Cicely Saunders International
Better care at the end of life

WHO Collaborating Centre for Palliative Care & Older People

KING'S College LONDON

Advanced Liver Disease

The Oxford Advanced Pain and Symptom Management Courses 2019

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King's College Hospital Foundation Trust
London

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'Is life worth living? It all depends on the liver'

William James, American Philosopher, 1842-1910

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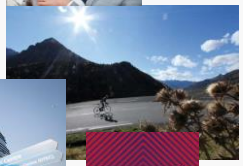
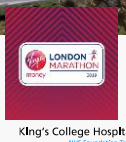
Nine years on…





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Nine years on…

- Numbers are still increasing
- Aetiology
- New models of care
  - emphasis on dual planning
- Increased awareness of best practice in prescribing
  - PCF
  - BASL / King's guidelines
- Increased recognition within the specialty

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What makes Liver Disease so special?

- Unpredictability
- Challenging symptoms often requiring admission to hospital
- Younger patients
- Maintaining hope
- Lack of evidence base; prognostication, symptom management and service configuration, although improving…

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AB, 27yr old man

- Ref urgently to team on a Friday morning
- 50 days on ITU
- Background history of mental health problems
- Presented with acute on chronic liver failure (alcohol)
- Multi Organ Failure
- Deteriorating; died on full organ support
- Mum and 2 siblings

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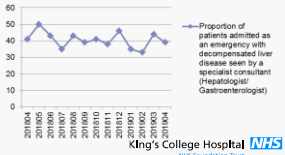
King's

- 80% of deaths within the liver unit occur in intensive care
  - 4-10 deaths per month

Emergency with decompensated liver disease seen by a specialist consultant



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Outline

- Facts and figures
- Identification – recap
- Models of care
- Management of advanced disease
  - Symptom prevalence
  - Complications
  - Prescribing – what's new?
- 'Shifting sands…'

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Chronic Liver Disease

- In the UK CLD now the fifth highest cause of mortality after heart, cancer, stroke and respiratory disease; only major cause of death increasing year on year
  - In England 2% all deaths; 4% all deaths if any mention of liver disease included from death certification
  - 9000 deaths /yr England and Wales
- Disproportionately affects younger age groups
  - 40-49yr old age group ALD most common cause of death, 1 in 10 all deaths
  - 70% deaths occur in hospital. More likely to be from deprived background.

National End of Life Care Intelligence Network, Deaths from liver disease, implications for end of life care in England. March 2012
Volk ML et al. Hospital readmissions among patients with decompensated cirrhosis. Am J Gastro. 2011 Sept 20.
Verne J, Pring A. Raising the profile of end of life care needs for patients dying from liver disease –using national mortality data.
Public Health England/ www.gov.uk/phe 2013

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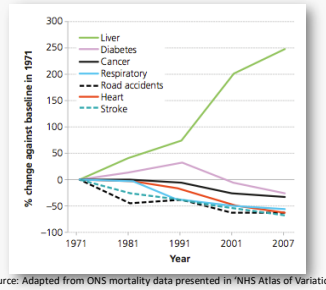
Chronic Liver Disease in the UK



Variable access to services

Variable quality…

Worldwide prevalence: 4.5-9%

Source: Adapted from ONS mortality data presented in 'NHS Atlas of Variation in Healthcare for People with Liver Disease' 2013. London: NHS Liver Care

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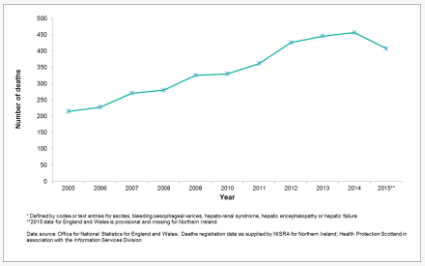
Impact of therapy on mortality HCV



Deaths from HCV or HCC in patients with HCV (PHE report on HCV 2016)

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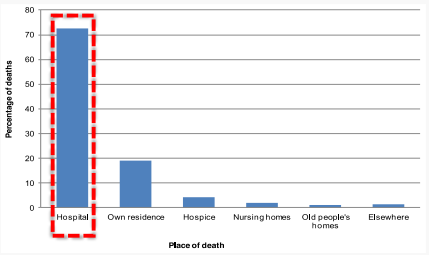
Place of death for patients dying of liver disease

Distribution of liver disease deaths by place of death, England 2001-2009



Source: Adapted from ONS data presented in "Deaths from Liver Disease", National End of Life Care Intelligence Network, London, 2012.

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HCC

Villanueva A. Hepatocellular Carcinoma. N Engl J Med 2019; 380:1450-1462

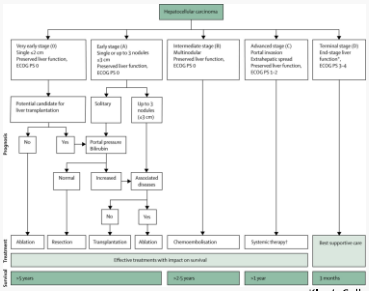

Fig 2: Barcelona Clinic Liver Cancer (BCLC) Staging
The Lancet 2018 391, 1301-1314DOI: (10.1016/S0140-6736(18)30010-2)

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Identification of advanced disease

