End stage Organ Failure Management Issues at End of Life

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Symptoms in ESRF

- Fatigue/sedation- consider whether accumulation of drugs contributing e.g. pregabalin
- Delirium
- Nausea and vomiting-
- Cramps/ neuromuscular irritability/myoclonic jerking/restless legs **
- Hiccups
- Seizures-BZD
- Itch **

** symptoms very responsive to low dose pregabalin

eg 25 mg daily or alt days

Nausea/vomiting in ESRF/ other metabolic causes

- Haloperidol generally useful for opioid induced and metabolic causes of nausea- avoid if Parkinson's or Parkinson's plus syndromes.
- Haloperidol dose initially 0.5-1mg BD plus 4/24 PRN- max 5mg in frail, elderly- as not significantly renally cleared, no need to dose adjust in ESRF. ‘O’ dose = s/c dose
- Ondansetron if haloperidol CI’d or ineffective

Drugs to avoid/dose adjust in ESRF

- Avoid morphine, NSAIDS
- Hydromorphone- safe but start low and 4/24 PRN spacing for PRN- preferably convert to fentanyl if background continuous opioid required
- Buprenorphine – safe in mild- mod RF
- Methadone safe but complex dosing
- Oxycodone – probably safe- evidence not well documented (maybe prolonged excretion of metabolites)
- Metoclopramide – if Cr Cl < 40 – halve dose- maximum 15 mg/d. Max dose recommended capped at 30mg/d even if Normal RF
- Gabapentanoids –Cr Cl 30-60, 50 % reduction. ESRF Pregabalin start with 25 mg once daily or even alt days for restless legs, uraemic itch, neuropathic pain

ITCH

- Usual topical management /good emollient care for dry skin
- Consider drug reactions
- Uraemic Itch: Gabapentin 100mg nocte, Pregabalin 25 mg nocte
- Cholestatic Itch: Biliary stenting if possible
- Rifampicin 150mg daily-300mg daily Or Sertraline 50-100mg/d
- UVB- effective x3/week, but often impractical
- Malignancy associated Itch (usually haematological e.g. Hodgkin's: cimetidine 400mg BD Or Dexamethasone 4 mg daily- reduce to minimum effective dose/ stop after 1/52 if not.
- Opioid induced itch(not allergy): trial opioid switch. Ondansetron 4mg TDS
- Non-specific causes: sedating antihistamines nocte. AD's – may only work for 4-6/52 Doxepin 10mg nocte, Mirtazepine 7.5-15mg nocte, Paroxetine 10-20mg nocte, Sertraline 50-100mg/day.

Intractable Hiccups – all causes EOL

1. Baclofen 5mg orally, 3 time daily
OR
2. Gabapentin 100 to 300mg orally, daily initially, increasing as tolerated and according to response. Maximum dose 1200mg daily in divided doses(dose adjust renal failure – start 100mg once daily- max 200mg/d)
OR
3. Clonazepam 0.5mg orally or sublingually, twice daily
OR
3. Haloperidol 0.5 to 1mg orally, daily
OR
3. Metoclopramide 10mg orally, 8-hourly (50% dose reduction in mod-severe RF)
OR
4. Chlorpromazine 10 to 20mg orally, at night

Diabetes at EOL

- In the deteriorating phase of illness (expected survival of weeks), a patient's food intake and weight will often decline, increasing the risk of hypoglycaemia and other adverse effects with antidiabetic drugs, particularly if the patient has kidney or liver impairment.

- For patients with type 2 diabetes, oral antidiabetic drugs and insulin can usually be reduced or stopped at this stage. Tailor treatment according to symptoms, aiming to avoid symptomatic hyperglycaemia while minimising the risk of hypoglycaemia. (aim BSL 10-20 mmol/L- PC TG, UK guidelines recommend 10-15)

- Limit monitoring to when BSL very unstable or symptomatic/ relax dietary restrictions

- For patients with type 1 diabetes, or patients with type 2 diabetes who have been prone to hyperosmolar hyperglycaemia, insulin is usually continued in the deteriorating phase, but treatment targets can be relaxed. A daily dose of long-acting insulin (e.g. insulin glargine) can reduce the risk of severe hyperglycaemia, with little risk of hypoglycaemia. If short-acting insulin is necessary, it should be adjusted according to the patient's oral intake.

