

## 9.1 Neutropenic Sepsis

H. Bertz

**Def:** Systemic reaction to an infection during neutropenia (particularly after chemotherapy or radiotherapy).

- *Severe sepsis*: temperature  $> 38.0^{\circ}\text{C}$  or  $< 36^{\circ}\text{C}$ , heart rate  $> 90/\text{min}$ , respiratory rate  $> 20/\text{min}$  or  $\text{PaCO}_2 < 32 \text{ mmHg}$
- *Septic shock*: hypotension with blood pressure (BP)  $< 90 \text{ mmHg}$  (systolic) or BP decrease by  $40 \text{ mmHg}$  and signs of organ failure: lactate acidosis, oliguria, multiorgan failure (MOF)

**ICD-10:** A41

**Ep:** Fever during neutropenia (FN; ► Chap. 4.2) is a common side effect after myelosuppressive chemotherapy or radiotherapy; the incidence correlates directly with length and severity of the neutropenia. Up to 15% of patients with febrile neutropenia develop severe sepsis or septic shock.

**Path:** *Risk factors* → *neutropenia* → *febrile neutropenia* → *sepsis*

### **Risk of Sepsis in Case of Granulocytopenia**

- *Low risk*: granulocytes  $0.5\text{--}1 \times 10^9/\text{l}$  for 2–7 days → in case of sepsis, mortality 14%
- *High risk*: granulocytes  $< 0.1 \times 10^9/\text{l}$  for  $> 7\text{--}10$  days → in case of sepsis, mortality 47%

Both proinflammatory (TNF $\alpha$ , IL-6, IL-8) and antiinflammatory (IL-1 RA, IL-10) cytokines play an important role.

**Sy:**

- Fever, general symptoms, weakness, reduced performance
- Local signs of inflammation: catheter infection, skin infections, mucositis, gingivitis, acral focal infections, abscesses
- Sinusitis, signs of pulmonary infection
- Gastrointestinal symptoms, pain, diarrhea
- Meningitis, headache, amnesia
- Sepsis: decrease in blood pressure, tachycardia, hypothermia

### **Dg: Medical History, Physical Examination**

- Medical history (fever, diarrhea, dysuria, etc.)
- Physical examination: intravenous access sites, catheter ports, skin, oral mucous membranes, perianal region, pulmonary auscultation and percussion, abdominal pressure pain, pain on tapping / pressure pain of the paranasal air sinuses, lymphadenopathy, monitoring of blood pressure and pulse, meningism

### **Laboratory Tests**

- Routine laboratory tests, parameters of inflammation, plasmic coagulation, antithrombin III (ATIII), plasminogen activator inhibitor (PAI 1), liver and renal function tests

### **Microbiology**

- Peripheral blood cultures and cultures from intravenous access and catheters (► Chap. 10.8). Aerobic and anaerobic blood culture, isolator tube bottle. Where applicable, remove catheter, microbiological analysis of the catheter tip.
- Urine culture, sputum culture, swabs from suspicious lesions, lumbar / pleural / ascites puncture and culture
- *With pulmonary infiltrates*: bronchoalveolar lavage (BAL)
- *With diarrhea*: stool culture, detection of enterotoxins from *Clostridium difficile*, Gruber-Widal reaction

**Imaging**

- Chest x-ray, possibly x-ray of paranasal air sinuses
- Abdominal ultrasound if indicated
- High-resolution CT scan if indicated

**Th: Emergency Treatment**

With fever during neutropenia, rapid initiation of treatment is essential:

1. Microbiological analysis
2. Immediate initiation of empirical antibiotic treatment: broad-spectrum antibiotic with effectiveness against *Pseudomonas* spp., where applicable in combination with an aminoglycoside and a glycopeptide (particularly in case of catheter sepsis). Rapid escalation with antimycotics has proven benefit (amphotericin B, lipid formulation amphotericin B, azoles, echinocandins) (► Chap. 4.2)
3. Optimization of tissue oxygenation. Administration of oxygen via nasal tube or mask, 2 l/min up to 12 l/min. Where applicable, respiration support (non-invasive: CPAP; invasive: intubation)
4. Volume substitution; where applicable, administration of catecholamines
5. Initiate intensive medical care at an early stage

**Further Measures**

- Further diagnosis (imaging, ultrasound, bronchoalveolar lavage (BAL), abscess aspiration / biopsy, etc.)
- In case of impaired renal function, initiate dialysis
- If persistence of neutropenia is expected, administer G-CSF to support bone marrow reconstitution. (► Chap. 4.3). Activated protein C demonstrated a positive effect on the overall survival of septic patients, but with marked side effects. Consider granulocyte transfusion (► Chap. 5.4).

