Management of malignant ascites in a Palliative Care/Oncology setting

This CPG was devised from a targeted literature review, rather than a more formal rigorous and very time consuming 'systematic literature review process' as defined by the 'Cochrane collaborative process'. The Cochrane database has been searched and referred to frequently for up to date information.[1] Recent articles were particularly looked for (since 1996), with an emphasis on finding and reading systematic literature reviews identified via Medline, CINAHL, Cochrane and the Journal of Palliative Medicine. The CPG derived has been peer reviewed locally for implementation and has been trialled in our hospital unit over the last six months and refined.

Major references used were:

- Smith E et al (2003) *The current and future management of malignant ascites* ***Clinical Oncology (2003) 15:59-72***
- Runyon B 1998 *Management of adult patients with ascites caused by cirrhosis* ***AASLD Practice Guidelines 1998***
- Stephenson J (2002) *The development of clinical guidelines on paracentesis for ascites related to malignancy* ***Palliative Medicine 2002; 16:213-218***
- Gines P et al (2004) *Management of Cirrhosis & Ascites* ***NEJM 2004; 350: 1646-54***
- Aslam N et al (2001) *Malignant Ascites* ***Arc Int Med 2001; 161: 2733-37***
- Preston N, Seers K, MacArthur V. (2003) *Interventions for the palliation of malignant ascites.* ***The Cochrane Database of Sytematic Reviews 2003, Issue 4. Art. No.: CD004528. DOI: 10.1002/14651858.CD004528***

The British Thoracic Society has provided a clear system for grading evidence and derived recommendations. This was published in *Thorax 2003; 58(Suppl II)* and summary tables, from the introduction, appear below:

Grading the evidence	Grading the recommendations
Ia Meta-analysis of randomised trials Ib Randomised controlled trial IIa Well designed controlled study without randomisation IIb Another type of well designed quasi-experimental study III Well designed non-experimental descriptive Studies such as comparative studies, Correlation studies & case control studies IV Opinion of expert committee reports or opinions and/or clinical experience of respected authorities	**A** (Supported by paper(s) of levels Ia or Ib) Requires at least one randomised trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation **B** (Supported by paper(s) of levels IIa, IIb or III) Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation (or poor/inadequate randomised trials not supported by sufficient other literature to achieve grade A) **C** (supported by level IV evidence) Requires evidence from expert committee reports or opinions &/or clinical experience of respected authorities.

Of course comparing trials is not at all easy as they usually have different endpoints and even if they use the same vocabulary they often mean different things:

- e.g. defining "complete response" vs "partial response" needs a consistent time endpoint and a non-intervention control group
- e.g. newer treatments such as intraperitoneal Vascular Endothelial Growth Factor (VEGF) & Matrix Metallo-Proteinase (MMP) inhibitors are often given in combination with systemic chemotherapy – therefore randomised control trials (RCT's) need to be done to compare chemotherapy alone with combination chemotherapy & novel intraperitoneal/intrapleural interventions.

Management of all malignant effusions in a palliative care setting should only be to maximise Quality of Life and/or at the patient's request.

Etiology:

80% Cirrhosis of Liver
10% Malignant

- 80% Ovarian, Breast, Colon, gastric & pancreatic
- 20% CUP

3% Cardiac
2% T.B.
1% Pancreatic
4% Other

Pathophysiology:

Much is still derived from the extensive literature on cirrhotic ascites, although there is now a growing literature looking specifically at malignant ascites:

(from Cochrane) …"Ascites is the accumulation of protein rich fluid in the peritoneal cavity. It occurs in cirrhosis of the liver, heart failure, tuberculosis and malignancy. Cancers most commonly associated with the development of ascites are ovarian, breast, and gastrointestinal. Ascites is more likely to occur as the disease advances. There are two principle approaches to managing malignant ascites. The first attempts to treat the underlying cause of the ascites, namely the cancer that led to the development of the ascites. The main treatments are chemotherapies, biological therapies and novel therapies such as matrix metalloproteinase inhibitors, radiolabelled mono-clonal antibodies and radio colloids. The second approach is palliative and relies upon reducing the volume of fluid through a variety of approaches; draining the fluid either for temporary relief or leaving the drainage catheter insitu for intermittent drainage until death, diuretic therapy, peritoneovenous shunting which is where a tube runs from the peritoneal cavity to the general circulation and drains fluid along it due to changes in pressure during respiration, breathing exercises to encourage the flow of lymphatic fluid throughout the lymphatic system, and steroid therapy."[ii]

