

GUIDELINES ON UROLOGICAL PAIN MANAGEMENT & PALLIATIVE CARE

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Hierarchy of general principles of cancer pain management

1. Individualised treatment for each patient.
2. Causal therapy to be preferred over symptomatic therapy.
3. Local therapy to be preferred over systemic therapy.
4. Systemic therapy with increasing invasiveness: World Health Organization (WHO) ladder.
5. Compliance with palliative guidelines.
6. Both psychological counselling and physical therapy from the very beginning.

The World Health Organization's 'analgesic ladder'

- **Step 1: non-opioid analgesic** Patients with mild to moderate cancer-related pain should be treated with a non-opioid analgesic.
- **Step 2: non-opioid analgesic + weak opioid** Patients who present with moderate to severe pain or who fail to achieve adequate relief after a trial of a non-opioid analgesia should be treated with a weak opioid (e.g. codeine or tramadol), typically by using a combination product containing a non-opioid (e.g. aspirin or paracetamol) and an opioid (e.g. codeine, tramadol or propoxyphene).
- **Step 3: non-opioid analgesic + strong opioid** Patients who present with severe pain or who fail to achieve adequate relief with step 2 drugs, should receive a strong opioid (e.g. morphine, fentanyl, oxycodone, methadon, buprenorphine,

or hydromorphone).

Treatment of neuropathic pain

Drug	Dosage	Frequency (maximum)
Amitriptyline (nortriptyline)	25-75 mg	Once per day
Gabapentin	600-1200 mg	Three times daily
Pregabalin	75-300 mg	Twice daily
Tramadol	50-100 mg	Four times daily

Recommendations	LE	GR
Offer amitriptyline and nortriptyline as a first line treatment for neuropathic pain, with nortriptyline having fewer side effects.	1b	A
TCAs must be used cautiously in patients with a history of cardiovascular disorders, glaucoma, and urine retention.	1b	A
Duloxetine is the first-line treatment for neuropathic pain due to diabetic polyneuropathy.	2a	A
Duloxetine may be tried as an analgesic in other neuropathic pain syndromes.	3	C

GR = grade of recommendation.

Pain management in urological cancers

Efficacy of the therapeutic options in pain relief (expert opinion)

Origin of pain/ therapeutic options	RCC	TCC	PCa	Penile cancer	Adrenergic cancer	Testicular cancer
Bone metastases						
Surgery	+++	?	+	?	?	+
Radiation	++	++	+++	!	!	!
Radionuclide	+	?	+++	?	++	-
Chemotherapy	-	?	+	?	-	
Immunotherapy	-	-	-	?	?	?
Hormone therapy	-	-	++	-	-	-
Analgesics	+++	+++	+++	+++	+++	+++
Soft tissue infiltration						
Surgery	+++	+++	-	?	?	+
Radiation	++	!	++	!	!	!
Chemotherapy	+	++	+	?	++	+++
Immunotherapy	+	-	-	?	?	?
Hormone therapy	-	-	++	-	-	-
Analgesics	+++	+++	+++	+++	+++	+++
Nerve compression/nerve infiltration						
Surgery	+++	+++	++	?	?	++
Radiation	+	!	++	!	!	!
Chemotherapy	+	++	+	?	?	+++
Immunotherapy	+	-	-	?	?	?
Hormone therapy	-	-	++	-	-	-
Analgesics	+++	+++	+++	+++	+++	+++

RCC = renal cell carcinoma; TCC = transitional cell carcinoma;
PCa = prostate cancer;

? = no conclusive data on pain control; - = no pain control; + = low pain control;

++ = moderate pain control; +++ = good pain control.

! Although studies are lacking, patients presenting with bone

metastases or soft tissue metastases should not be refused for radiotherapy as an antalgic effect can be expected.