- Px:**
- Basic hospital hygiene; conduct of invasive procedures under aseptic conditions
  - Patient hygiene, especially skin care, dental care, mucositis prophylaxis; avoid foods with high germ counts
  - If neutropenia persists for more than 7 days: regular monitoring, even if afebrile → blood cultures, fecal cultures, throat swabs, sputum. Consequent treatment of fever in neutropenia (► Chap. 4.2)
  - Administration of hematopoietic growth factors (G-CSF) according to current guidelines (ASCO / ESMO guideline; ► Chap. 4.3)

- Ref:**
1. Aapro MS, Cameron DA, Pettengell R et al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. *Eur J Cancer* 2006;42:2433–53
  2. Bertz H, Auner HW, Weissinger F et al. Antimicrobial therapy of febrile complications after high-dose chemo-/radiotherapy and autologous hematopoietic stem cell transplantation: guidelines of the AGIHO/DGHO. *Ann Hematol* 2003;82(suppl 2):S167–74
  3. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences and new directions for its management. *Cancer* 2004;100:228–37
  4. ESMO Guidelines Working Group. Hematopoietic growth factors: ESMO Recommendations for the application. *Ann Oncol* 2007;18(Suppl.2):ii89–91
  5. Penack O, Beinert T, Buchheidt D et al. Management of sepsis in neutropenia: guidelines of the AGIHO/DGHO. *Ann Hematol* 2006;85:424–33
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1. [http://www.nccn.org/professionals/physician\\_gls/pdf/fever.pdf](http://www.nccn.org/professionals/physician_gls/pdf/fever.pdf) NCCN

## 9.2 Superior Vena Cava Syndrome (SVCS)

H. Henß

**Def:** Obstruction of the superior vena cava due to tumor compression, tumor-induced thrombosis, or other causes. Characteristic clinical picture of congestion of the superior vena cava. Underlying malignancy in 75–80% of cases.

**Ep:** In approximately 5% of lung cancer patients (particularly small cell lung cancer, SCLC, ► Chap. 8.2.1) and approximately 2% of patients with aggressive non-Hodgkin's lymphoma (NHL, ► Chap. 7.5). Patients with indolent non-Hodgkin's lymphoma or Hodgkin's disease rarely develop SVCS.

**Pg:** Obstruction of the superior vena cava by compression:  
 → Secondary thrombosis due to venous stasis  
 → Distal venous distension  
 → Formation of collaterals if disease develops slowly

**Sy:** Usually, rapid onset (within 6 weeks):

- Venous congestion with facial swelling, edema of the arm, visible veins on the chest wall: 80% of cases
- Headache, central nervous symptoms: 60%
- Dyspnea, tachypnea, cyanosis, cough (occasionally): 60%
- Dysphagia: 5%
- Horner's syndrome (miosis, ptosis, enophthalmus): 3%

**Dg:** **Medical History, Physical Examination**

- Medical history (tumors, other risk factors)
- Physical examination including venous congestion, neurological signs, lymphadenopathy, spleen

### Histology

- Sputum cytology, effusion cytology (pleural effusion), immunocytology (► Chap. 2.5)
- Bone marrow analysis (exclusion of tumor invasion, lymphoma)
- Bronchoscopy with biopsy or brush cytology
- Lymph node biopsy (in cases of peripheral lymphadenopathy)
- CT-guided fine-needle biopsy
- Mini-thoracotomy (low complication rate)
- Mediastinoscopy. *ATTENTION: high complication rate: hemorrhage, edema, impaired wound healing, infection; only if other procedures do not provide definitive diagnosis*