Mechanisms:

Two key mechanisms are:

- **A. Overproduction**: (*High Output Failure*) – which relates to mechanisms that overwhelm the lymphatic removal and circulation of the normal amount of ascitic fluid produced by the movement through the capillaries of the peritoneal lining. In a healthy person there is normally about 50mls of ascitic fluid which drains away via the subdiaphragmatic lymphatics.[iii] This mostly relates to cirrhotic ascites with effects on 'Portal venous hypertension' and the 'Sodium/Water retention of the secondary effects on the Renin-Angiotensin mechanisms'.[iv] To some extent this may also be relevant to the effects of various trapped malignancy related proteins that make peritoneal capillaries more 'leaky' (such as Matrix metalloproteinases (MMP), Vascular endothelial growth factor (VEGF) (50,000 times more potent than histamine), Tumour Necrosis Factor (TNF) & various Interleukins (ILK) etc.)
- **B. Excess fluid accumulation**: (*Low Output Failure)* related to lymphatic obstruction by tumour, mainly of the diaphragmatic lymphatic vessels.[v]

  Specific major proteins: (that are trapped and stimulate capillary leakage)

  1. **VEGF: (stimulates angiogenesis)**
     - **50,000x more potent than histamine in increasing vascular permeability**
     - **many malignant cells overexpress VEGF**
     - **high levels have been found in malignant ascites/effusions & in serum of 49-96% of patients with malignant ascites**
     - **acts directly on endothelial cells, resulting in macromolecules leaking into the peritoneum, *functionally* impairing drainage**
     - **anti VEGF AB in animal studies decrease ascites**
  2. **MMP: (family of zinc containing enzymes)**
     - **degrade the extracellular matrix**
     - **important in tumour invasion & metastases by allowing breakdown of basement membrane**
     - **Important in tumour angiogenesis**
     - **overexpressed in cancers espec: colorectal, gastric & breast)**
  3. **Others: TNF, ILKs (6,10,2, Alpha & Beta)**

Practices identified as specific to our unit in initial information gathering phase:

Physician Survey in Ottawa (Canada) (2001)
91% - Repeated Paracentesis
61% - Trial use of diuretics

Mater Brisbane (2004)
98% - Repeated Paracentesis
2% - Trial use of diuretics

Use of Diuretics in Malignant Ascites

- No randomised control trials
- No consensus on effectiveness
- Serum to Ascites Albumin Gradient (SAAG) – seems a relevant measure to predict effectiveness of diuretic use, although not exclusive
- Phase II trial data suggest diuretics effective in 33% of patients with malignant ascites
- Doses used generally are:
  + Spironolactone 100 – 400 mg
  +/- Frusemide 40 – 160 mg (depending on K+)
  (N.B.doses are often too low or far too short a trial (<4 weeks) & problems with nephrotoxicity of diuretics and ChemoRx in an environment where renal obstruction due to malignancy is fairly frequent)

Paracentesis Notes: 1

- Indications for:
  + Nausea & "squashed stomach syndrome"
  + Abdo pain from distension
  + Dyspnoea or orthopnoea
- Efficacy >90%
- Risks:
  + Infection + Hypovolaemia
  + Bowel perforation + Hypoproteinaemia
  + Drainage nodules of cancer

Paracentesis Notes: 2

Equipment used & Costs:

- Cheapest: 16G or 18G Cannula, connector, tubing & sterile 2 litre urine drainage bag ~$15 (greater rate blockage, ?perforation)
- Medium: Thoracentesis/Paracentesis Kit ~$30 (<risk of bowel perf., rigid tube can be displaced more easily, more uncomfortable, greater leak risk around tube)
- Bonanno S.P. Catheter ~$80 (less risk of ejection or blockage, more comfortable for prolonged drainage times)
- Safe-T-Centesis Kit – with pigtail catheter ~$114

Paracentesis Notes: 3

- No consensus on fluid withdrawal speed (1litre with clamping over 1-2 hours to 4-5 litres in 1-2 hours) or amount to be drained in total
- No consensus on replacement of losses to decrease chances of changes in vascular volume: Some use 5% Dextrose, others use Albumin (8g/Litre ascites drained; 20% Alb. 20g = 100mls, or 4% Alb. 20g = 500mls per 2.5L ascites drained), most only replace volume if necessary.
- Evidence that Albumin replacement induces increased turnover rate and decreases intrinsic production, hence only short term benefit (no difference from using5%D)

