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Multidisciplinary care is key in chronic pancreatitis

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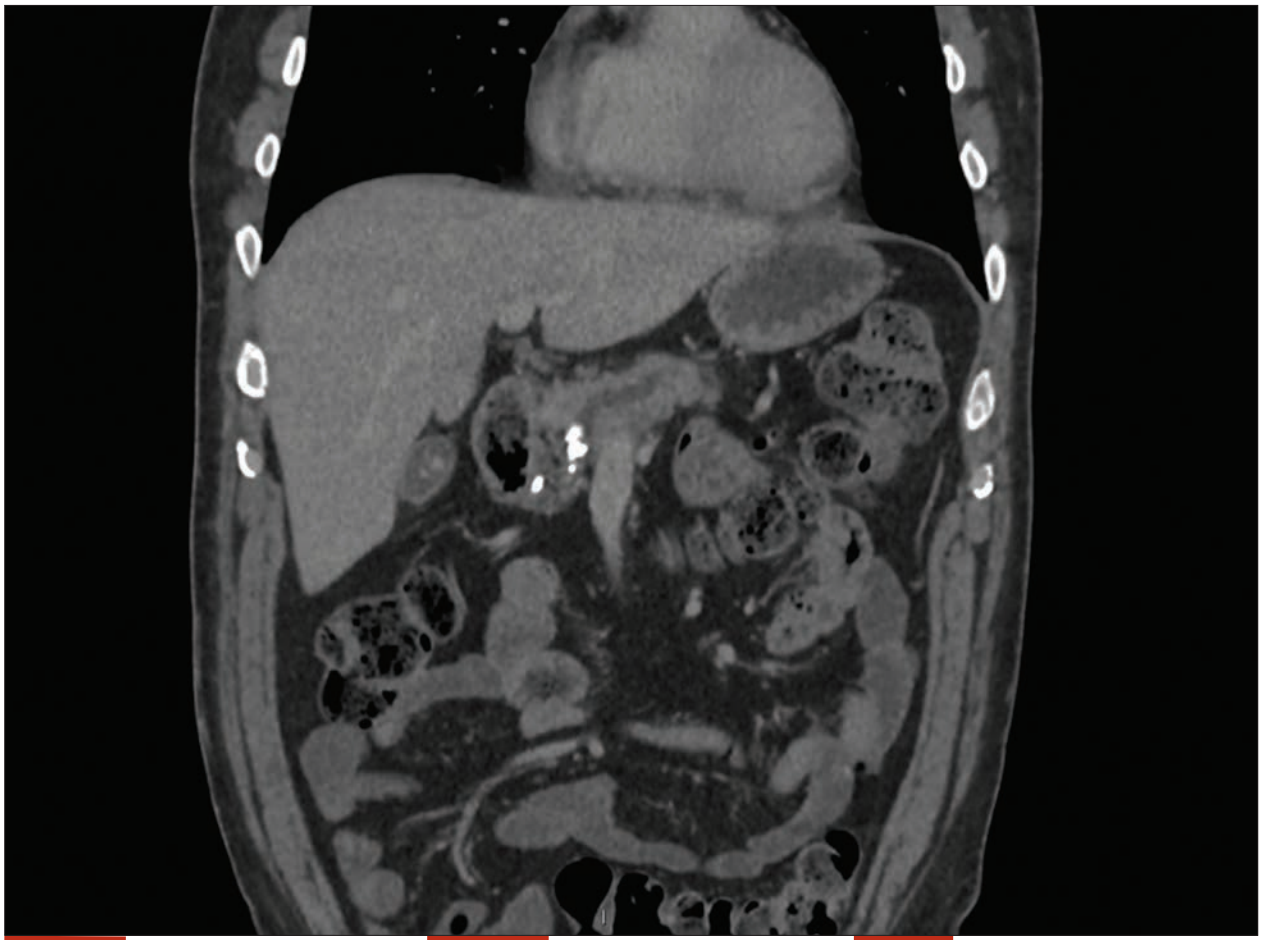


FIGURE 1
Coronal view of a contrast-enhanced CT scan demonstrating chronic calcific pancreatitis. Calcified stones are visible in the head of the pancreas

What are the common causes and risk factors?