- Synthetic and excretory function
  - INR > 2, albumin < 20mmol/l
  - Bilirubin > 100µmol/l
  - Thrombocytopaenia is a sensitive indicator of liver fibrosis
- Performance status over time
- De-compensation
- Child Pugh /MELD/UKELD score
- SPICT: PS↓, ≥2 unplanned hospital admissions in 6/12, wt↓,symptoms, LT CI

Medici V, Rossaro L, Wegelin JA, Kamboj A, Nakai J, Fisher K, Meyers F. The Utility of the Model for End-Stage Liver Disease Score: A reliable guide for liver transplant candidacy and, for select patients, simultaneous hospice referral. Liver Transplantation 2008;14: 1100-1106

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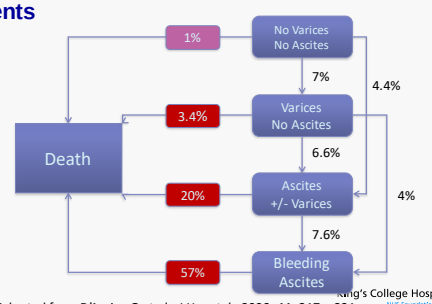
Child-Pugh score

Factor	Score of 1	Score of 2	Score of 3
Encephalopathy grade	None	1-2	3-4
Ascites	Absent	Mild	Moderate to severe
Bilirubin	<35micromol/l	36-60 micromol/l	>60 micromol/l
Albumin	>35g/l	28-35g/l	<28g/l
PT (secs prolonged) OR INR	1-4secs <1.7	4-6secs 1.7-2.3	>6secs >2.3
Child-Pugh score	**5-6 (A)**	**7-9 (B)**	**10-15 (C)**
Med. 1 yr survival	**95%**	**80%**	**45%**
Med. 2 yr survival	**90%**	**70%**	**38%**

NHS

Clinical course of cirrhosis: 1-year outcome probabilities according to clinical signs & events



Source: Adapted from D'Amico G et al. *J Hepatol.* 2006; 44: 217 – 231

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Proactive approach

- Increasing evidence that early palliative care intervention can improve symptom management and quality of life
  - Improved symptom burden and mood
  - Improved survival?
  - Less aggressive treatment and less hospitalization

- Temel JS et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N ENGL J Med. 2010:363(8):733-42
- Baumann AJ et al. Benefit of early palliative care intervention in End-Stage Liver Disease Patients awaiting liver transplantation. JPSM 2015:Dec 50(6);882-6 e2
- Walling AM et al. Impact of consideration of transplantation on end-of-life care for patients during a terminal hospitalization. Transplantation. 2013;95(4):641-6
- Early palliative care for adults with advanced cancer (Review) 2017 The Cochrane Collaboration
- Shinall MC et al. COMPASS: A pilot trial of an early palliative care intervention for patients with end stage liver disease. JPSM 2019;doi:https://doi.org/10.1016/j.jpainsymman.2019.06.023

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Proactive approach

Hudson BE et al. Frontline Gastroenterology 2017;8:45-52

- Development and evaluation of a prognostic screening tool and supportive care intervention
- University Hospitals Bristol, UK
- Quality improvement process
- PDSA cycle
  - Plan, Do, Study, Act

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Integration in practice

Hudson BE et al. Frontline Gastroenterology 2017;8:45-52

Screening criteria	Supportive care intervention
Childs Pugh C	Consultant led poor prognosis discussion
>2 liver related admissions in last 6 months	Poor prognosis letter to GP
Ongoing alcohol use in known ALD	Opportunity for advance care planning
Currently unsuitable for transplantation	Specialist palliative care review if complex symptomatic/social/psychological needs
WHO PS 3-4	Allocation of hepatology specialist nurse

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Proactive approach

- Advanced Chronic Liver Disease MDM
  - Likely to be mandated by NHS England
  - Poor prognostic criteria and management options as per Hudson paper
  - Evaluation of impact
    - Outcome measures – IPOS?
  - Costs: Evaluation of 13000 patients with cirrhosis in last year of life £7718/month/patient, spent 33% days in hospital and 52.5% re-admitted within 30 days of discharge. OP paracentesis services saved £4240 / patient

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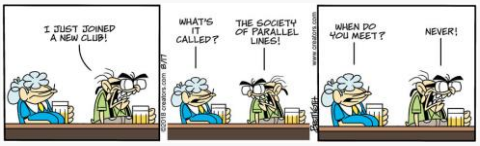
Parallel planning



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Supportive care nurse

- Should we aim to identify patients earlier and intervene
  - who should intervene?
- Role of supportive care liver nurse specialist
  - Acceptable intervention, access to additional expert advice, support and continuity of care
  - Acceptable and feasible
  - Outcome measures: POS and EuroQol-5D-5L

Kimbell B et al. Palliative care for people with advanced liver disease: A feasibility trial of a supportive care liver nurse specialist. Pall Med. 2018, vol 32(5) 919-929

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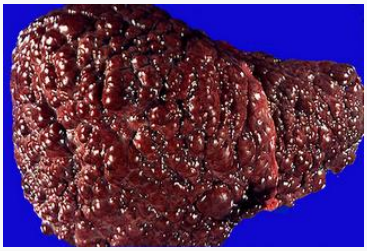
Management of advanced disease