DIABETES AT EOL

- When changes to diabetes management are made, it is important to recognise and acknowledge the symbolic importance of their changes to the patient. Many patients have strived to maintain strict glycaemic control for years, and it can be very distressing to be told that it is no longer necessary.

- Discuss that the aims are to maintain the patient's quality of life and to prevent harm.

End-stage Liver Disease and Pharmacokinetics

- In general not necessary to dose adjust even for drugs extensively metabolized in liver unless very impaired
- Portal hypertension/ impact on hepatic perfusion more of an issue

Drugs to avoid/adjust in Severe Hepatic Impairment/ Portal Hypertension

- 'TARGIN'- Slow Release formulation of Oxycodone combined with methylnaltrexone (latter is not cleared via first pass effect as intended , and crosses into systemic circulation, counteracting analgesic effect oxycodone- consensus opinion with colleagues is to avoid , especially with portal hypertension)
- Clonazepam, Midazolam, Morphine, Lorazepam – increased effect

Dyspnoea- Non drug options

Non-pharmacological interventions are the mainstay of dyspnoea management

- Cool air movement, open doors/windows.
- Hand held fan (pilot study very positive, as low cost/ no risk intervention cost of further trials not justified)

- Posture – physios can advise on diaphragmatic breathing techniques and decrease hyperventilation
- Most COPD patients have been taught pursed lip breathing

Dyspnoea (not imminently dying)

- Pacing activity to prevent severe episodes – OT for home modification
- Functional/Psychological Strategies (subacute) to reduce impact of anxiety/depression on perception of breathlessness.
- ACP, reassurance re medication availability and effectiveness
  - Relaxation techniques
- Pulmonary Rehab where possible

Dyspnoea- Non drug options

- The evidence emphasises the importance of a diagnostic workup to consider disease modifying therapies, and concomitant non-pharmacological interventions for managing chronic breathlessness
- However:
- Recent delineation of a chronic breathlessness *syndrome (*disabling breathlessness which persists despite optimal Rx of underlying pathophysiology) underlines the importance of BOTH :
- ***Optimised disease- treatments***
- ***AND***
- ***The need for breathlessness-directed interventions***

(Ref Johnson & Currow BMJ 2020)

Drug Treatment of Dyspnoea

- O_2 if hypoxic
- Opioid ‘o’ or s/c
- +/- benzodiazepine

Opioids for Dyspnoea (ref PC TG)

Opioid naïve intermittent dyspnoea

- Morphine IR 1-2.5mg 1/24 PRN (R/V if x 3 doses and no relief)
- Or S/C 0.5-1mg PRN 1/24

Opioid naïve and continuous dyspnoea

- Morphine 1-2.5mg 4/24 regular
+ 1-2.5mg 1/24 PRN
- Or Morphine 0.5-1mg S/C 4/24
+ 0.5-1mg 1/24 PRN
- Or Morphine MR 5-10mg BD

(Above are TG recommendations - I would start with 10mg Kapanol once daily after a day or so of regular IR)

Plus PRN 1-2.5mg 1/24 PRN (NB**: Use of IR PRN opioid for dyspnoea is contentious)**

- R/V if x 3 doses -> adjust background
- If patient cannot swallow and regular S/C is needed, then a CSCI will be needed

On Opioid already

- Intermittent dyspnoea – use pain B/T dose, OR 1/10-1/6 daily dose
- If continuous dyspnoea and already on background opioid for pain, increase dose by 25-50%**

Nebulised opioids not found to help

Opioids for Dyspnoea

2019 Australian TGA

First in world to extend licence for Kapanol (SR morphine) for treatment of Chronic breathlessness

Opioids for Dyspnoea :

- What's the evidence?

- HOW do they work?
- What are the gaps in our knowledge?

- What are the risks?

Opioids for Dyspnoea- evidence summary

(ref Johnson &Currow BMJ Supportive and PC 2020;10: 287-295)

Box 1 Summary basic science: opioids and breathlessness

- Endogenous opioids modify perception of breathlessness.
- Evidence for a central modulation is the dominant evidence in the literature.
- Opioids reduce the sensation 'urge to breathe' through cortical mechanisms.
- The response to opioids is reduced by impaired affect (anxiety, depression).
- Opioids appear to be able to modulate anticipatory breathlessness as well as the sensation of breathlessness itself.
- There is interindividual breathlessness response to opioids due to varying affective state and pharmacogenetics.