IN CHRONIC PANCREATITIS CHRONIC INFLAMMATION OF THE PANCREAS RESULTS IN IRREVERSIBLE injury and fibrosis. This can lead to local and systemic complications.

The annual incidence of chronic pancreatitis in Europe, based on estimates published in 2010, is 6 to 7 per 100,000 population per annum,[1] while NHS Hospital Episode Statistics data in England indicate that there are 8.6 hospital admissions per 100,000 population due to the condition.[2] In the UK, there are approximately 12,000 admissions due to chronic pancreatitis per year.[3] Mortality rates in patients with chronic pancreatitis are five-fold greater than in the general population.[4]

Chronic pancreatitis can be difficult to recognise as its clinical features overlap with other gastroenterological disorders, and ineffective management can have significant effects on quality of life.[5]

The presenting features, diagnostic investigations and evidence-based management strategies for chronic pancreatitis have been detailed in recent NICE[6,7] and international guidelines,[8,9,10] to aid early recognition, prompt referral and appropriate follow-up in primary care.

What are the potential complications?

How should patients be followed up?

CAUSES AND RISK FACTORS

The diverse range of aetiologies and risk factors for chronic pancreatitis are summarised by the TIGAR-O classification system (see table 1, p12). For most of these aetiologies, the common pathological pathway is increased trypsin activation in the pancreas leading to inflammation, fibrosis and obstruction of pancreatic ducts.

The most common causal factor in chronic pancreatitis is excess alcohol consumption. In western populations, studies indicate it is a causal factor in 45-82% of cases.[11,12] However, only 10% of those dependent on alcohol develop »

chronic pancreatitis,[12] highlighting the complex interplay between alcohol and other genetic and environmental risk factors in disease development. NICE cautions against assuming chronic pancreatitis is alcohol-related in patients 'just because they drink alcohol.' Tobacco smoking is an independent risk factor for chronic pancreatitis.[12]

Genetic mutations, in the PRSS1, SPINK1 and CFTR (as part of cystic fibrosis) genes can lead to hereditary chronic pancreatitis, which is inherited in a Mendelian manner. Idiopathic disease, where no clear associated cause can be identified, accounts for 20-30% of cases.[13]

Table 1

TIGAR-O version 2 classification system for chronic pancreatitis risk factors and aetiologies (adapted from Whitcomb 2019)[14]

Toxic-metabolic
- Alcohol
- Tobacco smoking
- Hypercalcaemia
- Hypertriglyceridaemia
- Medications (e.g. azathioprine)
- Chronic kidney disease
- Metabolic syndrome
- Oxidative stress associated factors (post-irradiation/chemotherapy, ischaemia)
- Other toxins (scorpion venom, anticholinesterase pesticides)

Idiopathic
- Early onset (< 35 years of age)
- Late onset (≥ 35 years of age)

Genetic
- Autosomal dominant (e.g. PRSS1 mutations)
- Autosomal recessive (e.g. CFTR, SPINK1 mutations)
- Complex genetics (non-Mendelian, complex genotypes ± environment)
- Modifier genes
- Hypertriglyceridaemia syndromes
- Rare, non-neoplastic pancreatic genetic variant associated syndromes

Autoimmune pancreatitis (AIP)
- AIP type 1 – IgG4 related disease
- AIP type 2

Recurrent and severe acute pancreatitis
- Recurrent acute pancreatitis
- Severe acute pancreatitis

Obstruction
- Pancreatic divisum
- Ampullary stenosis
- Main duct pancreatic stones
- Widespread pancreatic calcifications
- Main pancreatic duct strictures
- Localised mass causing duct obstruction (e.g. tumour)

CLINICAL PRESENTATION

The typical presenting feature is upper abdominal pain which may radiate to the back.[6] Pain can be continuous with acute flares or episodic. The pain is commonly triggered or exacerbated by eating or alcohol consumption. The pain is caused by pancreatic inflammation and pancreatic duct obstruction due to strictures and stone formation (see figure 1, p11). Patients may also present with relapsing acute pancreatitis.

Inflammation of the pancreas can also lead to distal bile duct strictures resulting in biliary obstruction with jaundice. Disruption of the pancreatic duct from previous episodes of pancreatitis can lead to pseudocyst formation (see figure 2, p13), which may be asymptomatic but can result in pain, infection or gastric outlet obstruction. Pancreatic pseudocysts are fluid-filled sacs surrounded by granulation tissue which can bleed, rupture, become infected or cause obstruction of the biliary tree or duodenum.