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Chronic Liver Disease

- Physical symptom burden
  - Complex and dramatic
  - Often require hospital admission
  - Poor evidence base with regard to pharmacology
- Psychosocial issues
  - Liver disease often associated with stigma
  - Complex socioeconomic background
  - Uncertainty; re-compensation, transplantation

Boyd K, Kimbell B, Murray S, Iredale J. Living and dying well with end stage liver disease: Time for palliative care? Hepatology vol. 55 (6), 1650-1651, June 2012

Morrison RS, Hope AA. Integrating palliative care with chronic liver disease. J of Pall Care 27:1/ 2011; 20-27

Mazzarelli C et al. Palliative Care in End-Stage Liver Disease: Time to do Better? Liver Transplantation 24 961-968, 2018 AASLD

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Living and dying with liver failure

Kimbell B, Kendall M, Boyd K, Murray S, 2013

- Serial interview study
  - 15 patients with advanced liver disease, 11 informal carers and 11 case-linked health / social care professionals, interviewed over a year
- High and prolonged burden of physical, psychological and social needs
- High level of information needs; poor understanding of liver disease
- Lack of continuity and holistic support

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What do patients experience?

- Scanty evidence, mainly in transplant pop.
- Pain – severe pain/opiate prescriptions are common as in advanced cancer [1,2]
- Fatigue – often profound [3]
- Sleep disturbance [4]
- Depression, anxiety (up to 50%) [5]
- Uncertainty / information need [6]
- Social isolation & stigma [7,8]

1. Rogal et al. *Dig Dis Sci.* 2013; 58(10):2276-85
2. Roth et al. *J Am Geriatr Soc.* 2000; 48(5): S122-30
3. Van der Plas et al. *Qual Life Res.* 2007; 16(3):375-8
4. Mostacci et al. *Neurol Sci.* 2008; 29: 237-
1. Bianchi et al. *Dig Liver Dis.* 2005; 37: 593-600
2. Bjork & Naden. *Nurs Inq.* 2008; 15: 289-98
3. Brown et al. *Qual Health Res.* 2006; 16: 119-36
4. Wainwright et al. *J Clin Nurs.* 1997; 6: 43-5

Symptom prevalence and QOL

Peng et al. Symptom prevalence and quality of life of patients with end-stage liver disease: A systematic review and meta-analysis. Pall Med 2019, vol. 33(1)24-36

- Systematic review and meta-analysis
  - 8 electronic databases (Jan 1980-June 2018)
  - 80 studies (30 SP, 41 QOL, 4 both)
    - Pain (30-70%), breathlessness (20-88%), muscle cramps (56-68%), sleep disturbance (insomnia 26-77%), psychological symptoms (depression 4.5-64%, anxiety 14-45%), erectile dysfunction prevalent in men (53-93%)
    - HRQoL patients with ESLD significantly impaired compared with healthy controls or patients with CLD

Complications of advanced disease

Refractory ascites

- Mortality of 50% at 6 months
- Transjugular intrahepatic portosystemic shunt
- Paracentesis
  - Risks of precipitating hepatorenal syndrome
  - Colloid volume expansion is probably unnecessary for safe withdrawal of < 5 L ascitic fluid
  - Implanted, externally draining peritoneal catheter
- Challenge regarding place of care

EASL. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome in cirrhosis. J of Hepatol 2010 vol. 53:397-417
Runyon BA. Treatment of patients with cirrhosis and ascites. Sem Liver Dis 1997;17(3):249-260
Reisfield GM, Wilson GR. Management of intractable, cirrhotic ascites with an indwelling drainage catheter. J of Pall Med, 2003. Vol 6 (5): 787-791

Refractory ascites

- Co-ordinated care
  - Planned follow up by MDT in OP
  - Reduced readmissions, 12 month mortality & costs
- The alfapump® system
  - IP catheter connected to a subcut implanted battery powered device that moves fluid from peritoneal cavity & a 2nd that connects the pump to the urinary bladder
  - 2019 NICE – *not* approved for routine use 'serious and well recognised safety concerns'

Ge PS and Runyon BA. Care coordination for patients with cirrhosis: a 'win-win' solution for patients, caregivers, providers, and healthcare expenditures. J Hepatol 2013 vol 59. 203 204 https://www.nice.org.uk/guidance/IPG631Nov18

Implantable tunnelled catheters

- NICE approval in malignant setting
- Established guidance in place at King's but variable use
- REDUCe (Reduced Drainage Untreatable Cirrhosis) trial – feasibility study completed
- Anecdotal use across UK

Macklan L. Palliative long-term abdominal drains versus repeated drainage in individuals with untreatable ascites due to advanced cirrhosis: study protocol for feasibility randomised controlled trail. BMC Open Access 2018 19:401

REDUCEe

Macken L et al. Long term palliative abdominal drains versus large volume paracentesis in refractory ascites due to cirrhosis: a multi-centre feasibility randomised controlled trial (the REDUCe Study). J Hepatol 2019; Suppl 70:e660

- Feasibility study
  - 12 wk feasibility RCT, LVP vs. LTAD
  - 36 pts randomised (19 LVP, 17 LTAD)
  - No LTAD related SAE, including infection
  - Preliminary safety and efficiency data collected
  - Reduction in time spent in hospital, health resource utilisation and carer burden
  - Inconsistent improvement in symptoms and QOL
  - Plans for multi-centre RCT but challenges regarding funding and agreement of primary outcome measure