ANTICANCER TREATMENT		
Recommendation	LE	GR
Hormonal therapy (orchiectomy, LHRH analogues, diethylstilboestrol equivalent)	1a	A
Total androgen blockade: flare prevention, second-line	2b	B
Intermittent androgen suppression experimental	3	B
Monotherapy with anti-androgen is an option	2	B
First-line treatment controls disease for 12-18 months, second-line individualised	1b	A
Supportive care		
Low-dose glucocorticoids	1b	A
Chemotherapy		
Mitoxantrone plus prednisolone	1b	B
Estramustine + vinblastine or etoposide or paclitaxel	2b	B
Docetaxel	1b	A

PAIN MANAGEMENT		
Recommendation	LE	GR
Pain assessment (localisation, type, severity, overall distress)		B
Pain due to painful or unstable bony metastases (single lesions)		
External beam irradiation	1b	A
Pain due to painful bony metastases (widespread)		
Radioisotopes (89Sr or 153Sm-EDTMP)	2	B

Pain due to painful metastases (many spots)		
Bisphosphonates	1b	A
Denosumab	1b	A
Systemic pain management		
WHO analgesic ladder step 1: NSAID or paracetamol	1a	A
Opioid administration		
Dose titration	2	B
Access to breakthrough analgesia	1b	A
Tricyclic antidepressant and/or anticonvulsant in case of neuropathic pain	1a	A

Criteria for selecting patients for primary therapy for spinal cord compression

Absolute criteria	Surgery	Radiotherapy
Operability	Medically operable	Medically inoperable
Duration of paraplegia	< 48 hours	≥ 48 hours
Life expectancy	> 3 months	< 3 months
Radiosensitivity		Highly sensitive
Relative criteria		
Diagnosis of primary tumour	Unknown	Known
Bone fragments with compression	Present	Absent
Number of foci of compression	1 focus	> 1 foci

Pain management in transitional cell carcinoma patients

Recommendations	LE	GR
In locally advanced bladder cancer, palliative cystectomy or exenteration might be an option for symptom relief	3	B
Use radiotherapy to reduce pain and symptoms of locally advanced bladder cancer	1a	B
Use radiotherapy to reduce pain due to bone metastases	1b	A

Specific pain treatment after different urological operations

Recommendations	LE	GR
Analgesics should be given on demand during and after ESWL because not all patients need pain relief.	3	B
Premedication with NSAIDs or midazolam often decreases the need for opioids during the procedure.	2b	B
Intravenous opioids and sedation can be used in combination during ESWL; dosage is limited by respiratory depression.	3	C
Post-ESWL, analgesics with a spasmolytic effect are preferable.	3	C

NSAID = nonsteroidal anti-inflammatory drug.

Transurethral procedures

Recommendations	LE	GR
Post-operative analgesics with a spasmolytic effect or mild opioids are preferable.	3	C
Antimuscarinic drugs could be helpful in reducing discomfort resulting from the indwelling catheter.	3	B
Antimuscarinic drugs may reduce the need for opioids.	3	B

Laparoscopic procedures

Recommendations	LE	GR
Low intra-abdominal pressure and good desufflation at the end of the procedure reduces postoperative pain.	1b	A
NSAIDs are often sufficient for postoperative pain control.	2a	B
NSAIDs decrease the need for opioids.	1b	B

NSAID = non-steroidal anti-inflammatory drug.

Open surgery

Recommendations	LE	GR
For postoperative pain control, multimodal analgesia with a combination of NSAIDs or paracetamol plus local anaesthetics should be used.	3	B
If possible, avoid opioids for outpatients.	3	C

Transvaginal surgery

Recommendations	LE	GR
NSAIDs are often sufficiently effective after minor or moderate surgery.	2a	B
NSAIDs decrease the need for opioids.	1b	B

Transperitoneal laparotomy

Recommendations	LE	GR
The most effective method for systemic administration of opioids is PCA, which improves patient satisfaction and decreases the risk of respiratory complications.	1b	A
Epidural analgesia, especially PCEA, provides superior postoperative analgesia, reducing complications and improving patient satisfaction, and is preferable to systemic techniques.	1b	A