Box 2 Summary effectiveness

- Opioids have moderate level 1a evidence (systematic review and meta-analysis) for effectiveness for breathlessness.
- Most evidence is in people with chronic obstructive pulmonary disease.
- The largest randomised clinical trials use regular, low-dose, sustained release morphine de novo in opioid-naïve participants.
- Opioids are most effective in steady state rather than single-dose studies.
- There is preliminary evidence to support prophylaxis for exertion-induced breathlessness for both morphine and fentanyl but the risk–benefit balance is not known, especially with longer term use.
- Not all disease states may have breathlessness which respond to morphine.
- Not all opioids show reduction in breathlessness.
- There are very few placebo-controlled data to date regarding medium or long-term use. Recent trials are due to report soon.

Opioids for Dyspnoea (Johnson & Currow)

Box 3 Summary clinical studies: dose and safety

- Most of those with morphine-responsive breathlessness respond to doses of ≤30 mg/24 hours orally.
- Seventy per cent of responders do so by 10 mg/24 hours orally.
- Respiratory adverse effects appear to be minimal especially when using regular, sustained release morphine, and clinically relevant respiratory depression limited to single case reports from suboptimally monitored clinical practice.
- Placebo-controlled trials report no excess serious treatment-emergent adverse events in the morphine arm.
- Morphine-related adverse events are generally mild and include constipation, nausea and vomiting, the latter two of which are mostly self-limiting.
- Morphine-related adverse events in steady state are more likely in people with fluctuating renal function, especially if renal function was reduced in the first place.

Opioids for Dyspnoea

- **Non-pharmacological interventions remain the mainstay and should be optimised before using opioids.**
- **As with pain, depression and anxiety have been shown to reduce the beneficial effects of opioid for dyspnoea, and to be similarly associated with difficulties with dose escalation and difficulties reducing dose**
- **There is a good evidence base for use of morphine and fentanyl**
- **Oxycodone has shown no signal of benefit yet**
- **Dyspnoea related to Pulmonary /hypertension did not show benefit, but rather worsening of all symptoms measures with opioid**
- **CCF- 2019 study showed some benefit over placebo in all dyspnoea measures exept av. Breathlessness- closed early due to difficulties with recruitment**
- **As people with chronic lung and heart conditions may live with chronic breathlessness for some years, we should not initiate morphine for breathlessness in those with only mild or moderate symptoms, or in those whose disease modifying and non-pharmacological treatments have not been optimised**

Ref : Johnson & Currow BMJ SPC 2020: 10:287-295

Benzodiazepines and dyspnoea

- Are not first line drug Rx for dyspnoea as may increase morbidity/mortality
- Don’t relieve dyspnoea per se but have a role when anxiety exacerbates dyspnoea
- Try short acting benzodiazepines
- E.g. oxazepam 7.5mg-15mg - Repeat after 1/24 PRN* (TG- I would start at low end)
- OR Lorazepam 0.5mg -1mg and repeat once at 1/24 if no relief.
- Or Midazolam 2.5mg s/c and repeat once at 1/24 if no relief.
- If x 2 doses don’t provide relief, anxiety probably not contributing significantly.

Benzodiazepines and Dyspnoea (cont)

If dyspnoea has responded well to the addition of short-acting benzodiazepine, consider definitive medication/ non-pharmacological Rx for patient's anxiety.

Antidepressants being 1st line drug treatment for severe anxiety when prognosis allows for benefit/possibly weeks to therapeutic effect.

Whilst waiting, or if shorter prognosis, consider longer-acting benzodiazepine in addition to opioid

For example:

- Diazepam 2mg orally BD TDS

OR

- Clonazepam 0.5-1mg sublingual or subcutaneous BD (I would start lower, esp in frail, elderly, cachectic)

If opioid via CSCI – easier to add Midazolam 5-10mg over 24-hours to pump

Acute Severe Dyspnoea in Palliative Care – Management- ALL CAUSES

- Sit up or whichever posture most comfortable
- Reassure will do what it takes to control symptoms
- Staff member to stay with patient

High flow O_2 - may provide relief (may benefit in absence of hypoxia)
- Patient holding mask may alleviate claustrophobia
- Risks of CO_2 retention less relevant
- Direct air flow may be additionally beneficial

CPAP or BiPAP may be considered if in line with GOC

Medications for Acute Severe Dyspnoea

Carefully adjusted doses opioid +/- benzodiazepine to level dyspnoea will minimise risk of respiratory depression.

