

Persistent Pain in Chronic Pancreatitis

South Thames Acute Pain Conference
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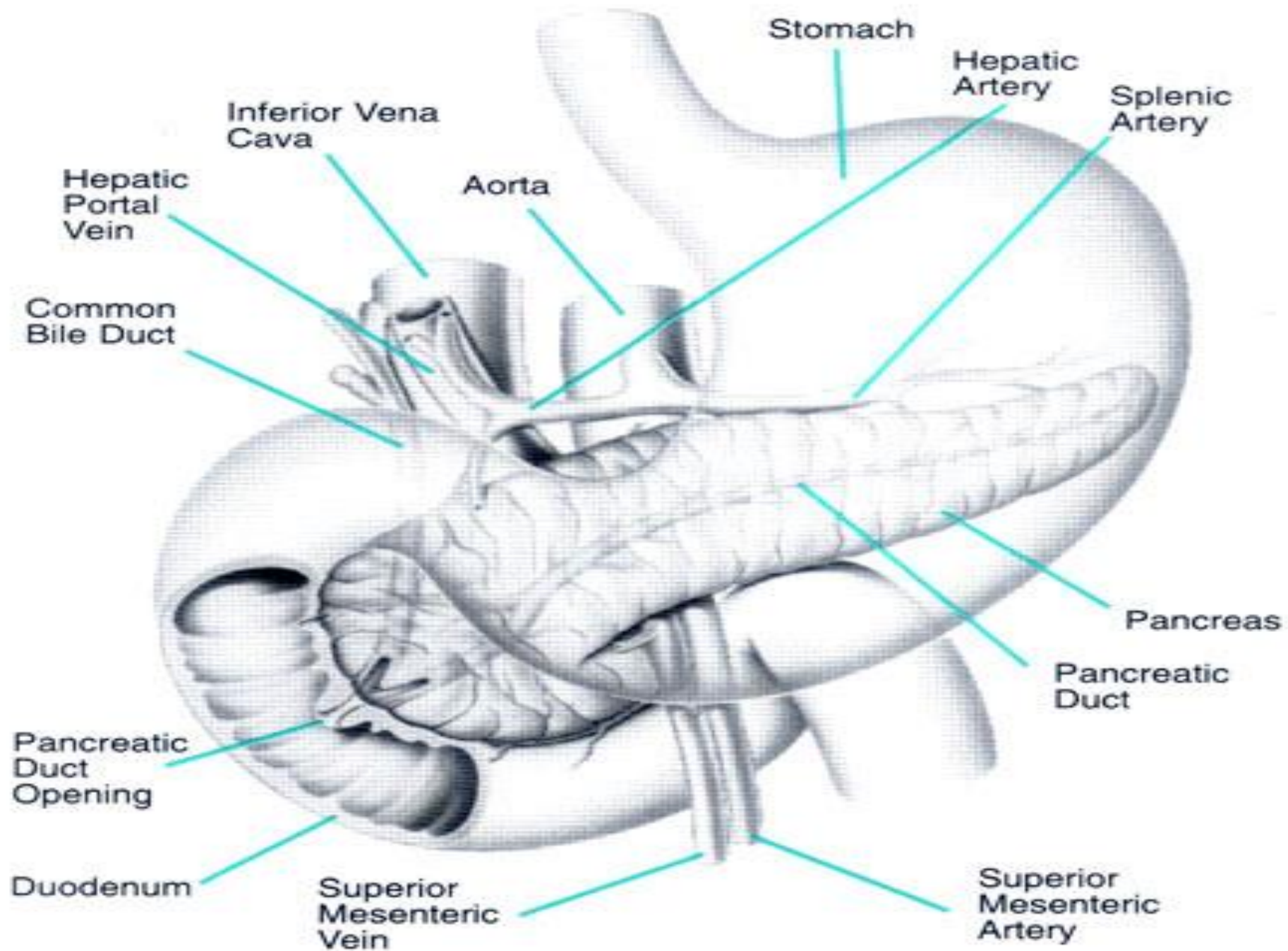






The Royal Liverpool and
Broadgreen University Hospital
NHS

Welcome to
The Royal Liverpool
University Hospital





Background to my involvement in pancreatic pain

- Royal Liverpool University Hospital is a tertiary referral centre for hepatobiliary and pancreatic surgery
- I am a Consultant Anaesthetist and Lead clinician for the Acute Pain Service
- Patients having pancreatic surgery have complex perioperative analgesic requirements
- No-one else wanted to do it!