Paracentesis Notes: 4

Permanent Drains (risk of blockage ~30%, mean duration 25 days)

- Advantages:

+ Decreased hospital & OPD Stays
+ Decrease risk of Ca dissemination, blockage & Coagulopathy assoc. with PNV shunts

- Risks

+ Increased risk of infection (peritonitis 35% in some trials)
+ Increased risk of hypovolaemia (~5%)
+ Increased protein loss vs PNV Shunts

- Consider in:

+ Those who need repeated paracenteses
+ When PNV Shunt contraindicated (e.g. liver failure & coagulopathy, severe electrolyte disturbance following paracentesis)

Paracentesis Notes: 5

Peritoneovenous shunts (in pateints who may last >6/12 – no survival & little QOL advantage over repeated paracenteses) (Le Veen or Denver)

- Advantages

+ Allow continuous re-infusion of ascites
+ Avoid repeated paracenteses
+ Avoid massive protein loss (serum albumin remains preserved or even improves)

- Complications

+ Shunt occlusion (~3%) (26 days mean if positive ascites ca. cytology, 140 days mean if neg. ascites ca. cytology)
+ Increased infection & loculation of ascites risk
+ Increased risk of DIC (usually subclinical, prob. in 2%)
+ Tumour dissemination risk (autopsy rate is 5-7%, but often not cause of death)
+ Increased risk of pulmonary oedema

Paracentesis Notes: 6

Intraperitoneal measures:

- **Chemotherapy**

(e.g. Cisplatin or Bleomycin for ovarian Ca or Carcinomatosis peritoneii)
+ Overall control of ascites ~ 47%
+ Usefulness where systemic chemo has lost its effect is unclear.
(N.B. Effects of intraperitoneal chemo approx.= efficacy of diuretics, ? Additional benefits if combined, ?increased nephrotoxicity if combined)

- **Radio-isotopes:**

+ Colloidal radio-active gold
+ Radio-active phosphate

(response rate is ~50% overall, best rate is ~85% with ovarian Ca.)

Paracentesis Notes: 7

What's New :

+ Anti-VEGF: (mice experiments, inhibiting tyrosine kinase activity of VEGF receptors)
+ PTK 787 – tyrosine kinase inhibitor, that decreases TK activity of VEGF receptors after VEGF binding
+ Monoclonal antibody (DC101) against VEGF receptor Flk-1
+ SU 5416 - ?mechanism
+ Avastin – rhuMAB VEGF anti VEGF drug trialled in NSC Lung Ca. ? Use in malig. ascites
+ Anti MMP's (human trials) e.g. Batimast

(both VEGF & MMP important in malignant pleural effusions as well)

+ Immunotherapy

(stimulate immune system to respond and control ascites)

e.g. Interferon: (s.e. fevers, pain etc.)
e.g. TNF – ?weekly dosing decreases ascites **vs** ?daily dosing increases ascites
e.g. Corynebacterium parvum – coating peritoneal cancer cells with fibrin, therefore hinder exudation)
e.g. OK 432 – challenge with a non-active infectious agent to help activate macrophages and 'killer T cells', intraperitoneal infusions weekly for 6 weeks, more effective in cell +ve ascites
e.g. Radio-immunotherapy I131 labelled monoclonal antibodies that bind and decrease exudate formation

+ Other:

e.g. Octreotide (somatostatin analogue)
200-600 mcg/24 hours used to decrease secretions in Palliative care espec. in bowel obstructions, intractable diarrhoea, fistulae etc., (as it increases electrolyte & H2O re-absorption) (1x study of 99 patients: 2/3 patients had a marked reduction of ascites and needed no further treatment – Dr. Will Cairns in Townsville)

Unit specific suggested Guidelines for Managing Malignant Ascites:
(cleared with Gastroenterology, Oncology, Radiology & ID teams)