Spontaneous Bacterial Peritonitis

- Patients with SBP have an in hospital mortality of 20%
- Cumulative recurrence rates are 70%, median survival of nine months
- Prophylaxis
  - If suffered recurrent episodes then long term antibiotics may be appropriate
  - Norfloxacin / Ciprofloxacin recommended
  - NB antibiotic induced complications

Variceal bleeding

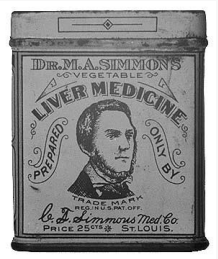
- Mortality from first presentation variceal bleed is about 50%, although influenced by severity of underlying liver disease
- Crisis planning, patient preferences
- Child-Pugh class, one year mortality rates from subsequent variceal haemorrhage:
  - A 5%
  - B 25%
  - C 50%

Encephalopathy

- Metabolically induced, potentially reversible, functional disturbance of brain
  - Severe intrinsic hepatic dysfunction
  - Portosystemic shunts leading to the diversion of portal blood to the systemic circulation before removal of toxic intestinal substances
- Personality changes, impaired intellect, disturbed sleep pattern and depressed level of consciousness
- Marker of decompensation

Cash WJ et al. Current concepts in the assessment and treatment of Hepatic Encephalopathy. QJMed 2010; 103:9-16

Prescribing in liver disease



Prescribing in liver disease: key points

- Little evidence to guide practice; there is little information to guide drug dosing
- Liver has a huge reserve and damaged significantly before it starts to have an effect
- Unpredictable and each patient needs to be treated as an individual
  - Function of the heterogeneous pathophysiology of liver disease with respect to hepatocellular function, protein binding and hepatic blood flow
  - Aetiology may have an impact on how drugs are affected

Drug handling in liver disease

- Patient factors
  - Diagnosis and signs and symptoms of liver disease
  - LFTs (trends not in isolation); markers of synthetic function
- Drug factors
  - Pharmacokinetic properties
    - Bioavailability, vol. of distribution, clearance
  - Pharmacodynamic properties
    - Relationship between drug conc. and response
  - Side effect profile and therapeutic index
  - Route of administration

North-Lewis P (ed). Drugs and the Liver. Pharmaceutical Press, 2008

Hanna M. The effects of liver impairment on opioids used to relieve pain in cancer patients. Pall Med 2011 25(5) 604-605

PCF6+ 2019

- Drug induced hepatotoxicity: intrinsic vs. idiosyncratic
- Pharmacological impact of hepatic impairment
  - Pharmacokinetic
  - Pharmacodynamic
  - Secondary phenomena necessitating extra caution
    - Ascites, coagulopathy, disruption of blood-brain barrier, encephalopathy, QT prolongation, renal impairment
- 'Safer drugs'
  - High PO bio-availability, min hepatic metabolism, low-moderate protein-binding, short half life, no sedative, constipating or hepatotoxic effects

PCF6+

- 'Generally safer'
- 'Use cautiously'
- 'Avoid if possible'

Non-opioids

- Paracetamol
  - 'Safe' for the majority of patients with liver disease
  - Oral administration at normal doses for **short** periods
  - **But** consider reduction in dose (2g/24hr) if prolonged therapy or malnourished (<50kg), chronic alcoholism, dehydration (glutathione depletion)
    - PO/PR 500mg q8h; maximum 1g q8h
  - Anecdotal experience from King's/liver units: IV paracetamol should be given tds (but contraindicated by manufacturers in severe impairment)
- NSAIDs
  - Risks outweigh any benefits
  - If unavoidable; ibuprofen PO 200mg tds

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Weak opioids

- Codeine and dihydrocodeine
  - Extensive liver metabolism - active metabolites
  - Dihydrocodeine preferred due to PK profile
- Tramadol
  - Extensive liver metabolism - predominantly one active metabolite (O-demethyl-tramadol)
  - 90% renal elimination
  - Product literature reports significant increase in t1/2
  - Adverse effects, inc. lowering of seizure threshold
  - If renal and liver impairment or severe liver disease reduce frequency to bd or tds
- For all groups – generally avoid
  - If unavoidable start at lowest dose possible

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Opioids

- Limited studies - many single dose
- Half life variable (range approx 2-5hrs)
- Most opioids undergo extensive liver metabolism and produce active metabolites, major metabolic pathway is oxidation, exceptions are morphine and buprenorphine which undergo glucuronidation
- No. of confounding factors make it difficult to predict pharmacokinetics in liver disease
- Pharmacodynamics - alteration end organ sensitivity
- Adverse effects - constipation and sedation
- Increased risk of toxicity with all opioids

Tegeder I et al. Pharmacokinetics of opioids in liver disease. Clin Pharmacokinetics. 37(1):17-40, 1999 Jul

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Opioid analgesics

Rhee C, Broadbent AM. Palliation and Liver Failure: Palliative Medications Dosage Guidelines. JPM 2007,vol 10, no. 3:677-685