Chronic Pancreatitis

- Continuing inflammatory disease of the pancreas
- Results in irreversible destruction of both the endocrine and exocrine pancreatic tissue
- Early stages of the disease may be characterised by episodes of acute pancreatitis
- Pancreas may appear macroscopically normal
- Late stage of disease is characterised by pancreatic fibrosis and calcification
- Pancreatic duct dilatation and stricture formation occurs
- Cysts form within the pancreatic tissue



Aetiology

- Alcohol (60-70%)
- Gall stones
- Pancreatic duct strictures
- Cystic fibrosis
- Chronic renal failure
- Hypercalcaemia
- Hyperlipidaemia
- Autoimmune
- Smoking
- Pancreatic trauma
- Hereditary/genetic pancreatitis
- Idiopathic

Pancreatic duct dilatation and calcification



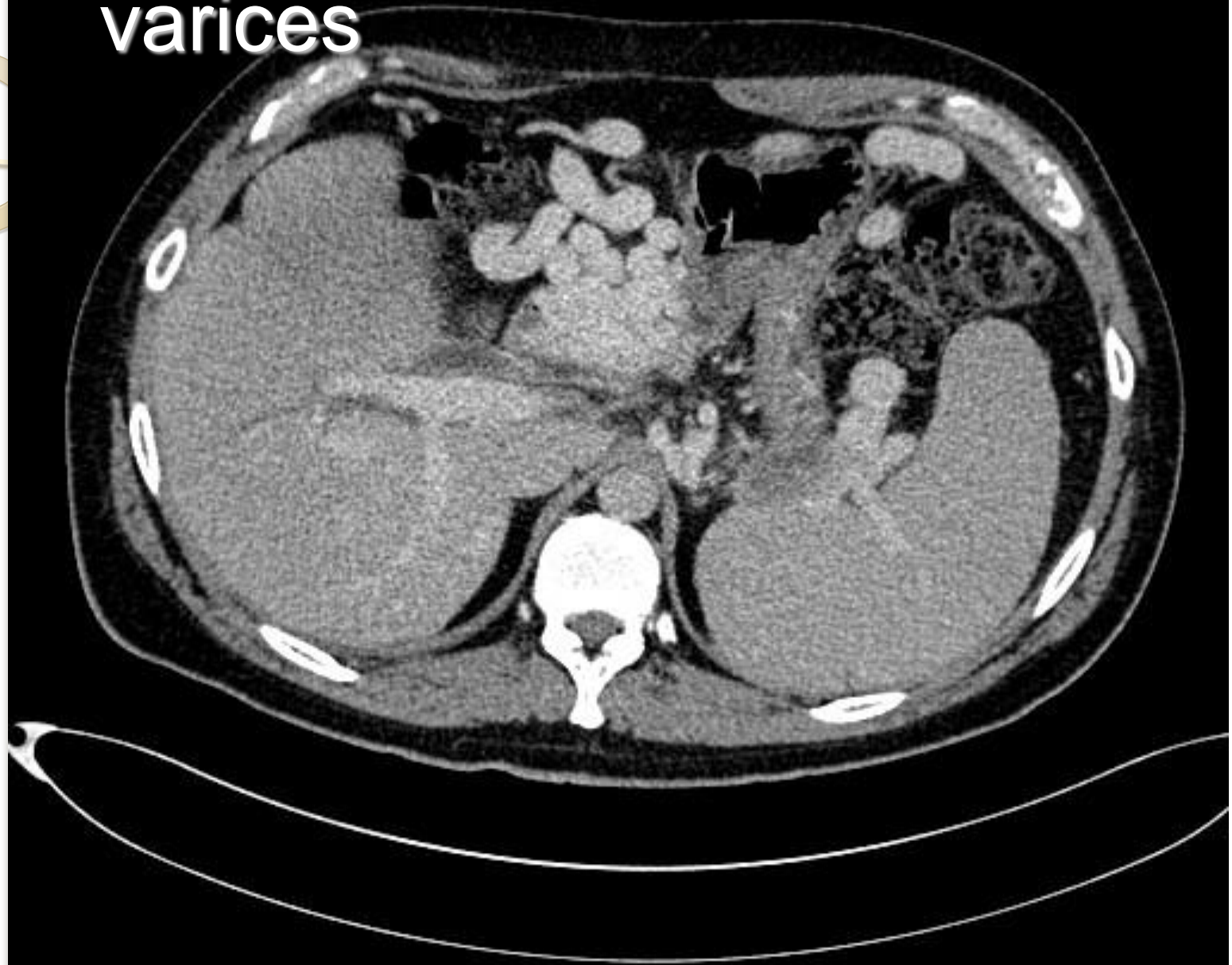
Large stone in the head of the pancreas

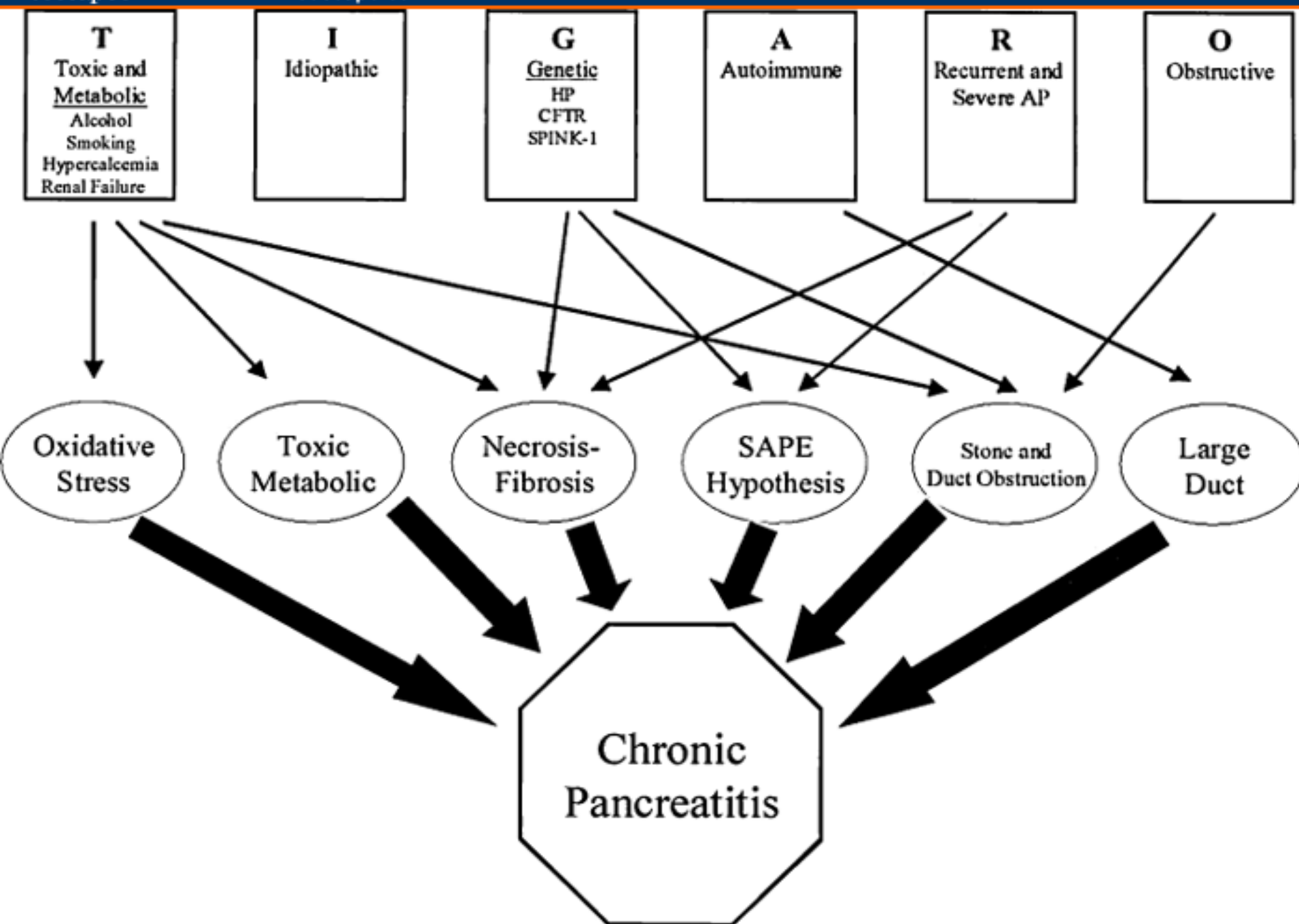


Massive pseudocyst



Portal hypertension with varices





4,517

under-18s
taken to
hospital
last year

92,308

boozers treated
for alcohol
poisoning
in 2012

TOP TEN NHS TRUSTS FOR CASES OF ALCOHOL POISONING IN 2012