- **Common indications for Palliative Drainage:(up to 90% relief for symptoms below)**
  Nausea & "squashed stomach syndrome" with early satiation, abdominal pain from distension, dyspnoea or orthopnoea **(Level C)**
- **Ascitic fluid analysis: (Level C)**
  + Cell count & differential (if PMN >$250x10^6$ or >50% total then suggests infection)
  + Serum Ascites Albumin Gradient (SAAG) (serum albumin conc. – ascites albumin conc.), if >11 increased chance of responding to diuretics, and more likely to need fluid replacement on drainage (with 5% dextrose)
  + Culture fluid especially if abdo. tenderness or unexplained fever
- **Ultrasound Investigation & "marking the spot" with an 'X':** only in cases of diagnostic uncertainty (e.g. if dilated bowel loops or if suspect loculated ascites, or there is a decreased area of flank dullness to percussion) **(Level C)**
- **Paracentesis equipment:** use 18G -16G cannula, connector and tubing and drainage bag, 'fix in' using 'inverted cup' for comfort & stability **($15)**; use 'paracentesis kits' without "pig-tail' **($40)** when unsure of safety or with "pig-tail" **($116)** if want prolonged drainage (>3-4 hours), or patient is recurrently coughing, vomiting or cannot stay still **(Level C)**
- **Risk of haemorrhage** – proceed with great caution if PT or APTT >2x normal or there is moderate to severe renal failure or platelets are <50,000 and carefully consider need for paracentesis also consider use of FFP **(Level C)**
- **Procedure:** sterile technique, op-site over skin site after washing, fenestrated sheet, local anaesthetic, **drain up to 5 litres ascites (Level B)** without automatic volume replacement, if symptoms of hypovolaemia then slowly replace with 5% dextrose solution, do not leave drain in >4 hours unless "pig-tail" that can be sealed with overlying op-site dressing **(Level C)**
- **Intraperitoneal measures:** if cancer is responsive to chemotherapy then use this systemically, as intraperitoneal measures of chemotherapeutic agents as well as others such as anti-VEGF or MMP compounds and other novel agents such as Octreotide are not proven treatments (if these are used they should form part of a multi-centre randomised trial **(Level C)**
- **Use of antibiotics:** if PMN >$250x10^6$/L or unexplained fever >38^0C +/- abdo tenderness then empirically give Cefotaxime 2g TDS (to cover E.Coli, Klebsiella Pn, Pneumococcus & await results of ascitic fluid culture. If culture +ve then need norfloxacin for 2 weeks once afebrile for 48 hours. **(Level C)**
- **Use of diuretics – effective in markedly decreasing re-accumulation rate in ~30% of patients with malignant ascites (Level B):** if SAAG >11 or for a trial for 4 weeks use Spironolactone and monitor K^+, Na^+ , Urea & Creatinine twice weekly for 4 weeks, if K^+ increases add in Frusemide in the ratio of Spiro: Frusemide of 100:40 mg, start with 50-100 mg Spiro., & do weekly weights during trial 4 weeks.**(Level C)**

N.B. There is a need to design audit sheets from these guidelines on malignant effusions to monitor: quality, adherence, variations & reasons, successes or failures, complications & patient satisfaction)

A suggested example of an audit sheet:

- Name/Age etc./Primary Ca/Known Mets
- Success of Paracentesis in relieving symptoms (good, partial, none)
- Equipment used
- Infected fluid? Ascites Cell Count & Diff
- SAAG (serum to ascites albumin conc. gradient)
- Volume drained and time taken
- Volume replacement? (with 5%D, Alb. How much and indication criteria used)
- Use of Diuretic
  - + Dose of Spironolactone/Frusemide
  - + Twice weekly electrolytes, urea & creat.
  - + Weekly weights
  - + Length of time to recurrence needing paracentesis
- Albumin – measure serum albumin weekly during trial time (e.g. 4-6 weeks)
- FBC + Coags (PT, APTT, INR)
- Complications:
  - + Perforation – bowel causing peritonitis
  - + Post drain infections (local & of ascitic fluid)
  - + Leaking around drain
  - + Haematoma of site
  - + Patient rating of procedure (Pain/discomfort, Relief of symptoms, Attitude of staff etc.)
  - + Other

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[i] Preston N, Seers K, MacArthur V. *Interventions for the palliation of malignant ascites.* ***The Cochrane Database of Sytematic Reviews 2003, Issue 4. Art. No.: CD004528. DOI: 10.1002/14651858.CD004528***

[ii] Preston N, Seers K, MacArthur V. *Interventions for the palliation of malignant ascites.* ***The Cochrane Database of Sytematic Reviews 2003, Issue 4. Art. No.: CD004528. DOI: 10.1002/14651858.CD004528***

[iii] Hirabayashi K, Graham J (1970) *Genesis of ascites in ovarian cancer* ***Am. J of Obs & Gynec. 1970; 203(6):644-51***

[iv] Runyon B 1998 Management of adult patients with ascites caused by cirrhosis **AASLD Practice Guidelines 1998**

[v] Feldman G, et al. (1972) *The role of lymphatic obstruction in the formation of ascites in a murine ovarian cancer* ***Cancer Research 1972; 32(8): 1663-6***