Chronic pancreatitis is also a common incidental finding on routine imaging of the abdomen, and even with advanced radiological features of chronic pancreatitis the patient may be entirely asymptomatic.

Symptoms resulting from pancreatic exocrine insufficiency (PEI) include weight loss and steatorrhoea, and patients may have other clinical signs of malnutrition. Steatorrhoea indicates a significant loss of exocrine function as it occurs only when lipase secretion is reduced by more than 90-95%.[15] Endocrine insufficiency will lead to diabetes mellitus and its associated symptoms.

On examination, patients may have signs of chronic liver disease (suggestive of excess alcohol consumption), upper abdominal tenderness or abdominal distention due to a pseudocyst.[6]

The presenting features of chronic pancreatitis are non-specific and overlap with other gastrointestinal conditions leading to a wide differential diagnosis (see table 2, below left).

A medical history including a thorough account of alcohol consumption, tobacco smoking, previous hospital admissions with abdominal pain and family history is invaluable in determining the index of suspicion for chronic pancreatitis.

Pancreatic cancer is difficult to distinguish clinically from chronic pancreatitis as there are overlapping features such as weight loss, change in bowel habit and jaundice. Chronic pancreatitis is also a risk factor for pancreatic cancer.

Patients aged 40 and over with jaundice and those aged 60 and over with weight loss and one other specified symptom related to pancreatic cancer should be referred along a suspected cancer referral pathway for investigation of pancreatic cancer.[16]

In those not meeting the criteria for referral along a suspected cancer pathway, but with evidence of a complication of chronic pancreatitis (e.g. biliary obstruction or malabsorption leading to weight loss and diarrhoea) NICE advises urgent referral to gastroenterology. This will facilitate timely investigation and help exclude malignancy promptly.[6]

Table 2

Differential diagnosis of chronic pancreatitis (adapted from Jalal et al, 2018)[8]

Hepatobiliary
- Acute cholecystitis
- Biliary colic
- Acute pancreatitis
- Pancreatic cancer

Gastrointestinal
- Irritable bowel syndrome
- Peptic ulcer disease
- Gastroparesis
- Intestinal obstruction, ischaemia or infarction

Other
- Abdominal aortic aneurysm
- Thoracic radiculopathy
- Myocardial infarction
- Postherpetic neuralgia

INVESTIGATIONS AND DIAGNOSIS

In patients with suspected chronic pancreatitis, the aims of investigations are to confirm the diagnosis, demonstrate any sequelae and to determine the underlying cause.

Biopsy is almost never undertaken owing to the risk of precipitating pancreatitis so imaging is used instead to provide evidence of characteristic features such as calcification, atrophy or pancreatic duct dilation.

CT is the first-line imaging modality for chronic pancreatitis.[8] It has similar

diagnostic accuracy to MRI and endoscopic ultrasound (EUS), with a sensitivity of 75% and specificity of 91%,[17] and has the advantage of quantifying the presence of pancreatic calculi (which are usually calcified unlike gallstones), and parenchymal calcification.

MRCP (magnetic resonance cholangiopancreatography) has an advantage over CT in elucidating the pancreatic ductal anatomy in much greater detail than CT, which is useful in determining if there is pancreatic obstruction and anatomical anomalies such as pancreas divisum. Abdominal ultrasound can only diagnose chronic pancreatitis at an advanced stage[9] but can be useful to rule out differential diagnoses as well as eliciting the presence of gallbladder gallstones as a potential precipitant for previous acute pancreatitis.