### Imaging

- Chest x-ray (mediastinal or hilar expanding lesion in 80% of cases, pleural effusion, pulmonary infiltrates)
- Thoracic CT / MRI (where applicable)

**Dd:** **Differential diagnosis of SVCS**

Diagnosis	Frequency (%)
<i>Malignant tumors</i>	85
Lung cancer (esp. small cell lung cancer)	65
Lymphomas (esp. high-grade NHL)	10
Metastases (esp. from breast cancer, seminomas, sarcomas)	10

**Dd:** Differential diagnosis of SVCS (*continued*)

Diagnosis	Frequency (%)
<i>Benign lesions</i>	12
Teratomas, thymomas, goiter, sarcoidosis	
<i>Mediastinal fibrosis</i>	1
Inflammatory disease (histoplasmosis, actinomycosis, tuberculosis)	
After mediastinal radiotherapy, thyroiditis, retroperitoneal fibrosis	
<i>Thrombosis of the Superior Vena Cava</i>	2
Behçet's disease, myeloproliferative syndromes (P. vera)	
Foreign body mediated (pacemaker, central venous line)	

**Th:** Indications for immediate therapy (emergency situations): cerebral symptoms, cardiac dysfunction (impairment of diastolic filling, LVEF ↓), respiratory obstruction

**Emergency Treatment**

1. Bed rest, upper body in elevated position, aspiration prophylaxis
2. Oxygen (nasal tube or mask), 2–12 l/min
3. Steroids (efficacy uncertain), e.g., prednisolone 100 mg i.v.
4. Anticoagulation, heparin 10,000–15,000 IU/day

**Further Measures**

- Histology (see above). **ATTENTION: histological analysis is essential for effective antineoplastic treatment**
- Treatment of the underlying disease:
  - Radiotherapy: only indicated in exceptional cases as emergency radiotherapy; total dose 30–50 Gy; response at the earliest after 3–7 days; response rate: 75% (lymphomas) to 25% (lung cancer)
  - Chemotherapy: indicated in patients with lung cancer and lymphomas
  - Surgery is not indicated (except for histology)
- In selected cases: stent insertion into the superior vena cava (decompression) possible

**Prg:** According to the prognosis of the underlying disease; SVCS alone is not an independent prognostic factor.

- Ref:**
1. Aurora R, Milite F, Vander Els NJ. Respiratory emergencies. *Semin Oncol* 2000;27:256–69
  2. Kanani RS, Drachmann DE. Malignant obstruction of the superior vena cava. *N Engl J Med* 2006;354:e7
  3. Rowell NP, Gleeson FV. Steroids, radiotherapy, chemotherapy and stents for superior vena caval obstruction in carcinoma of the bronchus. *Cochrane Database Syst Rev* 2001;CD001316
  4. Wilson LD, Detterbeck FC, Yahalom J. Superior vena cava syndrome with malignant causes. *N Engl J Med* 2007;356:1862–9

- Web:**
1. <http://www.emedicine.com/emerg/topic561.htm> E-medicine
  2. <http://www.cancer.gov/cancertopics/pdq/supportivecare/cardiopulmonary/patient> NCI Cancer Topics
  3. <http://www.fpnotebook.com/CV303.htm> Family Practice

## 9.3 Spinal Cord Compression / Cauda Equina Syndrome

H. Henß

**Def:** Malignancy-induced spinal cord compression with resulting neurological deficits.

**Ep:** Cerebral metastases in 15% of all solid tumors, signs of spinal cord compression eventually occur in 5% of all tumor patients.

**Pg:** ***Etiology***

Occurrence with various solid tumors and hematological neoplasia → most common: lung cancer, breast cancer, prostate cancer, melanoma, lymphoma, multiple myeloma.