PCA = patient-controlled analgesia; PCEA – patient-controlled epidural analgesia

Retroperitoneal approach - flank incision - thoracoabdominal approach

Recommendations	LE	GR
Epidural analgesia, especially PCEA, provides superior postoperative analgesia, reducing complications and improving patient satisfaction and is therefore preferable to systemic techniques (see Sections 5.3.5.2 and 5.3.5.3).	1b	A

PCEA – patient-controlled epidural analgesia

Dosage and method of delivery of some important analgesics

Dosage and delivery of NSAIDs		
Drug	Daily dose	Route of administration
Conventional NSAIDs (non-selective COX inhibitors)		
Ketorolac	10-30 mg four times daily	Orally or iv
Ibuprofen	400 mg three times daily	Orally
Ketoprofen	50 mg four times daily	Orally or iv
Diclofenac	75 mg twice daily	Orally or iv
	50 mg three times daily	Orally or iv
	100 mg twice daily	Rectally
COX-2 selective inhibitors		
Meloxicam	15 mg once per day	Orally
Lornoxicam	4-8 mg twice daily	Orally or iv
Celecoxib	200 mg once per day	Orally
Parecoxib	40 mg once or twice daily	iv form only
Etoricoxib	90-120 mg once daily	Orally

Dosage and delivery of paracetamol, metamizole and its combinations with opioids

Drug	Method of administration	Single dose (mg)	Maximal dose (mg/day)
Paracetamol	Orally	500-1000	4000 (50 mg/kg)
Paracetamol	iv	1000	4000 (50 mg/kg)
Metamizole	Orally	500-1000	4000
Metamizole	iv	1000-2500	5000

Paracetamol	Opioid	Times per day	Route of administration
Paracetamol 1 g	Codeine 60 mg	Four	Orally or rectally
Paracetamol 600-650 mg	Codeine 60 mg	Four	Orally or rectally
Paracetamol 500 mg	Codeine 30 mg	Four	Orally or rectally
Paracetamol 300 mg	Codeine 30 mg	Four	Orally or rectally
Paracetamol 650 mg	Dextropropoxyphene 65 mg	Four	Orally
Paracetamol 600-650 mg	Tramadol 75-100 mg	Four	Orally
Paracetamol 325 mg	Oxycodone 5 mg	Four	Orally

Dose and delivery of opioids			
Drug	Method of administration	Common single dose (mg)	Maximal dose (mg)
Tramadol	Orally	50	400-600
Tramadol	iv	50-100	400-600
Dihydrocodeine	Orally	60-120	240
Piritramid	sc/im	15-30	120
Pethidine	Orally	25-150	500
Pethidine	Rectally	100	500
Pethidine	sc/im	25-150	500
Pethidine	iv	25-100	500
Morphine*	Orally	Starting with 10	No maximal dose
Morphine*	Rectally	Starting with 10	No maximal dose
Morphine*	sc/im	Starting with 5	No maximal dose
Morphine*	iv	Starting with 2	No maximal dose
Morphine*	iv (PCA)	0.5-2.5 mg bolus	
10-15 min lockout	No maximal dose		

**Strong opioids have no real upper dose limit (except buprenorphine). The dose must be titrated in correlation with pain relief and depending on the individual strength of unwanted effects such as respiratory depression.*

**A simple way of calculating the daily dose of morphine for adults (20-75 years) is: 100 - patient's age = morphine per day in mg.*

Common equi-analgesic doses for parenteral and oral administration of opioids*

Drug	Parenteral (mg)	Oral (mg)
Morphine	10	30
Fentanyl	0.1	-
Pethidine	75	300
Oxycodone	15	20-30
Dextropropoxyphene	-	50
Tramadol	37.5	150
Codeine	130	200

*All listed opioid doses are equivalent to parenteral morphine 10 mg. The intrathecal opioid dose is 1/100, and the epidural dose 1/10 of the dose required systemically.