PEI should be looked for in all patients using a stool sample for faecal elastase-1 (FEL-1) and by performing a nutritional assessment, measuring body mass index (BMI), prothrombin time, albumin, haematinics, calcium, phosphate, magnesium and fat-soluble vitamins (A,D, E and K).[8,9] Screening for diabetes mellitus should be considered in all patients and should include both HbA_{1c} and a fasting glucose measurement as a normal HbA_{1c} does not exclude diabetes in this patient group.[9] Pancreatic enzymes may be only mildly elevated or normal in chronic pancreatitis and so serum amylase is not a useful measurement in these patients.[6]

In cases where the aetiology is not clear from the history, calcium and triglyceride levels should be measured and serum IgG4 to check for autoimmune pancreatitis.[9] In patients under 35 years of age, clinical and genetic testing for hereditary causes including cystic fibrosis, PRSS1 and SPINK1 mutations should be carried out.[8]

NICE recommends urgent referral to gastroenterology if the patient presents with a complication of chronic pancreatitis (e.g. biliary obstruction). Otherwise, a routine referral is appropriate and GPs can conduct initial blood tests (e.g. liver function tests) and an abdominal ultrasound to rule out differential diagnoses while awaiting specialist input.[6] This may present an opportunity for GPs to perform the biochemical investigations for functional abnormalities, as above, and identify patients requiring input from diabetologists or dietitians.

Table 3

Complications of chronic pancreatitis

Local
- Pancreatic cancer
- Pancreatic pseudocyst
- Biliary obstruction
- Duodenal obstruction
- Splenic vein thrombosis

Systemic
- Pancreatic exocrine insufficiency
- Endocrine insufficiency (type 3c diabetes mellitus)
- Metabolic bone disease
- Ascites and pleural effusions

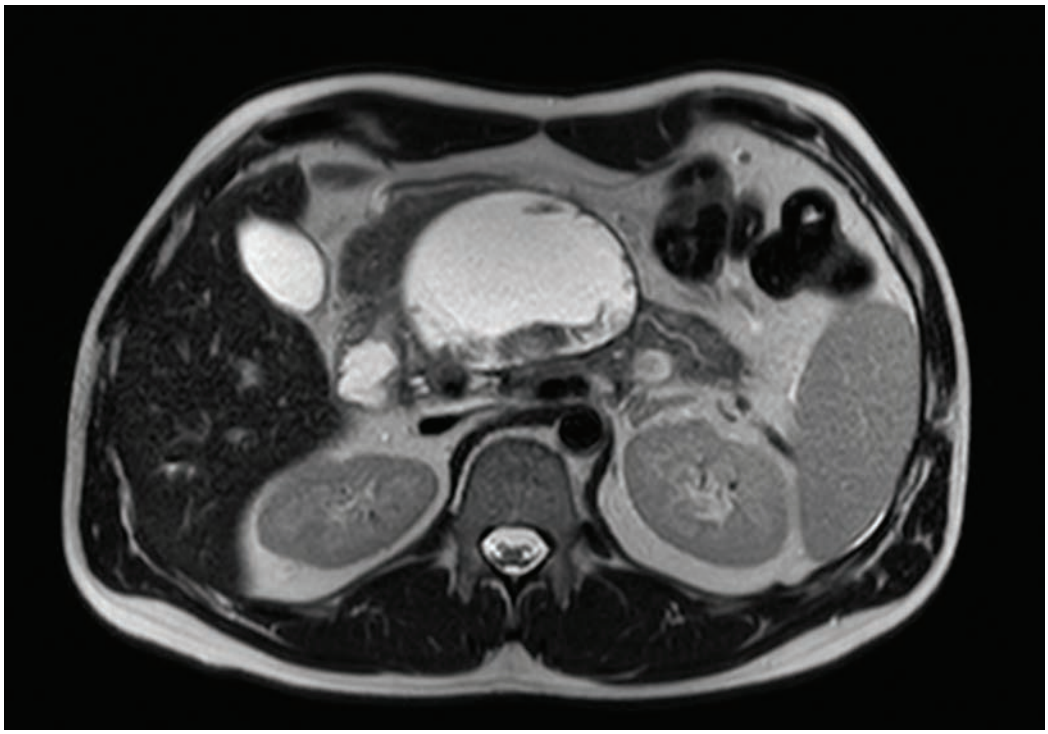


FIGURE 2
Axial view of a T2-weighted MRI scan showing a pancreatic pseudocyst

COMPLICATIONS

The complications of chronic pancreatitis can be divided into local and systemic (see table 3, left). The risk of pancreatic cancer in chronic pancreatitis has been shown to be 4% at 20 years after diagnosis.[18] This risk is higher in those with a ≥ 60 pack-year smoking history, in those who are older at age of diagnosis and is much higher in those with hereditary pancreatitis.[19,20]