Opioid dosing in acute severe dyspnoea

- Opioid naïve patient
  - 1) Morphine 2.5-5mg IV 5 minutely PRN - if not controlled by 3rd dose seek specialist support
  - Or Morphine 2.5-5mg s/c 10 minutely PRN –if not controlled by 3rd dose seek specialist support
  - Or Fentanyl 25-50 mg IV 5 minutely PRN
  - Or Fentanyl 25-50mg or s/c 10 minutely PRN
  - OR Fentanyl 25-50mg intranasally – ideally use nasal atomiser

- Intra nasal Fentanyl give 0.3ml of solution into each nostril in turn up to desired dose (greater volumes will be swallowed with poor bioavailability)

Benzodiazepine for Acute Severe Dyspnoea

- Midazolam 1-2mg IV 5-10 minutely PRN
- Or Midazolam 2.5-5mg s/c 30 minutely PRN
- Or Clonazepam 0.5mg s/c or s/L 30 minutely PRN

- If already taking opioids
- Convert their usual PRN dose to IV or s/c equivalent
- IV 5 minutely - not controlled by 3rd dose >>specialist support
- S/C 10 minutely - not controlled by 3rd dose >> specialist support

Acute Severe Dyspnoea cont.

- When symptomatic treatment of dyspnoea has started to settle situation, depending on GOC and possible underlying aetiology relevant investigations might include:
  - Chest X-Ray – pneumonia, effusion, pulmonary oedema, pneumothorax
  - ECG- Acute coronary syndrome
  - Echo cardiogram – pericardial effusion, acute RH strain
  - CT – PE, SVC obstruction, progressive airway obstruction

- Avoid taking ABG – as very uncomfortable in an already very distressed patient
- Usually pulse oximetry and venous blood gas provide sufficient information