Recommendations	LE	GR
Transdermal fentanyl is equally effective to morphine. The incidence of side effects is lower than for morphine.	1b	A
Oral transmucosal administration of fentanyl should be used to provide rapid relief of breakthrough pain. The starting dose is 400 µg, or 200 µg in the elderly and those with a history of opioid sensitivity or underlying pulmonary disease.	2a	B

Recommendations	LE	GR
Dexamethasone 1-2 mg twice daily can be a valuable adjuvant in the treatment of pain in advanced cancer.	2a	B
If possible, avoid opioids for outpatients.	3	C

Typical PCA dosing schedule			
Drug (concentration)	Bolus size	Lockout interval (min)	Continuous infusion
Morphine (1 mg/mL)	0.5-2.5 mg	5-10	0.01-0.03 mg/kg/h
Fentanyl (0.01 mg/mL)	10-20 µg	5-10	0.5-0.1 µg/kg/h
Pethidine (10 mg/mL)	5-25 mg	5-10	-

PCA = patient controlled analgesia

Recommendations	LE	GR
The use of intravenous patient controlled analgesia is recommended because it provides superior postoperative analgesia, improving patient satisfaction and decreasing risk of respiratory complications.	1b	A

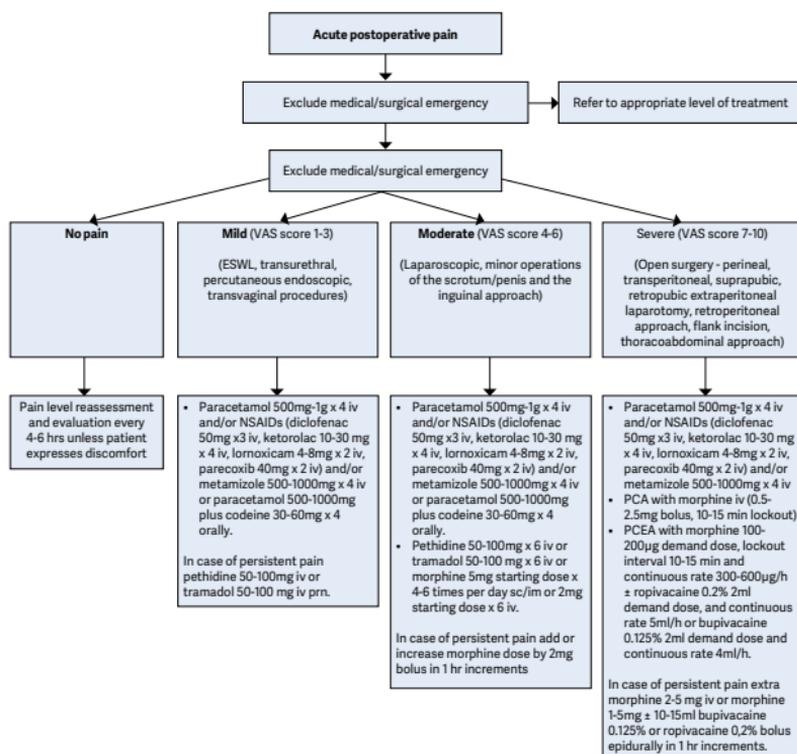
Typical PCEA dosing schemes			
Drug	Demand dose	Lockout interval (min)	Continuous rate
Morphine	100-200 µg	10-15	300-600 µg/h
Fentanyl	10-15 µg	6	80-120 µg/h
Pethidine	30 mg	30	-
Bupivacaine 0.125% + fentanyl 4 g/mL	2 mL	10	4 mL/h
Ropivacaine 0.2% + fentanyl 5 µg/mL	2 mL	20	5 mL/h

Typical epidural dosing schemes*		
Drug	Single dose	Continuous infusion
Morphine	1-5 mg	0.1-1 mg/h
Fentanyl	50-100 µg	25-100 µg/h
Sufentanil	10-50 µg	10-20 µg/h
Pethidine	10-30 mg	10-60 mg/h
Bupivacaine 0.125% or ropivacaine 0.2% + fentanyl 2 µg/mL	10-15 mL	2-6 mL/h

*l-bupivacaine doses are equivalent to those of bupivacaine.