SOUTH TEES
HOSPITALS

1,244

EAST LANCASHIRE
HOSPITALS

1,326

PENNINE ACUTE
HOSPITALS

1,671

HEART OF
ENGLAND

1,246

IMPERIAL COLLEGE
HEALTHCARE

1,376

NORTHUMBRIA
HEALTHCARE

1,284

COUNTY DURHAM
AND DARLINGTON

1,177

LEEDS TEACHING
HOSPITALS

2,209

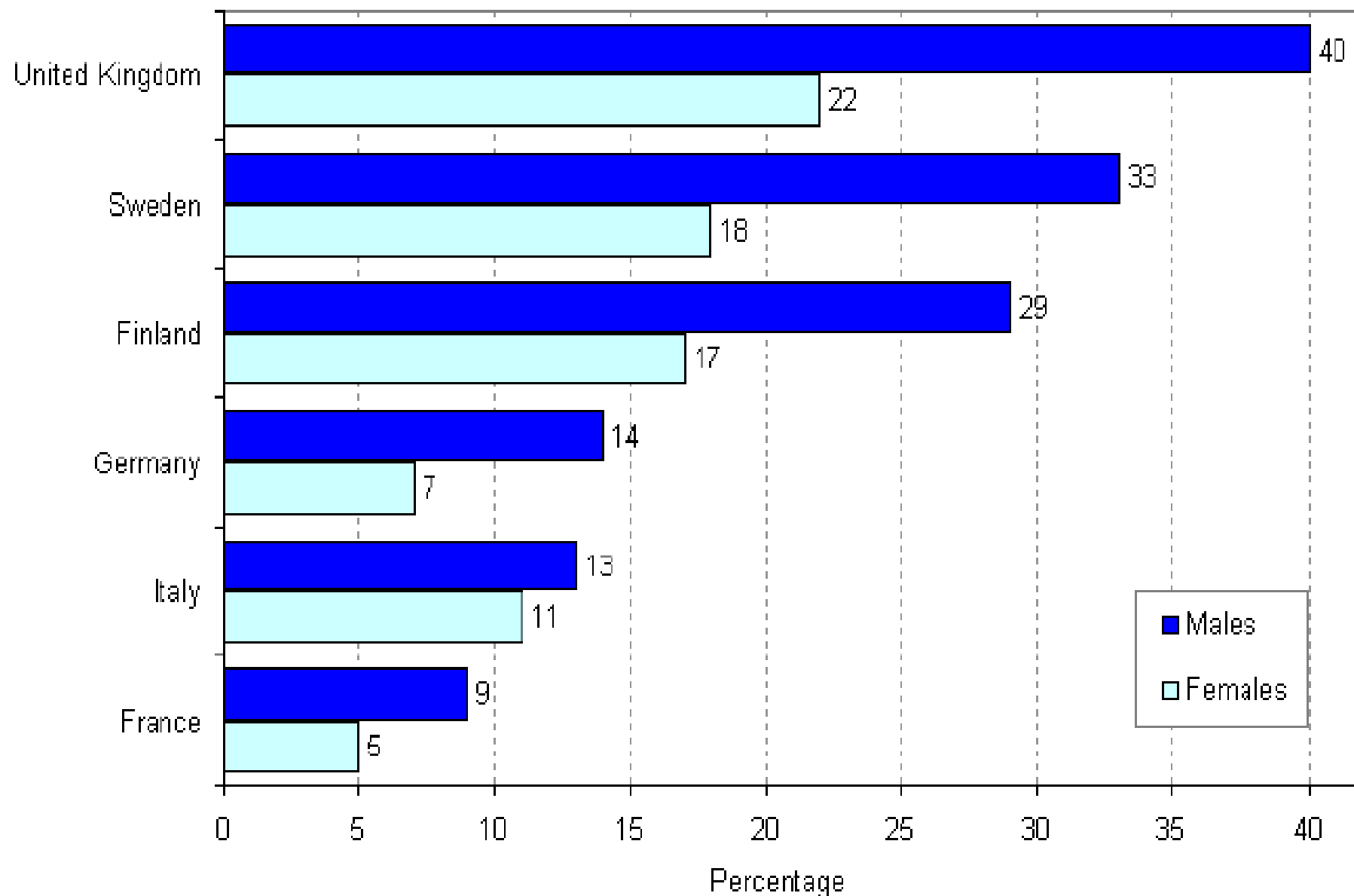
SANDWELL AND WEST
BIRMINGHAM HOSPITALS

1,430

BRIGHTON AND SUSSEX
UNIVERSITY HOSPITALS

1,398

Binge drinking as a percentage of all drinking occasions
in the past 12 months, selected countries in Eur-A, 2000



Source: Hemström et al. (2002).



Patient Profile in Chronic Pancreatitis

- History of alcohol abuse in majority
- Often have had multiple hospital admissions
- Social/Marital/Employment difficulties
- Depression/anxiety
- Poor sleep pattern
- Usually have a “favourite” opioid
- Usually have a favourite route of administration (intramuscular or intravenous)
- Polypharmacy



Pathogenesis of pain in chronic pancreatitis

- *PAIN* is the predominant symptom in most (80-90%) patients
- CP can be divided into small or large duct disease
- Pancreatic duct hypertension and ischaemia (compartmental model)
- Pseudocyst formation/worsening fibrosis
- Neuronal damage leading to peripheral and central sensitization
- Proliferation of local mediators eg prostanoids, bradykinin, serotonin
- Enhanced activity in K⁺ channels, TRPV1, PAR-2 receptors
- CNS changes in CP esp limbic system and anterior cingulate cortex
- “Salutogenic” generation of pain through abnormal immune responses.



Can CP pain fit into the pattern of other visceral pain?

Visceral pain has 5 important characteristics:

1. It is not evoked from all viscera
2. It is not (*always*) linked to injury
3. It is referred to the body wall
4. It is diffuse and poorly localised
5. It involves intense motor and autonomic reactions.

Cervero F and Laird JMA, Visceral Pain. *Lancet* 1999; 353: 2145-2148



Clinical features of pain in Chronic pancreatitis

- Arises in epigastrium
- Radiates through to back, right or left hypochondrium
- Severe, 'gnawing', 'aching', 'grinding', 'toothache'.
- Worse after food, nausea and vomiting common
- Associated autonomic symptoms eg sweating, bowel spasm, palpitations, bloating, muscle spasms.