End-stage heart failure: Palliative Management

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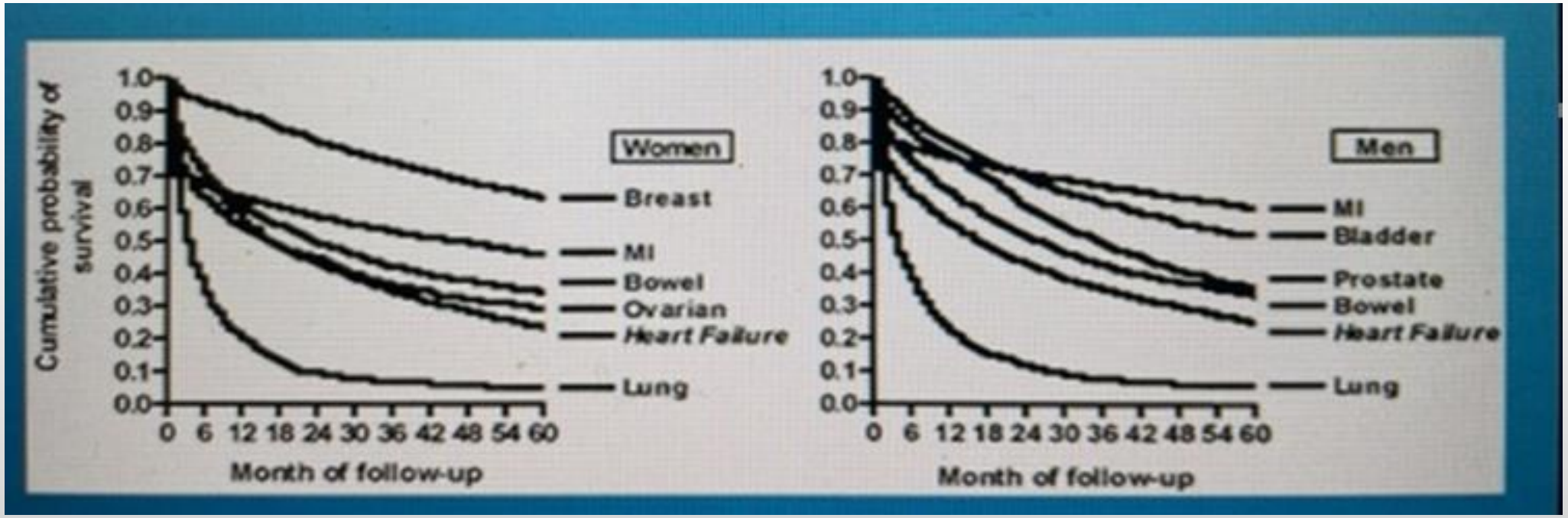
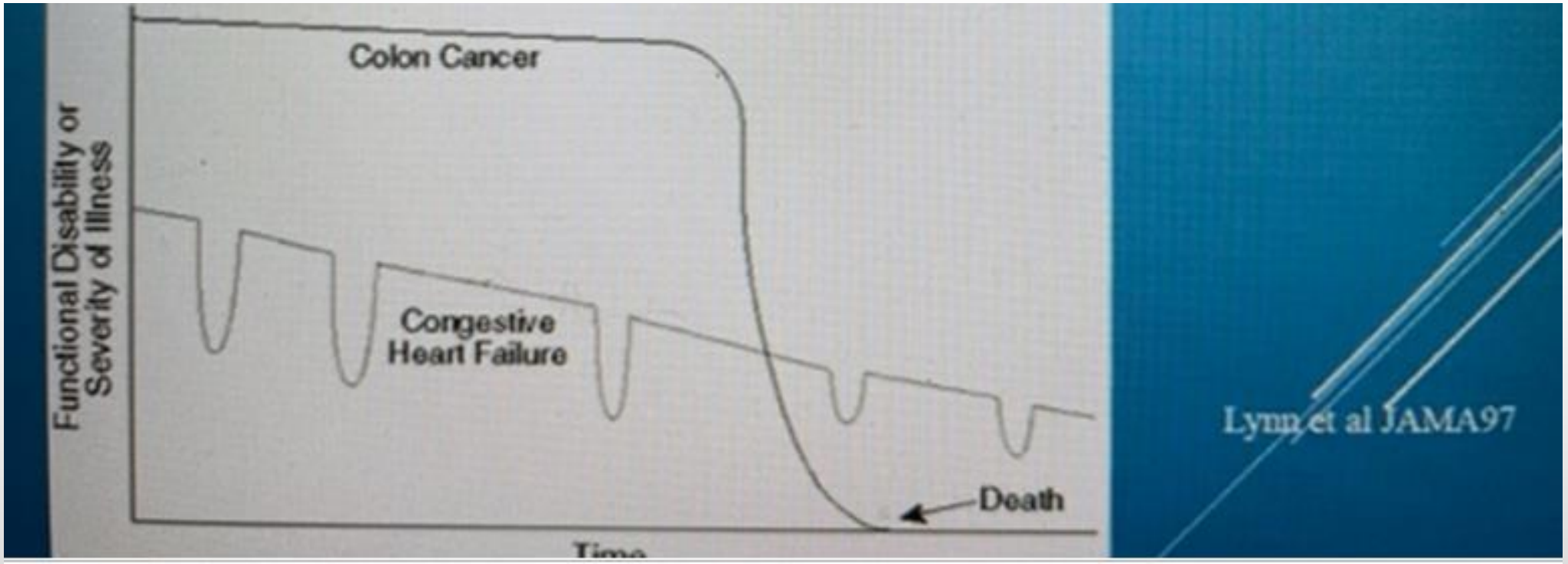
Prognostication CHF:

- Worse survival when cw many cancers
- 38% die within 1 yr Dx
- 50-75% die within 5 yrs
- Median survival 2.1 yr post Dx
- 2-17% pts admitted with CHF die prior to D/C



Prognostication cont.



Prognostication

Strong indicators of a limited life expectancy for a patient with heart failure include:

- Advanced age
- Recurrent hospitalisation for decompensated heart failure and/or a related diagnosis
- New York Heart Association (NYHA) Class IV heart failure symptoms
- Poor kidney function
- Cardiac cachexia
- Low serum sodium concentration
- Refractory hypotension necessitating withdrawal of medical therapy

- A patient with NYHA Class IV heart failure (severely symptomatic at rest) has an estimated 1 year mortality of 30-40%.

End-stage heart failure

The physical and psychological symptom burden in patients with end-stage heart failure is similar to that in patients with advanced cancer. (But traditionally less involvement from PC services)

Dyspnoea

Insomnia

Constipation

Difficulty Ambulating

Pain

Anorexia

Nausea and Vomiting

Depression

Anxiety

Fatigue

Oedema

Ref: TG PC & CVS

Severe oedema

A number of factors, such as immobility and hypo-albuminaemia, can contribute to generalised peripheral and pulmonary oedema. Continuing diuretic therapy is crucial to decrease the pulmonary fluid overload in a patient with end-stage heart failure and to minimise worsening of dyspnoea and cough. Diuretic resistance, which indicates a poor prognosis, becomes an increasing problem with end-stage heart failure.