Drug	T1/2 Normal	T1/2 Cirrhosis	T1/2 CP-A	T1/2 CP-B	T1/2 CP-C
Fentanyl	263min	304min			
Morphine (IV)	100min 1.7hrs	121min 4.2hrs	123.4min 3.4hrs	110min 4.35hrs	 4.47hrs
Morphine (o)	3.3hrs	5.5hrs	6.4hrs	6.85hrs	4.4hrs
Morphine SR	4.01hrs	No data	7.36hrs		
Oxycodone	3.4hrs (after transplant)	13.9hrs (before transplant)			
Methadone	18.8hrs	No data	11.3hrs	13hrs	35.5hrs

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Alfentanil and Fentanyl

Alfentanil

Moderate hepatic extraction ratio & lesser volume of distribution:

- Reduced enzyme activity as in cirrhosis and hepatitis – marked impact
- Liver blood flow changes – enterohepatic circulation
- Protein changes – major impact: less deep tissue depots 'buffer' free amount in plasma and reduce plasma fluctuations, and relative decrease in protein binding at higher doses

Fentanyl

High hepatic extraction ratio & greater volume of distribution:

- Reduced enzyme activity as in cirrhosis – little impact
- Liver blood flow changes – only makes a difference in severe liver disease and little impact
- Protein changes – limited impact: deep tissue depots 'buffer' free amount in plasma and reduce plasma fluctuations

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Opioid analgesics

- No 'ideal' opioid
  - Fentanyl for those with hepatorenal syndrome
  - Morphine and buprenorphine (glucuronidation)
- For any opioid
  - Start at the lowest dose possible
  - Carefully titrate monitoring clinical response and adverse effects, particularly constipation
  - Avoid controlled release preparations and opioids with long half lives
  - Consider increasing the dose interval

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Antidepressants

- Most antidpressants are highly protein bound and hepatically metabolised by one or more CYP450 enzymes; metabolism further impaired in constitutionally poor metabolisers and risk of toxicity increased from a pharmacokinetic drug-drug interaction involving an inhibitor of the CYP450 enzyme
- Long half lives increase the risk of accumulation and side effects often an issue

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Antidepressants

- TCAs not first line treatment for depression
  - Amitriptyline, half life is long but unaltered
- All SSRIs accumulate in severe impairment
- 'Use cautiously'
  - Amitriptyline PO: 5-10mg nocte
  - Citalopram (unless additional risk factors for QT prolongation or severe cholestasis) PO 10mg od
  - Mirtazepine (lower risk of bleeding than SSRI) PO 15mg nocte
- 'Avoid if possible'
  - Sertraline unless for cholestatic pruritus

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Antiemetics

- Prokinetics
  - Domperidone used first line, extensively metabolised by liver therefore dose reduce by 50% (risk prolonged QT)
  - Metoclopramide, clearance rate reduced in cirrhotic patients therefore dose reduce by 50%
- 5HT3 receptor antagonists
  - Ondansetron reduced doses (constipating)
- Centrally acting antiemetics
  - 'Avoid if possible'
  - If unavoidable – reduced dose cyclizine, haloperidol and levomepromazine

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Anti-epileptics

- A number of pharmacokinetic changes impact on many of the anti-epileptics used in PC, sedative effects may also worsen or mask encephalopathy
- 'Generally safer'
  - Levetiracetam - dose reduction required if renal impairment (PO/IV: 250mg bd)
  - Gabapentin - anti-epileptic or for neuropathic pain, dose reduction if renal impairment (PO: 100mg nocte, increase by 100mg/24hr every 2-3 days)
  - Pregabalin - anti-epileptic or for neuropathic pain, dose reduction if renal impairment (PO: 25-50mg bd)

Antipsychotics

- Limited data available
  - Many are highly protein bound
  - Many are extensively metabolised in the liver and dependant on one or more of CYP3A4, CYP2D6 and CYP1A2
  - Risks of prolongation QT – lowest for quetiapine
- Long term use should generally be avoided
- 'Use cautiously'
  - Quetiapine for psychosis PO: 12.5mg bd

Benzodiazepines and Z-drugs

- Extensive liver metabolism - active metabolites
- Generally avoid unless in last days of life, or use for short term only
- Short acting benzodiazepines can be considered if clinically indicated
  - 'Use cautiously'
    - trial of lorazepam as anxiolytic, also used short term to manage alcohol withdrawal
    - trial of zopiclone as night sedative
  - Midazolam appropriate to use in last days of life
- Longer acting benzodiazepines may be used but dose and dosage interval should be altered

Miscellaneous

- Antifungals
  - Fluconazole use with caution, 50mg od 7 days, avoid concominent use with fentanyl as CYP3A4 inhibition by fluconazole can result in accumulation
- Acid suppressants
  - PPIs in cirrhosis, limit use to specific indications, concerns re; poorer outcomes
  - Ranitidine – dose reduce renal impairment
- Antidiarrhoeals, antimuscarinics, bisphosphonates and denosumab, skeletal muscle relaxants, octreotide
- Systemic corticosteroids

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Pragmatism

- Assess each individual case
- Patients are often symptomatic
- Any drug prescribed should be used with caution and regularly reviewed
  - 'start low, go slow'
- Patients often have a fluctuating condition
- Overall goals of care need to always be considered
- Simplify long term hepatic drugs

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King's guidelines (BASL) / PCF6+

- Updated guidelines 2018
  - New evidence relating to use of fentanyl in high doses / continuous infusions
  - Clobazam added
  - Antidepressants – Citalapram / Mirtazepine – both with caution
  - Section on oral candidiasis added
  - Debate relating to recommended dose of paracetamol
- Palliative Care Formulary 2019