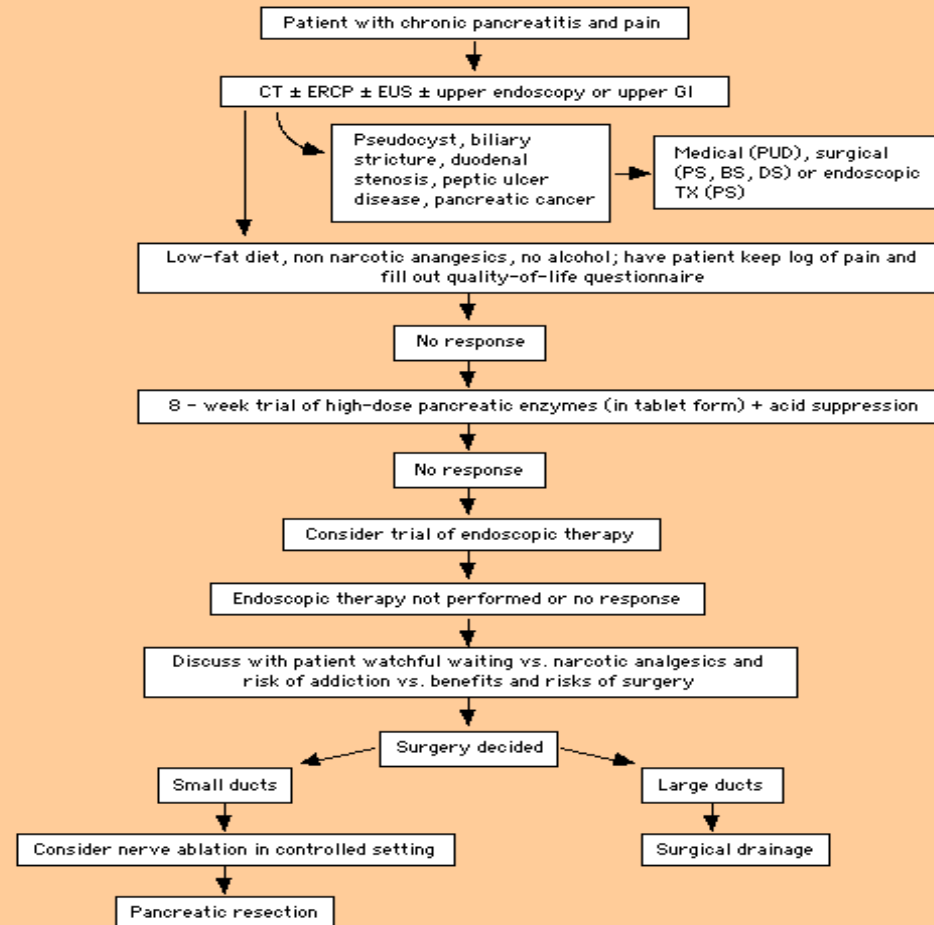
Additional symptoms

- Extra 'bad pain'
- Unexpected, 'out of the blue'
- Burning, ripping, bursting, stabbing, relentless, crushing, jolting, electric shock, hot poker
- Hyperalgesia and allodynia can be demonstrated
- Clear neuropathic symptoms
- Often under-diagnosed
- Usually the pain that is difficult to control and precipitates hospital admission



What can we do?

Guideline for Treatment of Pain in Chronic Pancreatitis*



*Adapted from Warshaw, AL, Banks, PA, Del Castillo, CF. AGA: Technical review: Treatment of pain in chronic pancreatitis. *Gastroenterology* 1998; 115:765.



Lifestyle changes

- **Alcohol:** If there is a history of alcohol misuse then abstinence is essential
- **Smoking:** Independent risk factor for CP, accelerates progression and perception of pain
- **Diet:** Malabsorption common, vitamin deficiencies. Low-fat diets, vitamin supplements and antioxidant therapies
- **Support groups:** Complex social/marital situations. Support groups can share experiences, medical information, treatment options. Can help alleviate social isolation.



Medical Treatment strategies in Chronic Pancreatitis

- **Expectant (nonspecific) therapy**
- Analgesics
- Antidepressants
- Anxiolytics
- Anti-emetics
- **Suppress secretion**
- Proton pump inhibitor or H2-blocking agents
- Pancreatic enzymes
- Octreotide



Medical Treatment strategies in Chronic Pancreatitis

Relieve obstruction

- ERCP (sphincterotomy)
- Stents
- Elimination of stones

Modify neural transmission

- Coeliac plexus block (EUS or CT guided)
- Bilateral thoracoscopic splanchnicectomy (BITS)

Reduce oxidative stress

- Vitamin and anti-oxidant therapy
- Allopurinol



Examples of analgesics in CP

- **Simple analgesics**
- **Weak Opioids**
- **Strong Opioids**
- **Antidepressants**
- **Gabapentinoids**
- **NMDA receptor antagonists**



In other words.....

- Every available analgesic has been studied in Chronic Pancreatitis
- No universal agreement on ideal recipe
- Understandable caution over the use of strong opioids in this group of patients
- Need to recognise opioid seeking behaviour
- Identify pattern to patient's pain (Type A or Type B Pancreatitis)



Oral maintenance regime (goals)

- Return control back to patient
- Explain need to avoid hospital admissions unless true worsening in condition eg pseudocysts, acute pancreatitis, intractable vomiting, bowel obstruction, GI bleeding
- Reduce severity of background pain
- Reduce frequency and severity of sudden “neuropathic” pain
- Optimise medical treatment eg diabetes, malabsorption, nausea/vomiting



My approach to analgesia in CP

**KEEP IT SIMPLE
AND SAFE!**



My approach to analgesia in CP

- Use multimodal analgesia
- Regular Paracetamol
- Anti-neuropathic agent
- Tramadol and Tapentadol
- Strong opioids (Oxycodone)
- Ketamine



My approach to opioid analgesics in CP

- Use one effective opioid (Always try to use the oral route where possible)
- Use regular slow release preparations
- Use rapid onset preparations for breakthrough pain
- Avoid pethidine (norpethidine toxicity, non-opioid side effects)
- Avoid ritualisation of opioid use



What is the best opioid for pancreatic pain?