Recommendations	LE	GR
Epidural analgesia, especially PCEA, provides superior post-operative analgesia, reducing complications and improving patient satisfaction, and is therefore preferable to systemic techniques.	1b	A
If possible, avoid opioids for outpatients.	3	C

Peri- and post-operative pain management



Recommendations	LE	GR
The use of paracetamol is recommended for postoperative pain management because it reduces consumption of opioids.	1b	B
Administer paracetamol as a single therapy to alleviate mild postoperative pain without major adverse effects.	2a	B
Avoid long-term use of COX inhibitors in patients with atherosclerotic cardiovascular disease.	2a	B

The use of intravenous patient controlled analgesia is recommended because it provides superior postoperative analgesia, improving patient satisfaction and decreasing risk of respiratory complications.	1b	A
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Neural blocks

Local anaesthetic blocks (intermittent and continuous) can be used after urological surgical operations to supplement postoperative analgesia.

Examples of neural blocks	
Procedure	Drug/dosage
Iliohypogastric or ilioinguinal nerve infiltration after hernia repair	10-20 mL bupivacaine or ropivacaine 0.25-0.5%
Intercostal nerve infiltration	5-10 mL bupivacaine or ropivacaine 0.25-0.5%
Continuous intrapleural infusion	10 mL/h bupivacaine or ropivacaine 0.1-0.2%

Perioperative pain management in children			
Drug	Dosing	Route of administration	Category
Ketamine	6 mg/kg	Oral, intranasal, im	NMDA antagonist
Midazolam	0.5 mg/kg	Oral, intranasal, rectally	Benzo-diazepine
Dexmedetomidine	4 µg/kg	Oral, intranasal	α ₂ -receptor agonist
Clonidine	4 µg/kg	Oral	α ₂ -receptor agonist

Pentobarbital	4-6 mg/kg	im	Barbiturate
Chloral hydrate	50-100 mg/kg	Oral	Barbiturate
Methohexital	25-30 mg/kg	Rectally	Barbiturate

Recommendations	LE	GR
Apply EMLA locally to alleviate venipuncture pain in children.	1b	A

Dosage of analgesics in children for postoperative analgesia			
Drug	Dose	Route of administration	Severity of surgical procedure
Paracetamol	10-15 mg/kg every 4 h 20-30 mg/kg every 6 h	Oral, rectally	Minor Minor
Ibuprofen	10-15 mg/kg every 6 h	Oral, iv, rectally	Minor, medium
Naproxen	6-8 mg/kg every 8-12 h	Oral, iv, rectally	Minor, medium
Codeine	0.5-1 mg/kg every 3-4 h	Oral	Minor, medium
Morphine	0.1 mg/kg every 2-4 h Infusion: 0.03 mg/kg/h 0.3 mg/kg every 3-4 h	Oral, iv, sc	Medium, major
Oxycodone	0.1-0.2 mg/kg every 3-4 h	Oral	Medium

Hydro-morphone	0.04-0.08 mg/kg every 3-4 h	Oral	Medium
Tramadol	1 mg/kg every 4-6 h	iv	Medium, major
Pethidine	2-3 mg/kg every 3-4 h	iv	Medium, major