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Psychosocial issues

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Psychosocial issues

- Prior coping strategies
  - Alcohol, drug use
  - Stigma associated with liver disease, hep B and C
- Complex treatment strategies
- Safeguarding issues
  - Fluctuating cognition - Role of advance care planning
- Carer stress
- Psychosocial issues relating to transplantation
  - Expectation vs. reality
  - Family dynamics esp. in relation to live related donation

Marie Curie, St Mungos (2011) Supporting homeless people with advanced liver disease approaching the end of life
Kalaitzakis E, Josefsson A, Bjornsson E. Psychological distress in patients with liver cirrhosis. Gastroenterology 2008; 134(4):A625-A25
Hansen L et al. Background and design of the symptom burden in end-stage liver disease patient-caregiver dyad study. Res Nurs Health. 2017;1-16

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Advance care planning

- In anticipation of the potential fluctuation in capacity associated with encephalopathy it is vital that clinicians engage patients early in advance care planning
  - Exploration of values and goals
  - Advance care planning documentation
  - Review of experience as disease progresses
- Sharing of information across all care settings
- What do patients really think of this approach and what do they really want?

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Advance care planning

Hudson B et al. The incompatibility of healthcare services and end-of-life needs in advanced liver disease: A qualitative interview study of patients and bereaved carers. Pall Med 2018

- Qualitative study – semistructured interviews analysed using thematic analysis; 17 participants
- Described escalating physical, psychological and social needs as disease progressed, disabling symptoms, emotional distress and uncertainty, addiction, financial hardship and social isolation
- End of life care needs were incompatible with the healthcare services available to address them; attitudes towards palliative care were mixed, however participants valued opportunities to express future care preferences and an increased focus on symptom control and logistical aspects of care

Transplantation

Transplantation

- Liver transplantation has become gold standard treatment for advanced chronic liver disease and fulminant hepatic failure
- 1 yr survival 80-90%, 5 yr survival 60-80%
- Yet approx. 50% of those assessed for transplant are declined and 20% of patients on the active waiting list will die
- Four people die for every one transplanted

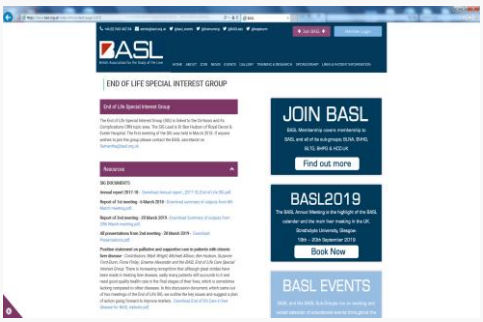
Transplantation

Potentially treatable yet often fatal illness

- Significant symptom burden as disease progresses
- Resource allocation
- Maintaining hope
  - Remaining listed vs. pure palliation; psychosocial support
  - 'ongoing presence' and 'non abandonment'
- Should we re-consider including a palliative care assessment within the assessment process?

Larson AM, Randall Curtis J. Integrating palliative care for liver transplant candidates: "Too well for transplant, too sick for life" JAMA 2006;295(18):2168-2176
Gott M et al. Transitions to palliative care in acute hospitals in England: qualitative study. BMJ 2011;342:d1773

The world of hepatology

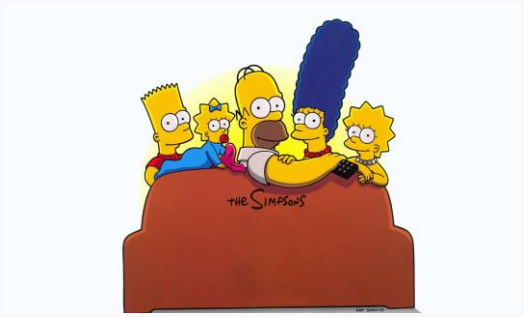


IQILS

Two levels of accreditation: level 1 – QI plan in place, level 2 external review and accreditation

Challenges and opportunities

- Incidence and prevalence of chronic liver disease is set to increase
- Patients often have a high symptom burden requiring complex and often acute management but often not referred for palliative care
- Little evidence to guide practice but increasing
- Paradox of potentially life saving options for treatment in the context of a fatal disease
- Current service provision doesn't meet need, but changing…



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Anti-depressants

- Citalopram
  - SSRI, which also acts as a H2 antagonist
  - Metabolised by various pathways and CYP2D6 plays a role in metabolism
  - May lower seizure threshold (less than other anti-depressants). SSRIs can increase the risk of peptic ulceration and bleeding disorders
  - The SPC recommends reducing dose in liver impairment. One study showed a prolonged half-life in cirrhotic patients
  - Avoid in liver impairment
- Mirtazapine
  - α2 adrenergic and 5-HT 2 antagonist antidepressant.
  - Metabolised by demethylation and oxidation followed by conjugation
  - Adverse effects: Increased appetite, weight gain, drowsiness. Can rarely cause hepatic impairment
  - Use with caution – start low and titrate slowly

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Antidepressants

- Sertraline
  - SSRI that also acts as a dopamine re-uptake inhibitor. Extensively metabolised by the liver (primarily by CYP3A4 pathway). Acts as a weak hepatic enzyme inhibitor
  - The SPC recommends reducing the dose/increasing dose interval in liver impairment and avoiding the drug in severe liver impairment (primarily as no clinical data is available). One study showed prolonged half-life in patients with liver cirrhosis
  - Avoid in severe liver impairment. Use with caution for cholestatic pruritus in view of increased risk of upper GI bleeding