- Not sure!
- Scientific literature suggestive that oxycodone may be superior in experimental visceral pain models*
- Large body of opinion believes that opioids should be used with great caution or not at all in chronic pancreatitis
- Need to monitor for complications of long-term opioid use (immune, endocrine, dental, psychological, overdose)

***Staahl,Dimcevski,Andersen,Thorsgaard, Christrup,
Arendt-Nielsen,Drewes *Scand.J.Gastro* 2007**



What do I think?

I use ***OXYCODONE*** as my first line opioid in chronic pancreatitis

Why?

- High oral bioavailability

- μ -receptor and κ -receptor activity

- Easy to titrate

- Usually achieve analgesic dose quickly

- Anti-neuropathic action

- Patients tolerate it well

- Fewer psychological side-effects eg hallucinations

- Simplicity

- Nursing staff like it



Starting regime

- Modified Release Oxycodone 20mg bd
- Immediate release Oxycodone 10mg prn (breakthrough analgesia)
- Tramadol 100mg qds
- Paracetamol 1g qds
- Pregabalin 150mg bd



Modifying the regime

- Many patients require higher doses
- Step-wise increases in dose may be necessary
- 10-20mg increase/24 hours period
- Close monitoring
- If large usage of breakthrough analgesia (eg Oxynorm) increase background dose (eg Oxycontin)



Modifying the regime

- If the patient does not tolerate oxycodone, use MST/Oramorph or Fentanyl patch/Actiq lozenges as alternatives.
- Perform appropriate drug conversions when patient stabilized on a particular dose.
- Look for side-effects
- Perform regular pain scores



BUT...

- We have many failures
- Complicated patient group
- Opioid-seeking behaviour can develop
- Escalation in opioid dosage not uncommon
- Is this tolerance or hyperalgesia?
- Opioid rotation often necessary
- Substance/alcohol abuse ongoing



Long-term opioid use

- Detailed discussion with patient, establish atmosphere of trust
- Patient education about risks, side effects
- Alcohol/Drug abuse monitored
- Regular out-patient clinics
- Liaison with GP/Surgical team
- Set realistic goals
- Elimination of pain unlikely, relief is possible



Non-pharmacological therapies

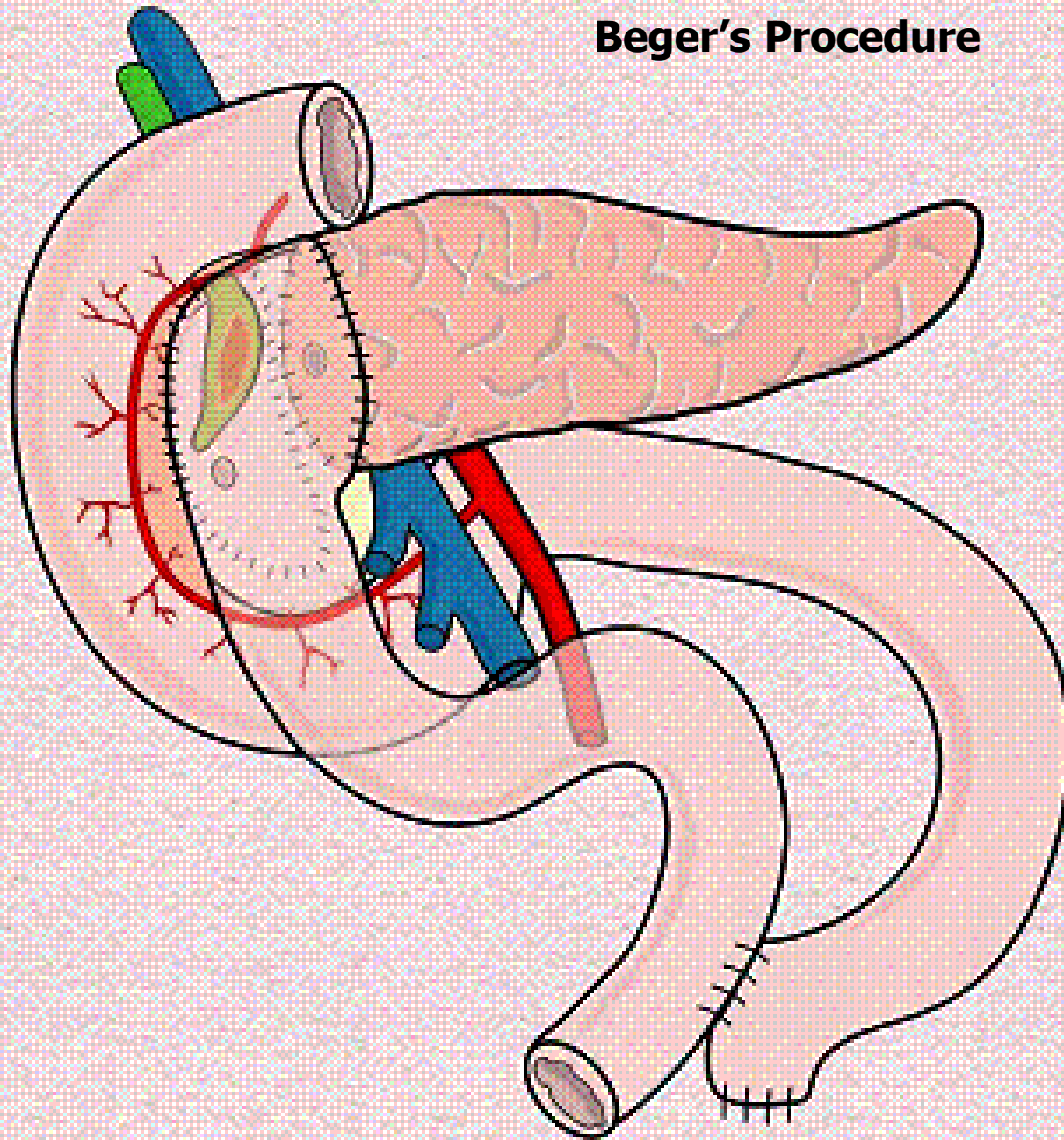
- **Coeliac plexus block** (CT or EUS)
- **Bilateral thoracoscopic splanchnicectomy** (BITS procedure)
- **Endoscopic therapies:** Pancreatic sphincterotomy, stricture dilatation, stents, stone extraction, lithotripsy
- **Surgery:** Decompression/drainage procedures (Puestow), resection procedures (Whipple, Beger, Frey)