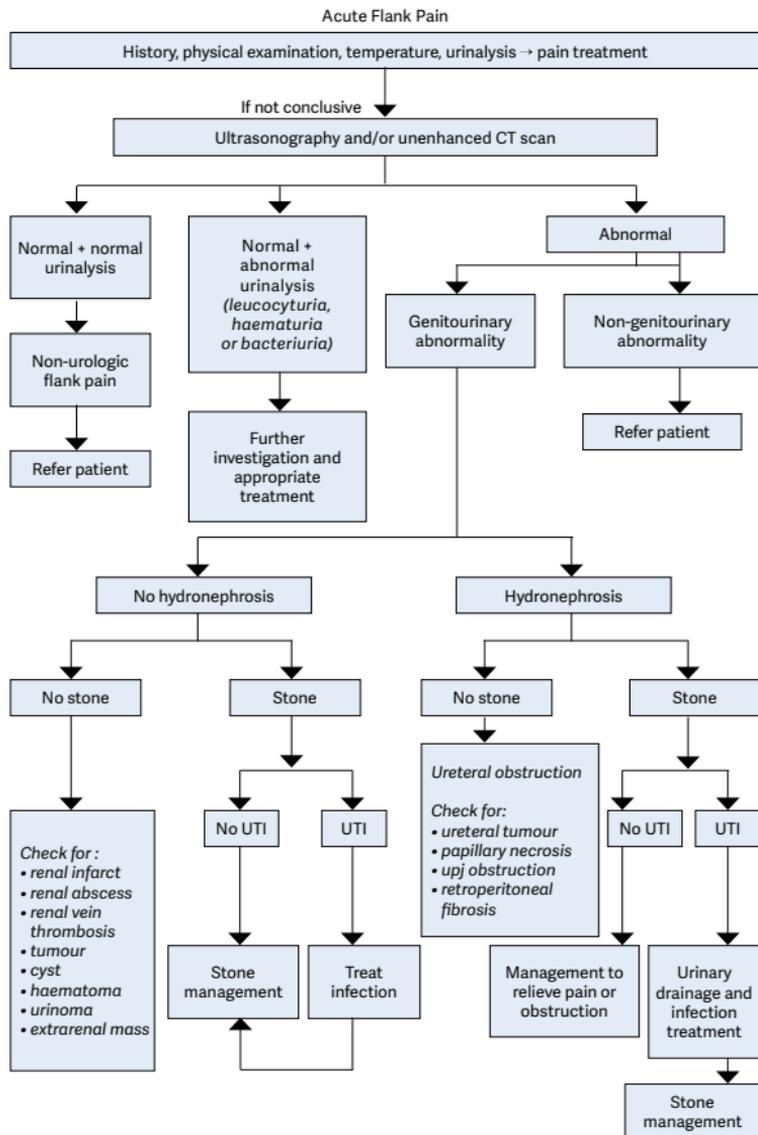
Non-traumatic acute flank pain

Laboratory evaluation

All patients with acute flank pain require a urine test (red and white cells, bacteria or urine nitrite), blood cell count, and serum creatinine measurement. In addition, febrile patients require C-reactive protein (CRP) and urine culture. Pyelonephritis ± obstructive uropathy should be suspected when the white blood count exceeds 15,000/mm³.

Recommendations	LE	GR
Febrile patients (> 38°C) with acute flank pain and/or with a solitary kidney need urgent imaging.	4	B
Unenhanced helical computed tomography is the diagnostic imaging modality with the highest sensitivity and specificity for evaluation of non-traumatic acute flank pain.		A
Ultrasound can be an alternative to unenhanced helical computed tomography in the initial approach to non-traumatic acute flank pain.		A
In patients presenting with acute flank pain NSAIDs such as diclofenac (75 mg bolus) and dipyrrone (1-2 g slow iv injection) are the drugs of first choice.	1a	A

Diagnostic approach to non-traumatic acute flank pain



CT = computed tomography; UTI = urinary tract infection.

Initial emergency treatment

Systemic analgesia

Pain relief is usually the first, most urgent, therapeutic step:

- A slow intravenous infusion of dipyron, 1 g or 2 g, is just as effective as diclofenac (75mg bolus) (LE: 1a).
- Intravenous papaverine (120 mg) can effectively and safely relieve patients not responding to conventional agents (diclofenac) and can be an alternative to diclofenac in patients with contraindications to NSAIDs (LE: 1b).
- The combination of intravenous morphine + ketorolac seems superior to either drug alone and appears to be associated with a decrease in rescue analgesia.

Upper urinary tract decompression

If pain relief cannot be achieved using medical therapy and there are signs of infection and of impaired renal function, upper urinary tract drainage should be carried out (Ureteral stenting or percutaneous nephrostomy).

