Gallstones, biliary pain, fatty liver and AlfaPump

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Honorary Senior Lecturer
Gallstones

• Common
• Fat, Fair, Fertile, Female, Forty!
• Women twice as likely as men
• Genetic predisposition

• Types of gallstone
  • Mixed (75%)
  • Cholesterol stones (20%)
  • Pigment stones (5%)
Pathogenesis

What is bile made of?

- Water (around 97%)
- Bilirubin (by-product of haemoglobin metabolism)
- Cholesterol (lecithin and bile salts are solvent)
- Bile salts (undergo entero-hepatic circulation)
- Lecithin (increases solubility of cholesterol)
- Inorganic salts such as sodium bicarbonate
Pathogenesis

- Imbalance between bile constituents (bile salts, lecithin, cholesterol)

- Stasis (e.g. Pregnancy, obstruction)

- Obesity and hypercholesterolaemia

- Ileal dysfunction (Crohn’s disease/resection reduces re-absorption of bile salts)

- Haemolytic anaemia (eg sickle cell) results in excess of circulating bile pigment
Complications of Gallstones

• Mostly symptomatic

• Do nothing
Biliary Pain / Colic

• Right upper quadrant or epigastric pain lasting 1 to several hours
• Mostly after eating fat. tends to be evening meal
• Radiates to back and right shoulder tip
• May be associated nausea and vomiting

• Management
  • liver/gallbladder U/S, LFTs and
  • advise low fat diet
  • refer for surgery
Infective complication involving the gallbladder

Acute cholecystitis
symptoms similar to biliary colic but associated with sepsis

Management:
• Refer to emergency surgical team
• Antibiotics
• Early vs delayed cholecystectomy

Worsening infection can result in
• Mucocoele/infected mucocoele
• Empyema
• Perforation

Differential
• Right lower lobe pneumonia
• Peptic ulcer disease
• MI
NICE Guidance for Acute Cholecystitis

Optimal management is early laparoscopic cholecystectomy within seven days of presentation
Laparoscopic Cholecystectomy

• Usually Day Case
• 98% Laparoscopic completion rate
• Conversion due to dangerous anatomy or pathology
• Two weeks to return to work, up to 6 to return to normal
• Specific risks:
  • bile leak (1-2%) may need further laparoscopy and bile duct stenting
  • Bile duct injury (0.3%) requires complex surgery
  • Chronic diarrhoea or even less frequently constipation
Stones in or compressing the bile duct

- Cause jaundice which is often painful and can be intermittent
- Superimposed infection results in cholangitis
- Stones can obstruct the bile duct from outside (compression while still in gallbladder - Mirizzi)
- Pancreatitis
treatment of bile duct stones

- MRCP replaced pre-operative ERCP which used to be routine practice but is associated with complications and was frequently negative for stones which had passed

- Endoscopic ultrasound is best for microlithiasis

- Intra-Operative Imaging with either operative ultrasound or cholangiogram and bile duct clearance

- There are still situations when ERCP is useful in unfit or elderly or those with undilated ducts
Ultrasound: Gallstones

• USS is very sensitive for gallstones - 98%

• Gallbladder wall thickness indicates chronic inflammation

• Intramural or peri-cholecystic fluid indicates acute inflammation

• CBD calibre - allow 1mm per decade of age
Liver Function Tests

• Bilirubin is raised in
  • Obstructive Jaundice
  • Decompensated cirrhosis
  • Gilbert’s syndrome
  • Haemolysis

• ALT is raised in
  • Acute Liver injury/hepatitis of any cause
  • NASH
  • Biliary Obstruction - usually transient with stone passage
  • Acute cholecystitis

• Alkaline Phosphatase:
  • Biliary Obstruction
  • Skeletal Pathology

• Gamma GT
  • Biliary Obstruction
  • Alcohol
  • NASH
Gallbladder Polyps

• Gallbladder lesions not casting an acoustic shadow are often mistakenly called polyps when they are stones.

• If the symptoms are suggestive of biliary colic the treatment is cholecystectomy.

• True polyps are associated with a risk of carcinoma. Usually require annual scans.