Pseudocysts < 4 cm in size are likely to regress spontaneously while larger ones are more likely to lead to further complications, as described earlier.[21]

Chronic pancreatitis leads to type 3c diabetes mellitus which is present in 5-10% of patients with the condition[8] and is difficult to control, often requiring insulin.[22]

Almost two-thirds of patients with chronic pancreatitis have osteoporosis or osteopenia and therefore this patient group has a high risk of fragility fractures.[23]

MANAGEMENT

The management of chronic pancreatitis requires a multidisciplinary team (MDT) approach involving GPs, gastroenterologists, surgeons, radiologists, dietitians and diabetologists. Treatment approaches aim to control pain, manage complications and target the underlying cause.

Pain has a significant impact on the quality of life of chronic pancreatitis patients.[24] NICE recommends initial treatment in primary care with paracetamol or ibuprofen, with progression to codeine if pain persists.[6] Additionally, abstinence from alcohol has beneficial effects on pain symptoms.[25] If these initial measures are unsuccessful referral to gastroenterology, pancreatobiliary surgery or a specialist pain clinic is required.[6]

Tricyclic antidepressants (e.g. amitriptyline) and neuropathic painkillers (e.g. pregabalin) can be started as further medical management in secondary care.

Psychiatric comorbidities in patients with chronic pancreatitis affect their level of pain and their quality of life. A recent study showed the prevalence of anxiety and depression (defined as

key points

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In chronic pancreatitis chronic inflammation of the pancreas results in irreversible injury and fibrosis. This leads to local and systemic complications. The annual incidence in Europe is estimated to be 6-7 per 100,000 population. Mortality rates in patients with chronic pancreatitis are five-fold greater than in the general population. The most common causal factor is excess alcohol consumption, estimated to be responsible for 45-84% of cases. However, it is important not to assume that chronic pancreatitis is alcohol-related just because the patient drinks alcohol. Tobacco smoking is an independent risk factor. Gene mutations can lead to hereditary chronic pancreatitis, (autoimmune pancreatitis type 1 is associated with increased levels of IgG4), and idiopathic disease, where no clear cause can be identified, accounts for 20-30% of cases.

Chronic pancreatitis can be difficult to recognise as its clinical features overlap with other gastrointestinal disorders. The typical presenting symptom is intermittent or continuous upper abdominal pain which may radiate to the back. The pain is commonly triggered or exacerbated by eating or alcohol consumption. Distal bile duct strictures may cause biliary obstruction and jaundice. Disruption of the pancreatic duct from previous episodes of pancreatitis can lead to pseudocyst formation. Pseudocysts may be asymptomatic but can result in pain, infection or gastric outlet obstruction. Pancreatic exocrine insufficiency (PEI) may cause weight loss and steatorrhoea, and endocrine insufficiency will lead to diabetes mellitus and its associated symptoms.

NICE recommends urgent referral to gastroenterology if the patient presents with a complication of chronic pancreatitis such as biliary obstruction. Otherwise, a routine referral is appropriate; while awaiting specialist input, GPs can conduct initial blood tests and request an abdominal ultrasound to rule out differential diagnoses. Pancreatic cancer is difficult to distinguish clinically from chronic pancreatitis, and an urgent suspected cancer referral may be indicated if the NICE criteria are met.

CT is the first-line imaging modality. MRCP has an advantage over CT in elucidating the pancreatic ductal anatomy in greater detail. PEI should be looked for with a stool sample for faecal elastase-1 and a nutritional assessment. Screening for diabetes mellitus should include both HbA_{1c} and fasting glucose as a normal HbA_{1c} does not exclude diabetes in this patient group. Serum amylase measurement is not useful in chronic pancreatitis.

Alcohol abstinence and smoking cessation are vital to reduce progression of the disease. Weight-bearing exercise reduces the risk of osteoporosis. Patients should have 6 monthly diabetes screening and yearly DEXA scans. NICE recommends initial pain management with paracetamol or ibuprofen, with progression to codeine if pain persists. Tricyclic antidepressants and neuropathic pain medication may be prescribed in secondary care.

a HADS score ≥ 7) among chronic pancreatitis patients to be 47% and 39% respectively.[26]

Patients with these psychiatric comorbidities had significantly higher pain prevalence and pain severity and lower quality of life scores. Early recognition and management of comorbid anxiety and depression can improve pain management and quality of life in these patients.