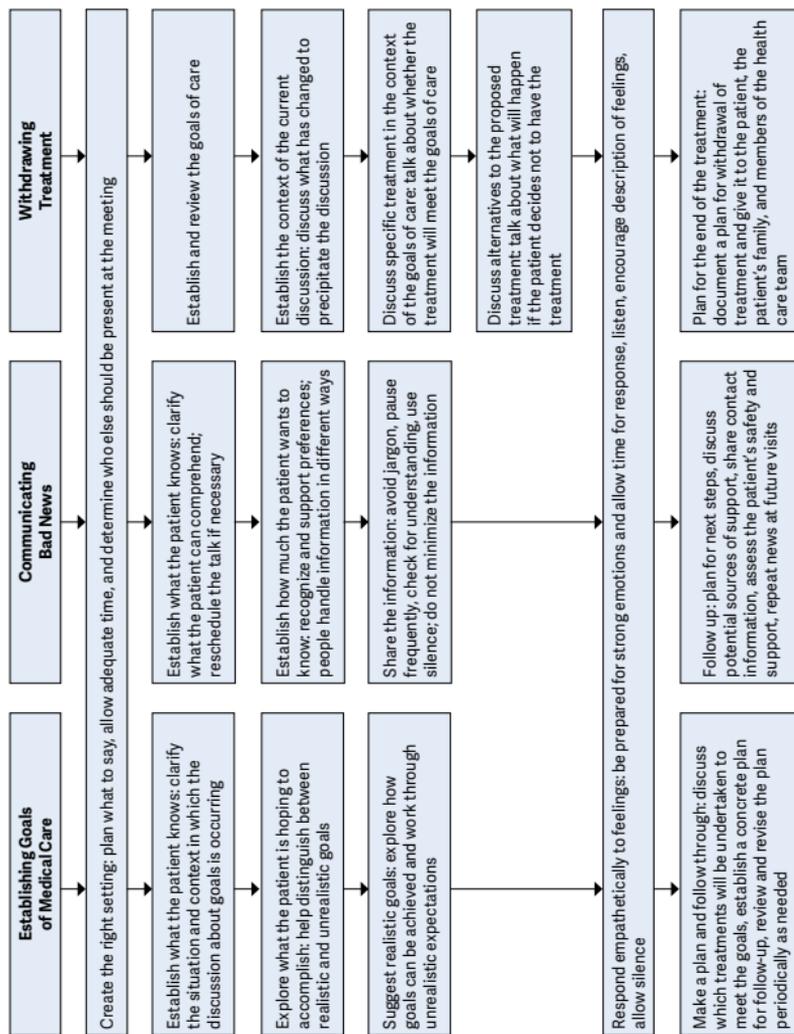
Indications for stenting for urgent relief of obstruction

- Urine infection with urinary tract obstruction
- Urosepsis
- Intractable pain and/or vomiting
- Obstruction of a solitary or transplanted kidney
- Bilateral obstructing stones
- Ureteral calculus obstruction in pregnancy

Palliative care

Before assuming the professional responsibility of terminal care, concepts on parenteral hydration and antibiotics usage should be clarified.

Protocols for communicating with patients about major topics in palliative care



Curriculum Emanuel LL, von Gunten CF, Ferris FD, eds. *The Education in Palliative and End-of-life Care (EPEC) Curriculum*: © The EPEC Project, 1999, 2003.