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Opioids

- Factors leading to *increased* opioid effects:
  - Reduced first pass metabolism secondary to impaired liver metabolism, reduced blood flow and portal hypertension
  - Fat soluble drugs may be increased in cachectic patients
  - Cholestasis may reduce the elimination of morphine and codeine in bile
  - Opioid receptor sensitivity may be enhanced

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Opioids

- Factors leading to *decreased* opioid effects:
  - Presence of ascites may reduce oral absorption
  - Distribution of water soluble drugs into ascitic fluid may reduce the amount available for circulation
  - Impaired metabolic capacity may decrease the conversion of drugs to active metabolites

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Encephalopathy: treatment

- Identification of precipitating factors
  - Infection, GI bleeding, medications, brain injury
- Diet - normoprotein
- Lactulose vs alternative laxatives
  - Reduces colonic pH and nitrogen load in gut, therefore reducing ammonia
  - In practice, probably acceptable to use alternative laxatives
- Enemas
- Second line agents; neomycin, rifaximin
- Antipsychotics - terminal agitation

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MELD: Model for End Stage Liver Disease

- Based on logistic regression multivariate analysis of predictors of 90 day mortality cirrhotic patients undergoing TIPS
- Bilirubin, creatinine and INR
- Range:
  - 6-10 = well compensated
  - 11-18 = moderate
  - 19-24 = advanced
  - 25-39 = critical
  - 40+ = terminal (71.3% PI 3 month mortality)

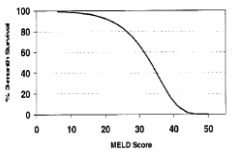

Figure 2. Estimated 3-month survival as a function of the MELD score.

www.unos.org/resources

Managing transitions

- Supportive and palliative care indicators tool
  - Look for 2 or more general indicators of deteriorating health
    - PS poor or deteriorating with limited reversibility, 2 or more unplanned admissions to hospital in past 6 months, wt loss (5-10%) over past 3-6 months and/or body mass index <20, persistent, troublesome symptoms despite optimal treatment of underlying condition(s), lives in nursing home/ NHS CC unit or needs care at home, patient requests supportive and palliative care, or treatment withdrawal

Boyd K, Murray SA. Recognising and managing key transitions in end of life care. BMJ 2010;341:c4863 / www.palliativecareguidelines.scot.nhs.uk/careplanning/supportive-palliative-indicators.aspx July 2012

Managing transitions

- Supportive and palliative care indicators tool
  - Clinical indicators of advanced conditions:
    - Advanced cirrhosis with one or more complications in past year:
      - Diuretic resistant ascites, hepatic encephalopathy, hepatorenal syndrome, bacterial peritonitis, recurrent variceal bleeds
    - Liver transplant contraindicated
- King's: Patients declined for LT
  - MELD and CP predictors of survival

Kriese S et al. Outcome of patients declined for liver transplantation: should prognostic scores guide proactive palliative care review? AASLD Nov 2012

Boyd K et al. A 'Good Death' with irreversible liver disease: Talking with patients and families about deteriorating health and dying. CLD, vol 6 (1) July 2015

Relevant Patient Groups

- End-stage chronic liver disease (CLD)
- Primary liver cancer on background of CLD
- Severe liver impairment from large volume metastases or malignant infiltration

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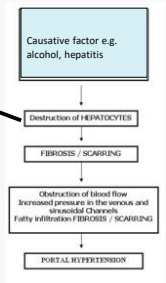
Liver impairment

- Reduced enzyme activity
- Liver blood flow changes
- Protein changes – reduced synthesis of albumin and α1-acid glycoprotein



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What does liver disease do?

Predominantly affecting liver tissue (cirrhosis and hepatitis):

- reduces binding site affinity for drug
- reduces metabolism of drugs by hepatocytes
- acute hepatitis mainly reduces oxidizing capacity of hepatocytes
- reduces albumin and α1-acid glycoprotein synthesis (but may increase α1-acid glycoprotein if inflammatory component)

Predominantly peri-portal pathology (PBC, localised cancers):

- reduces blood flow and hepatic extraction

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Pharmacokinetic Factors Affecting Drug Metabolism

- Bioavailability
  - Absorption may be reduced
  - Variable effect on volume of distribution, clearance (biliary, renal)
    - Protein binding
    - Cachexia
    - Ascites
- Metabolism: liver will continue to carry out drug metabolism even in cirrhotic patients
  - Hepatic Blood Flow
    - Cirrhosis
    - Cardiac Failure
    - Porto-systemic shunts
  - Enzyme capacity of liver
  - Type of metabolic reaction
- Consider route of elimination (e.g. biliary, renal)

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Pharmacodynamics in liver disease

Drug interaction with underlying condition may lead to patients being at risk of an increased toxicity, exaggerated response or reduced response

Special consideration:

- Encephalopathy
  - Increased sensitivity to sedatives, hypnotics and CNS depressants
  - Constipating agents can precipitate encephalopathy
- Ascites
  - High sodium content drugs e.g. gaviscon, NaCl 0.9%
  - Salt and water retaining drugs e.g. steroids, NSAIDS
- Coagulopathy
  - Anticoagulants e.g. warfarin
  - NSAIDS
- Renal impairment

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Drug Use in Liver Disease: Cardinal Rules

- Avoid drugs in severe disease especially if hepatotoxic
- Ideally use drugs with short $t^1/_2$
- If PT ↑ albumin ↓ bilirubin ↑ consider dose ↓
- Start with small dose and ↑ slowly or dose PRN. Monitor patient closely.