• Cholecystectomy is offered when polyp is larger than 10mm.
Post Cholecystectomy pain

• Retained CBD Stones?
• Surgical Complications?
• Subtotal Cholecystectomy with old or new stones?
• Sphincter of Oddi Dysfunction?
• Other Pathology/IBS?
Functional Pancreatico-Biliary Disorders
- Gallbladder dyskinesia
- Sphincter of Oddi dysfunction
Gallbladder dyskinesia

- Typical biliary pain in the absence of gallstones

- A gallbladder ejection fraction of less than 40% on HIDA scan

- Patients randomised to surgery rather than medical treatment had evidence of cholecystitis on histology and were symptom-free at 3 year follow-up. The control arm continued to have symptoms and most required a cholecystectomy subsequently
Sphincter of Oddi dysfunction

• The presence of biliary or pancreatic pain in the absence of demonstrable organic pathology on routine investigations (mostly after cholecystectomy)

• Intermittent high-pressure in the pancreatico-biliary sphincter secondary to spasm, hypertrophy or denervation
# Sphincter of Oddi dysfunction

<table>
<thead>
<tr>
<th>Type</th>
<th>Recurrent pancreatitis, typical biliary pain or both</th>
<th>Abnormal LFTs/amylase</th>
<th>Dilated CBD/PD</th>
<th>Delayed drainage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td></td>
<td>One or two of the above</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td></td>
<td>None of the above</td>
<td></td>
</tr>
</tbody>
</table>
Investigations

• Ultrasound scan: an increase in CBD diameter of more than 2mm in response to a fatty meal or stimulation with cholecystokinin

• Hepatobiliary scintigraphy scan demonstrating delayed excretion

• Provocation test

• Direct sphincter manometry at ERCP

• Secretin MRCP is our routine non-invasive test

Diagnosis of this condition remains a challenge
Treatment - pharmacological

- Anticholinergics
- Calcium channel blockers
- Nitrates
- Botulinum toxin
Treatment-endoscopic

- Endoscopic sphincterotomy-failure rate 12 to 40%

- Endoscopic stenting did not gain much support
Treatment-surgical

- Trans-duodenal sphincteroplasty – allows division of both the biliary and pancreatic sphincters

- Failure rate 7 to 35%
Conclusion

• The diagnosis and management of pancreatico-biliary functional disorders are notoriously difficult

• They are part of a general spectrum of gastrointestinal functional disorders and failure to appreciate this contributes to treatment failure
Fatty liver
Liver Disease

- Healthy liver
- Hepatic steatosis
- Hepatic fibrosis
- Hepatic cirrhosis
Risk factors

• Obesity
  – >90% if BMI >30.
  – 67% if BMI 25-30

• Type 2 diabetes or insulin resistance 40-70%

• Dyslipidaemia

Metabolic Syndrome
Non-alcoholic fatty liver disease NAFLD

- Fatty infiltration
- Steato-hepatitis NASH
- Fibrosis
- Cirrhosis
Diagnosis

NAFLD
- Fatty infiltration (steatosis)
- NASH
- Fibrosis
- Cirrhosis

LFTs
- ? Normal LFTs
- ALT++/AST+
- ALT+/AST+
- Child’s stage

Radiology
- Fatty infiltration
- Worsening fatty infiltration /stiffness
- abnormal stiffness
- Cirrhotic with remodelling
- ?less fat
- Little fat
Example algorithm for clinical assessment of patients at risk of non-alcoholic fatty liver disease (NAFLD), accepting the many uncertainties that currently exist in this field.

Anstee Q M et al. BMJ 2011;343:bmj.d3897
http://nafldsore.com

NAFLD fibrosis score
Online calculator

Angulo P, Hui JM, Marchesini G et al. The NAFLD fibrosis score
A noninvasive system that identifies liver fibrosis in patients with NAFLD

Age (years)
BMI (kg/m²)
IGF/diabetes

AST
ALT
Platelets (x10⁹/L)
Albumin (g/L)

BMI: body mass index
IGF: impaired fasting glucose

© 2009 nafldsore.com

concept: Dr Matthew Armstrong
site construction and design: Dr Jeremy Jones
Fibrosis 4 Score

Formula:

\[
\frac{(\text{Age} \times \text{AST})}{(\text{Platelet} \times \sqrt{\text{ALT}})}
\]

Explanation of Result:

For NASH: F4 score < 1.30 = F0-1; F4 score > 2.67 = F3-4

For HCV with or without HIV: F4 score < 1.45 = F0-1; F4 score > 3.25 = F3-4

The Fibrosis 4 score is a non-invasive scoring system based on several laboratory tests that help to estimate the amount of scarring in the liver. This score has been studied in liver disease due to Hepatitis C and NASH.
Fibroscan
Why bother?