Treatment of physical symptoms

Dyspnoea and respiratory symptoms

Recommendations	LE	GR
Benzodiazepines can be considered when opioids and non-pharmacological measures fail to control breathlessness.	1a	A

Anorexia

Recommendations
Thalidomide (50 mg/day, orally, for 2 weeks) is effective against cancer-related anorexia

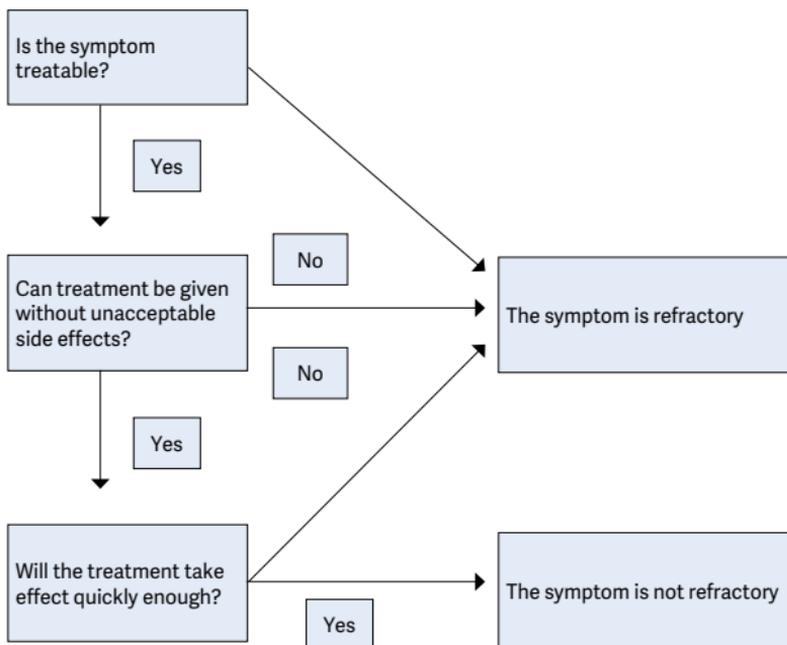
Vomiting

Recommendations	LE	GR
Dexamethasone is not effective in metoclopramide-refractory nausea.	1b	A
Patients with a high risk of vomiting are effectively treated with a combination of dexamethasone and 5-HT ₃ and neurokinin 1 receptor antagonists.	1a	A
In patients with moderate risk of vomiting, palonosetron combined with dexamethasone is recommended.	1a	A
Patients receiving radiotherapy and experiencing emesis can be effectively treated with combined 5-HT ₃ receptor antagonist and dexamethasone.	1a	A

Terminal care

Palliative sedation is one of the alternatives for terminally ill patients.

Algorithm for the decision on symptom refractoriness



Source: Royal Dutch Medical Association (KNMG). *Guideline for Palliative Sedation*. Utrecht, 2009.

Palliative sedation

Palliative sedation never aims to hastening death.

Subcutaneous administration is the preferred route and midazolam the drug of choice.

Drug	Bolus	Continuous administration
Midazolam	Start with 10mg s.c.If necessary every 2 hrs 5 mg s	Initial dose 1.5-2.5 mg/hr s.c./ i.v.If the desired effect is not achieved, in-crease the dose by 50% after a minimum of 4 hrs, always in combination with a bolus of 5 mg s.c. If risk factors are present (age>60,weight<60 kg, severe kidney or liver function disorder, very low serum albumin and/or co-medication that could exacer-bate the effect of sedation): - lower initial dose (0.5-1.5 mg/ hr), and - longer interval (6-8 hrs) before increasing maintenance dose. In the case of doses higher than 20mg/hr, see phase 2.
Levomepromazine	25 mg .c./i.v, possibly 50 mg after 2 hrs	0.5-8 mg/hr s.c./i.v. in combination with midazolam. After 3 days, halve the dose to prevent drug accumulation. If the desired effect is not achieved, stop administering midazolam and levomepromazine; see phase 3
Propofol	20-50 mg i.v.	20 mg/hr i.v., increase by 10 mg/hr every15 minutes. Administration under the supervision of an anaesthesi-ologist is advisable. In hospital, this may be considered for phase 2

Source: Royal Dutch Medical Association (KNMG). Guideline for Palliative Sedation. Utrecht, 2009.



This short booklet is based on the more comprehensive EAU guidelines (ISBN 978-90-79754-71-7), available to all members of the European Association of Urology at their website, <http://www.uroweb.org>.