Endoscopic or surgical approaches are used to treat pain resulting from pancreatic duct obstruction.

For uncomplicated chronic pancreatitis with an obstructed main pancreatic duct, most commonly due to stones or pancreatic duct strictures, endoscopic retrograde cholangiopancreatography (ERCP) is recommended.[10]

Extracorporeal shock-wave lithotripsy (ESWL), or more recently direct pancreatoscopy and electrohydraulic lithotripsy, is recommended for calculi within the distal pancreatic duct where endoscopic extraction therapy has failed.[10]

EUS-guided coeliac plexus block can be used but its efficacy is short-lived with the majority of patients experiencing recurrent pain after 24 weeks.[27] Surgical options including decompression and resection can be undertaken for pain relief and have been shown to be superior to endoscopic therapy for long-term pain relief.[28] NICE guidance suggests surgery as a first-line treatment in painful chronic pancreatitis with obstruction of the main pancreatic duct.[7] However, comorbidities and surgical and anaesthetic risk need to be weighed up before a decision is made on surgery.

Chronic pancreatitis related pseudocysts should be treated if they are symptomatic or present with complications. Endoscopic drainage is used in preference to surgery for uncomplicated chronic pancreatitis related pseudocysts that are within endoscopic reach.[10]

For patients with chronic pain or symptomatic pseudocysts from chronic pancreatitis it is recommended that the imaging is reviewed in a hepatobiliary MDT meeting to determine the best strategy for management of pancreatic calculi and strictures: conservative management, endoscopic approaches or surgery.

Patients with PEI and clinical or laboratory evidence of malabsorption should be treated with pancreatic enzyme replacement therapy (PERT).[29] Oral PPIs can be used to improve PERT efficacy.[29] NICE suggests considering assessment by a dietitian for all patients with chronic pancreatitis,[7] which can help improve patients' nutritional status and highlight patients requiring enteral tube feeding.[9] Guidelines have recently been published on PEI with useful advice on how PERT should be taken.[30] Diabetes in chronic pancreatitis is difficult to manage; up to 25% of patients have 'brittle diabetes' requiring specialist input.[6,9]

Abstinence from alcohol and smoking cessation are vital to reduce progression of the disease and these measures should be advised in primary care, alongside weight-bearing exercise to reduce the risk of osteoporosis.[6] These patients may require specialist alcohol or smoking services.

Metabolic disorders should be treated while drugs and other toxins should be removed as appropriate. Autoimmune pancreatitis is managed by a specialist hepatobiliary team with steroids or other immunomodulatory drugs.

FOLLOW-UP

In primary care, patients should have an annual review with blood tests to asses liver function and markers of malnutrition.[8] Because of the high risk of osteoporosis in chronic pancreatitis, patients should have a bone density assessment by dual-energy X-ray absorptiometry (DEXA) at diagnosis followed by yearly follow-up DEXA scans.[6,8] If patients have no evidence of PEI at diagnosis, a FEL-1 can be repeated if symptoms attributable to PEI occur.[9] Patients with no endocrine dysfunction at diagnosis should have a HbA_{1c} repeated every 6 months.[7] Pancreatic cancer screening should be considered only in those with hereditary pancreatitis and should occur annually with a pancreas protocol CT scan.[30]

CONCLUSION

Chronic pancreatitis is a disease with a diverse range of causes, of which alcohol is the most common. Patients present primarily with abdominal pain and may have features of PEI or diabetes mellitus.

Diagnosis is achieved primarily with cross-sectional imaging and screening for complications should occur simultaneously.

Management of chronic pancreatitis requires a multidisciplinary approach to monitor and treat the complex range of problems that develop in these patients. Early recognition and referral to a hepatobiliary MDT is a priority in primary care.

Competing interests
Dr Gavin Johnson has undertaken consultancy work for Boston Scientific, Olympus, Pentax and Cook Medical. The other authors have no competing interests.

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Useful information

For patients
Gut UK
Chronic pancreatitis factsheet
https://gutscharity.org.uk/advice-and-information/conditions/chronic-pancreatitis

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