A patient with severe oedema may not absorb oral frusemide due to oedema in the gastrointestinal tract; intravenous or subcutaneous frusemide can be adjusted against the baseline oral dose until symptoms are controlled

Continue concurrent management of other symptoms of end-stage heart failure and plan for when the patient is unable to swallow.

Pain

Optimise the treatment of ischaemic chest pain, unless it causes unacceptable postural hypotension or other adverse effects.

Not all pain in a patient with end-stage heart failure is due to ischaemic chest pain. Pain may also be due to increasing oedema, comorbid diabetic neuropathy, musculoskeletal pain or metabolic changes due to anorexia and cachexia.

Consider opioids for cardiac-related pain, irrespective of its cause; however, chronic ischaemic chest pain may be less opioid sensitive and require addition of an adjuvant analgesic.
Adjuvants recommended as for visceral pain- gabapentanoids or SNRI

Nausea

- Effective management of nausea in end-stage heart failure is aided by understanding its possible cause (eg cardiovascular drug toxicity, increasing fluid overload including oedema in the gastrointestinal tract, worsening uraemia., constipation)

- Treatment of fluid overload is important, along with concurrent use of antiemetic therapy when appropriate.

- Haloperidol may be the most effective antiemetic for nausea with a metabolic cause.

Other cardiac dysfunction-related symptom

- Uraemic nausea and itch can occur due to progressive kidney impairment – Itch may respond to Gabapentin 100mg nocte or Pregabalin 25mg nocte
  - UVB effective but impracticable
  - Naloxone effective – problematic if needing opioids for pain/dyspnoea
  - Thalidomide effective – rarely used
- Delirium – manage reversible causes when possible
- Constipation- manage actively (TG recommend avoid laxatives with electrolytes added e.g. Macrogol with electrolytes- use formulation without., however in practice cardiac failure specialists report they often use without problems.) Avoid lactulose if low fluid intake)
- Depression – selective serotonin reuptake inhibitors (SSRIs) (in particular sertraline) may be helpful for mild-moderate depression. Although they may potentially affect serum sodium concentration, SSRIs are recommended because they preserve ejection fraction and lack hypotensive or arrhythmogenic effects

Managing implantable cardiac devices

- Many patients with end-stage heart failure have implantable cardiac devices and careful thought should be given to how and when they might be turned off. If turned off too early, there is the risk of an untreated arrhythmia; if too late, the patient might be subjected to inappropriate defibrillation.

- The majority of implantable cardiac devices seen in palliative care patients are non-defibrillating pacing pacemakers or implantable cardioverter defibrillators (ICDs).

- A small group may have implantable ventricular assist devices, designed as mechanical circulatory support.- may be becoming more an ‘end-point’ therapy in Aus as in US

Cardiovascular conditions

Hypertension

In many patients, antihypertensive drugs can be stopped in the last few weeks of life because the expected long-term benefits are no longer relevant, or because the patient's blood pressure has dropped as a result of weight loss.

Previously tolerated antihypertensive doses can cause hypotensive symptoms (e.g. postural hypotension, fatigue).

Aim to withdraw or reduce the dose of antihypertensive drugs before the patient develops symptomatic postural hypotension, with the risk of falls.

Restrictions on dietary salt intake can be relaxed in the last months of life.

Dyslipidaemia:

The effects of lipid-modifying drugs are measured over a number of months, while the cardiovascular benefits are measured over years. In patients who are expected to live for months, lipid-modifying drugs can generally be stopped safely.

Impact of deprescribing on a patient and their family

Some patients are pleased or relieved to be able to stop taking their long-term medications; however, for other patients the idea of stopping these medications can be very distressing. They may fear losing control, feel that previous treatment has been futile, or realise that the suggestion to stop their medications signifies progression of disease or imminent death.

It is important to discuss any proposed changes to medications with the patient and their family, explaining the reason and how the changes will be made*. Ask them about their preferences and any concerns they have in relation to stopping medications. If a patient is reluctant to stop their medications*, try to address their concerns, and negotiate changes over time if appropriate. Sometimes it is helpful to 'give permission' to a patient to stop their medications.

