NOVEL DEVELOPMENTS IN PANCREATIC DISORDERS

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Prof Peter Layer from Germany analysed the recent novel findings with respect to pancreatic diseases.

First discussed was acute pancreatitis, still a devastating entity. Excessive alcohol intake and smoking are well established causes of chronic pancreatitis; their role in the pathogenesis of acute pancreatitis is less clear. A large case-control study with over 500 patients with acute pancreatitis compared to over 10,000 matched controls. It was clearly shown that the risk of acute pancreatitis rises with rising daily alcohol intake: ~50g-3 fold; ~70g-4.2fold; ~90g-5.3 fold; >100g-6.4 fold. Also, tobacco smoking increases the risk of acute pancreatitis approximately 2 fold, as shown in a meta-analysis of 12 studies. Clinicians should therefore be aware that smoking is a potential cause of 'idiopathic', especially relapsing acute pancreatitis. Such patients should therefore be strongly advised to quit smoking. How smoking leads to acute pancreatitis remains poorly understood.

What is also insufficiently realised in practice is that pancreatic cancer may occasionally present as acute pancreatitis. In a large American cohort with over 500,000 subjects, approximately 1 in 10 pancreatic cancers manifested first as acute pancreatitis. Most cancers became overt within 2 years post the presentation with acute pancreatitis. Whenever therefore, the cause of acute pancreatitis is not clear, meticulous EUS examination of the pancreas is indicated in order not to delay the detection of the underlying malignancy.

Hypertriglyceridemia is a well established cause of acute pancreatitis. Disease severity and risk of persistent organ failure are high, and parallel the severity of hypertriglyceridemia: mild < 200; moderate < 1,000; severe > 1,000 mg / dl. It is beyond doubt that hyper triglyceridemia is strongly associated with severe and complicated acute pancreatitis, either as the sole etiology or as amplifier of other causes. The involved pathogenetic mechanisms and therapeutic possibilities are insufficiently elucidated.

Most intriguing is the potential preventive role of statins in the prevention of acute pancreatitis, as analysed retrospectively in 4 million Californian subjects: acute pancreatitis risk (of any cause) was some 70% reduced in statin (simvastatin) users, especially with a dose of > 10 mg / d. As many confounders may be involved, these data beg for a prospective randomised study. How statins may be potentially preventive also needs further study.

Up to now, there has been little consensus with respect to the timing of cholecystectomy after (mild) biliairy pancreatitis. In an important study, over 250 patients with mild biliairy pancreatitis [CRP < 100mg / l;opiate-free pain control; oral refeeding] were randomized to immediate surgery (within 3 d of admission) versus delayed surgery (> 25 d after discharge). There was a ~70% decrease in relapse of biliairy symptoms and pancreatitis or death within 6 months in the Group with immediate surgery during the index hospital admission. These results are quite persuasive and deserve to be followed-up in practice.

Whether and when antimicrobials should be used in acute necrotising pancreatitis remains a moot and controversial point. An earlier meta-analysis showed a ~40% reduced mortality with antimicrobial therapy (betalactames, imipenem) but all studies had considerable methodological flaws and deficits. In a novel meta-analysis of 6 randomised controlled trials involving close to 400 patients with acute necrotizing pancreatitis, early antimicrobial administration led to a ~50% reduction in overall mortality and ~45% reduction in infected necrosis. Early antimicrobial therapy is probably useful in individual patients with extensive necrosis or a predicted severe disease course.

Previous studies have shown that oral refeeding may start early in mild, and even more severe pancreatitis, but refeeding attempts are not always successful, especially in patients with hypertriglyceridemia or with persistently elevated enzymes (lipase > 2 times the norm). It is preferred not to force oral feeding from day one but to use recurrence of appetite as a reliable indicator for successful oral refeeding.

Healing of severe acute pancreatitis may be associated with morphological and functional defects. A meta-analysis of 8 follow-up studies involving 234 patients with acute pancreatitis, revealed that 43% developed diabetes mellitus, 29% pancreatic exocrine insufficiency and 40% both sequellae. Appropriate follow-up is therefore mandatory.

Alcohol consumption is a well-known and established cause of chronic pancreatitis. A recent high-quality case-control study involving over 400 patients and over 1,000 matched controls revealed an impressive alcohol dose-response risk; for daily alcohol intake of ~30, ~50, ~70, ~90, and >100 g, the risk for chronic pancreatitis rose from 2.8, 3.2, 9.2, 13 and 19.5 times respectively. In simple terms: daily alcohol consumption <20 g: no risk; moderate risk with linear increase at 20–60 g / d; rapid increase in risk beyond 60 g / d (> 2 glasses of wine; > pints of beer). Correlation between symptom pattern and severity and morphological objective alterations is often poor in gastroenterology. The same holds for chronic pancreatitis where no correlation between pancreatic morphological changes (obstruction, inflammation, pseudocysts etc.) and symptom pattern or severity is apparent.

Interest in autoimmune pancreatitis remains intense. As a reminder, there are apparently 2 types: the more frequent type 1 (IgG4-associated systemic disease, often involving multiple organs) and type 2 (isolated pancreatic disease, concomitant IBD). Type 2 has been further characterized in 43 patients: 58% presented initially as relapsing acute pancreatitis; 36% presented initially as mass lesion and obstructive jaundice (mimicking can-

cer); 50% had associated IBD and 11% repased within 3 years after treatment. Early diagnosis is essential as the prognosis is excellent with adequate (corticosteroid) therapy.

There is consensus that in principle, main duct intraductal papillary mucinous neoplasm (IPMN) should be treated surgically as cancer will develop in 1 out of 3 patients within 3 years. For branch duct IPMN, surgery is indicated for lesions larger than 3 cm, diameter of the pancreatic duct > 5 mm, presence of intramural nodules and suspicious cytology. A large study evaluated the survival in patients with main duct IPMN that could not be resected for various reasons: 5 y survival in the resected group was 74% versus 58% in the non-resected group; those older than 70 y had a significantly worse outcome as expected (comorbidities, reduced operablity etc).

Statin use was also evaluated in the survival of over 200 patients resected for early-stage pancreatic cancer. Simvastatin reduced the mortality by 44% and the relapse rate by 39% if a high dose was used. It is utterly intriguing why simvastatin may improve the prognosis following curative resection of early-stage pancreatic cancer. Prospective, high-quality studies are urgently needed to consider simvastatin use as standard adjunctive anticancer therapy.