Do these therapies work?

- Coeliac plexus and BITS provide relief for many but less effective in CP than cancer
- Less likely to succeed if severe disease or previous surgery
- Time-limited effect usually up to a maximum of 18 months
- 20-40% have minimal short-lived benefit
- Associated morbidity

Beger's Procedure





Surgery?

- Drainage vs Resection Procedures
- Drainage procedures for dilated ducts (modified Puestow)
- Resection procedures: intractable pain, small duct disease, enlarged pancreatic head, suspicion of malignancy, failed drainage procedure.
- Short-term pain relief in 80%, relief at 2 years 60%
- Significant peri-operative morbidity/mortality
- Long hospital stay
- Diabetes, adhesions, chronic wound pain, “phantom pancreas pain”

Table II. Patient demographics

	<i>Patients without opioid use N = 66</i>	<i>Patients with opioid use N = 46</i>	<i>P[*]</i>
Age (y) [†]	48 (18-79)	42 (21-63)	.001
Male: Female	46:20	31:15	.83
Etiology			.40
Alcohol	31 (47%)	27 (59%)	
Idiopathic	27 (41%)	13 (28%)	
Hereditary	2 (3%)	3 (7%)	
Other	6 (9%)	3 (7%)	
Age at first symptoms (years) [†]	43 (9-77)	35 (8-59)	.004
No. of hospitalizations [†]	3 (0-42)	10 (1-30)	.001
Duration of symptoms (y)	2 (0-40.5)	5.9 (0.1-22.1)	.038
Weight (kg) [†]	65 (47-120)	74 (47-84)	.097

*P values calculated by using the χ^2 or Fisher exact test and the Mann-Whitney *U* test.

[†]Median with range.

Table III. Preoperative patient parameters

	<i>Patients without opioid use N = 66</i>	<i>Patients with opioid use N = 46</i>	<i>P *</i>
Indications for surgery			.001
Pain	31 (47%)	44 (96%)	
Suspicion of cancer	30 (46%)	1 (2%)	
Other	5 (8%)	1 (2%)	
VAS pain score†	8 (0-10)	9 (5-10)	.001
Pain type			.001
Excruciating	11 (17%)	16 (35%)	
Strong	8 (12%)	11 (24%)	
Severe	15 (23%)	15 (33%)	
Moderate	8 (12%)	4 (9%)	
No/minimal pain	24 (36%)	0	
Endocrine insufficiency	17 (26%)	19 (41%)	.08
Exocrine insufficiency	17 (25%)	31 (68%)	.001
Employment status			.09
Working	20 (30%)	6 (13%)	
Not working	40 (61%)	36 (78%)	
Retired	6 (9%)	4 (9%)	
Activity			.001
Severe restriction	25 (38%)	37 (80%)	
Moderate restriction	18 (27%)	6 (13%)	
Normal activity	23 (35%)	3 (7%)	
Alcohol group (N)	31 (47%)	27 (59%)	
Age of starting alcohol†	17 (13-38)	18 (13-21)	.25
Maximum weekly consumption in units†	100 (50-280)	130 (52-250)	
Active cigarette smokers	34 (52%)	33 (72%)	.049
ASA grade†	2 (1-3)	2 (2-3)	.80

ASA, American Society of Anesthesiologists.