When a patient enters the terminal phase, it is important to explain the changes to their medications to the family and carers, and reassure them that the patient's symptoms will continue to be managed.

Withdrawing or withholding treatment in palliative care

Key steps for deprescribing in palliative care

- Consider the patient's life expectancy and expected disease trajectory
- Determine the patient's goals of care and preferences
- Review the current medications; consider benefits and adverse effects, burden to the patient, and level of adherence. For each medication, ask 'Why should this medication be continued?'
- Discuss the options for medication withdrawal with the patient and family; consider the psychological impact
- Prioritise medications for discontinuation and develop a plan for withdrawal. Ideally, make one change at a time
- Consider whether slow withdrawal is required (e.g. some cardiovascular and psychiatric drugs, long-termed corticosteroids)
- Document the process
- Monitor the patient for withdrawal effects or return of symptoms

Cardiac Failure Nurse Practitioners available to help optimise MX at home of end stage CCF and to help negotiate de-activation of implanted defibrillators

THE UNIVERSITY of EDINBURGH

Supportive and Palliative Care Indicators Tool (SPICT™)

CARESEARCH
palliative care knowledge network

The SPICT™ is used to help identify people whose health is deteriorating. Assess them for unmet supportive and palliative care needs. Plan care.

Look for any general indicators of poor or deteriorating health.

- Unplanned hospital admission(s). ☐
- Performance status is poor or deteriorating, with limited reversibility. (eg. The person stays in bed or in a chair for more than half the day.) ☐
- Depends on others for care due to increasing physical and/or mental health problems. ☐
- The person's carer needs more help and support.
- Progressive weight loss; remains underweight; low muscle mass. ☐
- Persistent symptoms despite optimal treatment of underlying condition(s). ☐
- The person (or family) asks for palliative care; chooses to reduce, stop or not have treatment; or wishes to focus on quality of life. ☐

Look for clinical indicators of one or multiple life-limiting conditions.

Cancer

- Functional ability deteriorating due to progressive cancer. ☐
- Too frail for cancer treatment or treatment is for symptom control. ☐

Dementia/ frailty

- Unable to dress, walk or eat without help. ☐
- Eating and drinking less; difficulty with swallowing. ☐
- Urinary and faecal incontinence ☐
- Not able to communicate by speaking; little social interaction. ☐
- Frequent falls; fractured femur. ☐
- Recurrent febrile episodes or infections; aspiration pneumonia. ☐

Neurological disease

- Progressive deterioration in physical and/or cognitive function despite optimal therapy. ☐
- Speech problems with increasing difficulty communicating and/or progressive difficulty with swallowing. ☐
- Recurrent aspiration pneumonia; breathless or respiratory failure. ☐
- Persistent paralysis after stroke with significant loss of function and ongoing disability. ☐

Heart/ vascular disease

- Heart failure or extensive, untreatable coronary artery disease; with breathlessness or chest pain at rest or on minimal effort. ☐
- Severe, inoperable peripheral vascular disease. ☐

Respiratory disease

- Severe, chronic lung disease; with breathlessness at rest or on minimal effort between exacerbations. ☐
- Persistent hypoxia needing long term oxygen therapy. ☐
- Has needed ventilation for respiratory failure or ventilation is contraindicated. ☐

Kidney disease

- Stage 4 or 5 chronic kidney disease (eGFR < 30ml/min) with deteriorating health. ☐
- Kidney failure complicating other life limiting conditions or treatments. ☐
- Stopping or not starting dialysis. ☐

Liver disease

- Cirrhosis with one or more complications in the past year: ☐
  - diuretic resistant ascites
  - hepatic encephalopathy
  - hepatorenal syndrome
  - bacterial peritonitis
  - recurrent variceal bleeds
- Liver transplant is not possible. ☐

Other conditions

- Deteriorating and at risk of dying with other conditions or complications that are not reversible; any treatment available will have a poor outcome. ☐

Review current care and care planning.

- Review current treatment and medication to ensure the person receives optimal care; minimise polypharmacy. ☐
- Consider referral for specialist assessment if symptoms or problems are complex and difficult to manage. ☐
- Agree a current and future care plan with the person and their family. Support family carers. ☐
- Plan ahead early if loss of decision-making capacity is likely. ☐
- Record, communicate and coordinate the care plan. ☐

For more on palliative care visit www.caresearch.com.au

Please register on the SPICT website (www.spict.org.uk) for information and updates.

SPICT™, April 2019