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Metabolism

- Most opioids are metabolised in the liver
- Most opioids are cleared effectively by the liver and have a high first pass effect/intrinsic high clearance
  - Tramadol and methadone are EXCEPTIONS
- Clearance dependent predominantly on blood flow rather than capacity of hepatocyte enzymes
  - Most opioids undergo oxidation as major metabolic pathway (sensitive to changes in hepatic blood flow)
    - Disorders such as liver cirrhosis may reduce blood flow/clearance
    - Reduction in blood flow may ↓ metabolism – risk of accumulation
  - Morphine & buprenorphine undergo glucuronidation - affected by diseased hepatocytes
- End organ sensitivity increased in liver disease in terms of analgesic properties and adverse effects

Metabolism of opioids appears to be well preserved during acute liver dysfunction but can become altered in advanced disease

Lactulose

- Lactulose is useful in treating the hyperammonemia caused by hepatic encephalopathy, because it helps "draw out" ammonia (NH_3) from the body
- Metabolized in the colon by bacterial flora to short chain fatty acids (incl. lactic acid & acetic acid) ⟶ acidifying colonic contents ⟶ favors formation of non-absorbable NH_4^+ from NH_3, trapping NH_3 in the colon and effectively reducing plasma NH_3 concentrations
- Used in patients with cirrhosis/hepatic encephalopathy to limit the proliferation of ammonia-forming gut organisms and increase the clearance of protein load in the gut

Refractory ascites – tunnelled drains

- King's pilot:
  - 8 drains in 7 patients
  - All had CLD, 5 had liver tumour
  - Median survival 32d (10-102d)
  - Place of death – supported in place of patients preference in majority of cases
  - Complications
    - Drain displacement in 1 pt
    - Peritonitis (1 pt), leakage (1 pt)
- Formal studies being planned

Itch

- Severity of pruritis does not correlate with degree of cholestasis, but associated with poor quality of life
- Can be an indication for liver transplantation
- Variable evidence for management:
  - Cholestyramine / Ursodeoxycholic acid
  - Rifampicin / Thalidomide
  - Opioid antagonists: Buprenorphine / Naloxone
  - Gabapentin / Sertraline / Ondansetron

Reddy L, Krajnik M, Zyic Z. Transdermal buprenorphine may be effective in the treatment of pruritus in primary biliary cirrhosis. J Pain Symptom Manage 2007;34(5):455-456

Mayo M et al. Sertraline as a first-line treatment for cholestatic pruritis. Hepatology, 2007:45 (3): 666-674

Daly BM, Shuster S. Antipruritic action of thalidomide. Acta Derm Venereol 2000: 80: 24-25

Tandon P, Rowe BH, Vandermeer B et al. The efficacy and safety of bile acid binding agents, opioid antagonists, or rifampicin in the treatment of cholestasis associated pruritis. Am J Gastro 2007; 102(7):1528-1536

To T. *et al* The Role of Ondansetron in the management of cholestatic or uraemic pruritis. J Pain Symptom Manage. 2012; 44(5): 725 - 730

Grading of hepatic encephalopathy

Grade	*Description*	*Suggested operational criteria*
Zero/ Unimpaired	No encephalopathy currently or history of it	Tested and proved to be normal
Minimal	Psychometric or neuropsychological abnormalities *without* clinical evidence of mental change	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations
Grade I	• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep patterns	Despite orientated in time and space, the patient appears to have some cognitive or behavioural changes in comparison to his/her standard or in the opinion of family or informal caregivers
Grade II	• Lethargy or apathy • Disorientation in time • Obvious personality change • Inappropriate behaviour • Dyspraxia (poor coordination) • Asterixis or "liver flap"	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season or year) ± the other mentioned symptoms
Grade III	• Somnolence or semi-stupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behaviour	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city or place) ± the other mentioned symptoms
Grade IV	• Coma	Does not respond to stimuli

Adapted from EASL Practice Guidelines on Hepatic Encephalopathy http://www.easl.eu/assets/application/files/502226e23f291a50_file.pdf

Hepatic encephalopathy - treatment

- 1st presentation - identify underlying precipitant (bleeding, sepsis, shunting)
- Prevention
  - Education of patient and family
  - Nutrition – avoid low protein, high calorie, regular small meals
  - Non-absorbable disaccharides (lactulose) – alter gut pH and flora composition
    - In practice other laxatives may be used but no evidence
  - Non-absorbable antibiotics (Rifaximin) [1,2]
  - Other antibiotics (neomycin/metronidazole)
  - Enemas
- Terminal agitation - antipsychotics

1. EASL Practice Guidelines (in press). Published online: http://www.easl.eu/assets/application/files/502226e23f291a50_file.pdf. Last accessed 10 Oct 2014
2. Sanyal A et al. *Aliment Pharmacol Ther*. 2011; 34(8): 853 - 861