systemic exposure of the breastfeeding woman to pancreatic enzymes. Pancreatic enzymes can be used during breastfeeding. If required during pregnancy and lactation Creon® should be used in doses sufficient to provide adequate nutritional status. Paediatric Use The safety and efficacy of pancreatic enzyme products with different formulations consisting of the same active ingredient (lipases, proteases, and amylases) for treatment of children with exocrine pancreatic insufficiency due to cystic fibrosis have been described in the medical literature and through clinical experience. Dosing of pediatric patients should be in accordance with recommended guidance from the Cystic Fibrosis Foundation Consensus Conferences. Doses of other pancreatic enzyme products exceeding 6,000 lipase units/kg of body weight per meal have been associated with fibrosing colonopathy in children less than 12 years of age. Geriatric Use Clinical studies of CREON did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Creon® has no or negligible influence on the ability to drive and use machines. 4.8 UNDESIRABLE EFFECTS: In clinical trials, more than 1000 patients were exposed to Creon®. The most commonly reported adverse reactions were gastrointestinal disorders and were primarily mild or moderate in severity. The following adverse reactions have been observed during clinical trials with the below indicated frequencies:

Organ System	Very Common >1/10	Common >1/100 to <1/10	Uncommon >1/1000 to <1/100	Frequency not known
Gastrointestinal disorder	abdominal pain*	Nausea, vomiting, constipation, abdominal distention, diarrhea*		Strictures of ileo-caecum and large bowel (fibrosing colonopathy)
Skin and subcutaneous tissue disorders			rash	pruritus, urticaria
Immune system disorders				hypersensitivity (anaphylactic reactions).

*Gastrointestinal disorders are mainly associated with the underlying disease. Similar or lower incidences compared to placebo were reported for abdominal pain and diarrhea. Strictures of the ileo-caecum and large bowel (fibrosing colonopathy) have been reported in patients with cystic fibrosis taking high doses of pancreatin preparations (See section SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Allergic reactions mainly but not exclusively limited to the skin have been observed and identified as adverse reactions during postapproval use. Because these reactions were reported spontaneously from a population of uncertain size, it is not possible to reliably estimate their frequency. Paediatric population No specific adverse reactions were identified in the pediatric population. Frequency, type and severity of adverse reactions were similar in children with cystic fibrosis as compared to adults.ISSUED ON: 28-09-2023
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