• Provide incentive to encourage weight reduction by modification of diet and lifestyle

• Optimise treatment of insulin resistance or diabetes and prompt aggressive modification of cardiovascular risk factors

• Detect fibrosis/cirrhosis early and refer for surveillance e.g. varices and HCC
HCC in NASH cirrhosis
Mis-diagnosis
Questions?
AlfaPump system for ascites
UK liver cirrhosis deaths
Natural history of cirrhosis

Development of cirrhosis

Development of complications

COMPENSATED CIRRHOSIS

DECOMPENSATED CIRRHOSIS

Death

Median survival
~ 10 years

Median survival
~ 2 years

Orthotopic liver transplant (OLT)

Compensated cirrhosis
n=806

Decompensated cirrhosis
n=843

Journal of Hepatology 2006 44, 217-231 DOI:
(10.1016/j.jhep.2005.10.013)
Ascites: a debilitating condition

**Refractory Ascites**: Ascites that cannot be mobilized or the early recurrence of which cannot be satisfactorily prevented by medical therapy.

**Diuretic-resistant Ascites**: lack of response to dietary sodium restriction and intensive diuretic treatment (spironolactone 400mg/day, furosemide 160 mg/day.

**Diuretic-intractable Ascites**: development of diuretic-induced complications that preclude the use of an effective diuretic dosage.
Refractory ascites

• Estimated around 10% decompensated cirrhotics develop refractory ascites
• 100,000 pts per year will develop RA by 2020 (EU and USA)
• Considerable morbidity
• Poor quality of life
• Reduced life expectancy
Peritoneo-venous (LeVeen) shunt
Peritoneo-venous (LeVeen) shunt

- Patency
- Infection
- Pulmonary oedema
- Procedure largely abandoned
Large volume paracentesis
But ........

- Hospital attendance (OPD v.s Inpatient)
- Post-paracentesis circulatory dysfunction (PPCD)
- Albumin cover (> 5 litres drained)
- Infection/SBP
- Loculated ascites
- Uncomfortable and unpopular with patients
- Malnutrition (protein and complement depletion)
Costs

- Albumin costs
- £3146* Inpatient paracentesis (without albumin)
- £1457* Outpatient paracentesis
- £38,000 + per annum

*NICE medical technology guidance 9 March 2012
T.I.P.S

Contraindicated - CCF, severe pulmonary hypertension, severe spontaneous encephalopathy, Child C, MELD >18, PVT

Technical difficulties

Encephalopathy: 20 - 30%

Shunt dysfunction

Fig 2. Schematic representation of a transjugular intrahepatic portosystemic stent shunt (TIPSS) (a radiologically placed stent through the liver parenchyma) decompressing the portal circulation into the systemic circulation.
Automated Low Flow Pump System for the treatment of refractory ascites: alfapump
alfapump system components

- Completely implantable under general (or local anesthesia)
- Charged transcutaneously, daily for 20 minutes
- Programmable
- Requires SBP prophylaxis administered
alfapump system components

1. During charging data are transferred from alfapump to Smart Charger.

2. alfapump data transferred via phone network to data specialists.

3. alfapump data specialists analyse data. Reports sent as often as requested.

4. Fewer follow-up visits, latest data always available, saves time and resources.

DirectLink Technology secure 24/7 monitoring
Patient selection

• Cirrhosis of the liver defined by histological and/or clinical, and/or radiological criteria
• Refractory ascites (1-2 drains/month)
• Fit for GA
• Life expectancy 6-12 months or more
• Ambulant Child-Pugh B ideal
  – No complex abdominal surgery/hernia!
• Capable of giving written informed consent and ability to operate the device
Avoid pump

• Renal failure defined as serum creatinine higher than or equal to 2 mg/dl (180 μmol/L)
• Clinical Evidence of recurring bacterial peritonitis
  – defined as 2 or more episodes over the last 6 months or a single episode within the last 2 weeks
• Clinical evidence of recurring urinary infections
  – defined as 2 or more episodes over the last 6 months or a single episode within the last 2 weeks
• Clinical evidence of loculated ascites
• Advanced hepatocellular carcinoma (exceeds Milan criteria)
• Obstructive uropathy, residual urinary volume exceeding 100ml, or any bladder pathology
alfapump® System vs Large Volume Paracentesis in the Treatment of Refractory Ascites: A Multicentre Randomised Controlled Study