**P* values calculated by using the χ^2 or Fisher exact test and the Mann-Whitney *U* test; *P* < .05 is significant.

†Median with range.

Case 1:

39 year old unemployed female. Chronic Pancreatitis following an attack of acute pancreatitis when 24 years old. Cause of acute attack was gallstones. Originally from Belgium where she underwent cholecystectomy, and 2 coeliac plexus blocks. No improvement in pain. Commenced on MST/oramorph in Belgium.

Moved to North Wales 8 years ago. Referred to gastroenterologists and DGH pain service. Endoscopic drainage procedure, no success. Referred to Pancreatic Unit at Royal Liverpool Hospital.

Ongoing psychiatric problems with severe anxiety/obsessive/phobic behaviour. Out-patient psychiatric care.

Mother moved from Belgium 6 years ago to care for her. Previous employment as a freelance artist, currently not working.

After visit to Professorial Surgical Unit assessed as not suitable for surgery.

Offered BITS procedure which she underwent 4 years ago.

Referral to Royal Pain clinic. First appointment was taking MST 150mg bd, oramorph 20mg 7-8 times/ day, amitriptyline 50mg nocte, diazepam 5mg tds.

Pain scores; 8-9/10 most days. Predominant neuropathic symptoms.

Diagnosed with breast cancer 3 years ago.

Case 2:

28 year old civil servant. Hereditary chronic pancreatitis. Long-term surveillance since childhood. Partial pancreatectomy (Beger's) performed when 21 years old.

Scar related pain and persistent pancreatic pain.

Referred to Royal Liverpool pain clinic due to ongoing bloating, pain, adhesional symptoms. Refused further surgery. Keen to avoid strong opioids. Ambitious, in regular employment, active social life.

Last clinic visit showed continued improvement in pain and quality of life.

Case 3:

36 year old unemployed man. Married with 2 children. 10 year history of alcohol-related chronic pancreatitis. Beger's procedure 6 years ago. 1 year of relief, then worsening pain. Referred to Royal pain clinic on MST 100mg bd. Pain scores 8-9/10. Established on Oxycodone/Pregabalin regime. Marked improvement in pain for several years. Then 3 years ago breakdown in relationship with GP. Stockpiling opioids, restrictions put by new GP on amount dispensed. Offered completion pancreatectomy by surgeons. Complicated peri-operative course, resulting in splenectomy, renal infarct and multiple gastric ulcerations.

2012-2013 spent 180 days in hospital, multiple readmissions

Case conference called due to concerns over opioid use and multiple readmissions.

Ongoing review in pain clinic, persistent pancreatic pain. Poor diabetic control.



Ongoing changes, new therapies

- Increased involvement of pain team at pre-op assessment
- True informed consent prior to surgery
- Enhanced Recovery principles in pancreatic surgery
- Increased use of psychologists/psychiatrists particularly in managing opioid withdrawal
- Consistent prescribing
- Ketamine infusions
- Topical 5% lidocaine patches
- Transcranial magnetic stimulation
- Alternative therapies eg hypnosis, TENS, aromatherapy, acupuncture, cognitive behavioural therapy
- Patient support groups
- Stricter criteria for surgical intervention?



Ketamine infusion at RLUH

- Patients admitted as day-cases
- Infusion started in an anaesthetic room
- Midazolam 5mg plus ketamine 0.5mg/kg bolus
- Infusion continued for 6 hours 0.5mg/kg/hour
- Dedicated nurse to manage side effects
- Patients go home after infusion and told to decrease opioid dose by 50%
- Majority have reduction in pain for 4-12 weeks
- Regular out-patient follow up
- Shortest time 24 hours!
- Longest time 4 months
- Most patients want to repeat infusion
- One patient has had 7 treatments.



In Summary...

- Chronic pancreatitis is a severe, complex, debilitating disease that has a devastating impact on the patient.
- Huge resources and multi-disciplinary input required.
- Large range of treatments available but no consistently successful strategy agreed.
- Significant minority of patients are resistant to treatment (30-40%) with pain being the predominant symptom.
- Potential “pain time-bomb” along with other alcohol related disease.
- Pathophysiological and neurological factors determining the experience and magnification of pain in CP are poorly understood. Therein lies the key to unlocking this dreadful disease.



What do many patients say to me about how they are viewed by medical professionals?

- “The doctors think I’m making the pain up so I can have morphine”
- “It’s in my head”
- “They think I’m a drug-addict”
- “They always ask how much alcohol I drink”
- “I wish I’d never had the operation, they told me my pain would be gone”
- “They make me wait for my pain-killers”
- “They think I’m a weak person because I’m always in hospital”
- “You’re the first person to believe me”

Thank you for your attention



what's your poison ?

BINGE DRINKING, FUN ISN'T IT ?

If you drink more than 4 or drinks in one sitting, then you are a fully qualified binge drinker. This means you're likely to suffer from memory loss, kidney damage, and dancing like a complete prat!