• Danielle Adebayo¹, Christophe Bureau², Mael Chalret de Rieu², Dominique Valla³, Laure El Krief⁴, Markus Peck-Radosavljevic⁵, Simona Bota⁵, Anne McCune⁶, Reyad Abbadi⁶, Victor Vargas⁷, Macarena Simon-Talero⁷, Juan Cordoba⁷, Paolo Angeli⁸, Silvia Rosi⁸, Steve Whittaker⁹, Claudia Trepte⁹, Rajiv Jalan* ¹
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>alfapump system (AP) N=27</th>
<th>Standard of Care (SoC) N=31</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>61.1 (8.52)</td>
<td>62.6 (8.39)</td>
<td>0.537</td>
</tr>
<tr>
<td>Gender, male (n,%)</td>
<td>21 (77.8%)</td>
<td>25 (80.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>BMI, kg/m² (SD)</td>
<td>27.7 (4.84)</td>
<td>27.3 (5.67)</td>
<td>0.596</td>
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<tr>
<td>MELD Score*</td>
<td>12.2 (2.50)</td>
<td>11.3 (3.89)</td>
<td>0.121</td>
</tr>
<tr>
<td>Child-Pugh score† (SD)</td>
<td>8.2 (1.09)</td>
<td>8.4 (1.15)</td>
<td>0.780</td>
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<tr>
<td>Child Pugh Class (n,%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>22 (81.5)</td>
<td>24 (77.4)</td>
<td>0.855</td>
</tr>
<tr>
<td>C</td>
<td>3 (11.1)</td>
<td>5 (16.1)</td>
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</tr>
<tr>
<td>Aetiology of Liver Cirrhosis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Alcohol, n (%)</td>
<td>20 (74.1)</td>
<td>21 (67.7)</td>
<td>0.773</td>
</tr>
<tr>
<td>Non-alcohol, n (%)</td>
<td>6 (25.9)</td>
<td>10 (32.3)</td>
<td></td>
</tr>
<tr>
<td>Time since start of paracentesis treatment (yrs)§</td>
<td>1.1 (1,2)</td>
<td>1.0 (1,2)</td>
<td>0.512</td>
</tr>
<tr>
<td>Hospitalised in previous 3 months, n (%)</td>
<td>14 (51.9)</td>
<td>21 (67.7)</td>
<td>0.285</td>
</tr>
</tbody>
</table>

* n=26 (AP), n=29 (SoC)
† n=25 (AP), n=29 (SoC)
§ n=27 (AP), n=30 (SoC); NASH – non-alcoholic steatohepatitis
Quality of Life

HRQoL score by treatment arm over time

Number of patients completing survey for abdominal and activity

<table>
<thead>
<tr>
<th>Month</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP</td>
<td>27</td>
<td>26</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>SoC</td>
<td>31</td>
<td>29</td>
<td>29</td>
<td>27</td>
</tr>
</tbody>
</table>
Serum creatinine

Change in Creatinine Over Time

Change in Creatinine from Baseline Over Time

Day 180 p=0.060

Day 180 p=0.281

AP, alfapump system
SoC, standard of care

Acute Kidney Injury (AKI) = onset within 2 days and serum creatinine doubled from baseline. Classification based on AKIN criteria, J Hepatol. 2010 Sep;53(3):397-417.
Royal Free Hospital nutrition sub-study (n=16)

Improvement in nutrition seen in alfapump group
The Alfa Pump has been fitted for 9 months now and has changed my life. Previous to the insertion which was a very quick operation I was attending hospital every ten days or so to have a manual drain. On occasions they drained as much as 10 litres of fluid off which took around 6-7 hours. I was then fitted with a PleurX drain which enabled us to drain at home but again was a lengthy process and at times very painful. I was then given the chance to have the Alfa Pump fitted which has changed my life completely, no more visits to be drained and no build up of fluid. The pump requires charging twice a day which is painless and all data recorded automatically goes to the main department in Zurich who in turn send details back to the BRI who keep a regular check on it. I am very grateful for the Hepatologist Team in agreeing that I should be fitted with this great device, my thanks go to them all and I hope that others may be given the chance to experience this wonderful change in lifestyle.

Best wishes

Sylvia
Patient feedback

• Mr JC had the pump fitted in June 2014 for intractable ascites due to underlying alcohol related cirrhosis. Before insertion he says “ascites kept filling my abdomen necessitating drains every 12-14 days. I felt breathless, loss of mobility, unable to eat without being sick and totally unwell”

• His quality of life has changed dramatically since the pump was inserted. He has not required any further drains at all- “My ascites is controlled. Although breathless at times, my mobility has improved immensely. I can dress myself. Anxieties about having so many drains, avoiding infections and severe pain/discomfort have gone”

• “… definitely gives one a better life” and “just having a brief walk in the sunshine is achievable”. “an excellent invention!”, “easy to use” and “very beneficial to me”
Patient feedback

• Mr AM with underlying Non-Alcoholic Steatohepatitis (NASH) related cirrhosis had a pump inserted in Dec 2014.
• He describes breathlessness and abdominal distension before the pump was placed. He now has “more freedom” and “thoroughly” recommends the pump to other similarly affected patients.
• His ability to enjoy life changed with “no more bloating, consequently no pain”