### ***Mechanisms of Tumor-Induced Spinal Cord Damage***

Usually extracordal compression of spinal cord or cauda equina:

- Tumor invasion from the vertebral body into the epidural space → spinal cord compression (common with lung cancer, breast cancer)
- Tumor invasion through the intervertebral foramina → spinal cord compression or nerve root compression (lymphoma)
- Direct metastasis into the spinal canal (rare)
- Tumor-induced vascular damage → malperfusion, spinal cord damage due to infarction
- Paraneoplastic syndromes (► Chap. 8.13)

**Path:** Location of spinal cord compression:

- Cervical: 10%
- Thoracic: 70%
- Lumbosacral: 20%
- Multifocal: 25%

**Sy:** Often protracted process over a longer period of time, however, neurological deficits may develop within a few hours (especially with rapidly proliferating neoplasia such as lung cancer, renal cell carcinoma, melanoma, or lymphoma).

- *Most common symptom:* pain (> 90% of patients) as “back ache,” “lumbar syndrome,” etc.
- *Radicular deficits:* dermatoma-specific sensory and motor deficits; band-like pain; in some cases unilateral
- *Segmental myelopathy:* motor deficits / paresis, segmental sensory deficits
- *Generalized myelopathy:* bilateral motor disorders / pareses, sensory deficits; compression around cauda equina: “saddle anesthesia,” bladder / colon paralysis, anal sphincter tone ↓, tendon reflexes ↑, positive Babinski’s sign

**Dg:** ***Medical History, Physical Examination***

- Medical history (tumors, risk factors)
- Physical examination including neurological status

### ***Imaging***

- Plain x-ray, spinal MRI
- CT or bone scan if diagnosis uncertain

### ***Histology***

- Lumbar puncture (spinal tap) if suspected meningeal involvement
- Needle biopsy (if surgery is contraindicated)

**Dd:**

- Benign tumors: meningioma
- Epidural expanding lesions: hematoma, abscess
- Slipped disk, spondylolisthesis, osteoporotic fracture of a vertebral body
- Guillain-Barré syndrome, plexus lesion (congenital / acquired)
- Infection (e.g., tuberculosis)

**Th:** *Emergency Treatment*

1. Steroids, e.g., dexamethasone initially 10 mg i.v., then 4–8 mg every 6 h
2. Neurosurgical options must be considered at an early stage. Surgery within 6 to maximum 24 h. If symptoms have persisted longer than 24 h, risk of irreversible damage

**Further Measures**

- Histology
- Treatment of the underlying disease, taking into consideration the dynamics of progression and severity of neurological deficits:
  - Neurosurgery: laminectomy or resection of vertebral bodies
  - Radiotherapy: primary irradiation or adjuvant radiotherapy after surgical decompression, especially with radiosensitive tumors (breast cancer, lymphomas, plasmacytoma); target dose: 30–40 Gy over 2–4 weeks
  - Combined radiochemotherapy
  - Chemotherapy alone only with minor deficits, slow progression, or chemosensitive tumor

**Treatment Objectives**

- Improvement or normalization of neurological deficits
- Mobility and stability preservation of the vertebral column / spine
- Analgesia

**Prg:** *Prognostic Factors*

- Time between diagnosis and initiation of therapy
- Extent of neurological deficits before start of treatment
- Nature of the primary tumor

- Ref:**
1. Bagley CA, Gokaslan ZL. Cauda equina syndrome caused by primary and metastatic neoplasms. *Neurosurg Focus* 2004;16:e3
  2. Byrne T. Spinal cord compression from epidural metastases. *N Engl J Med* 1992;327:614–7
  3. Loblaw DA, Laperriere NJ. Emergency treatment of malignant extradural spinal cord compression: an evidence based guideline. *J Clin Oncol* 1998;16:1613–24
  4. Maranzano E, Bellavita R, Rossi R et al. Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial. *J Clin Oncol* 2005;23:3358–65
  5. Quinn JA, DeAngelis LM. Neurologic emergencies in the cancer patient. *Semin Oncol* 2000;27:311–21

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- |  |                     |
|--|---------------------|
| 1. <a href="http://www.caudaequina.org/">http://www.caudaequina.org/</a>   | Cauda Equina Portal |
| 2. <a href="http://www.emedicine.com/EMERG/topic85.htm">http://www.emedicine.com/EMERG/topic85.htm</a>             | E-medicine          |
| 3. <a href="http://www.merck.com/mmhe/sec06/ch093/ch093c.htm">http://www.merck.com/mmhe/sec06/ch093/ch093c.htm</a> | Merck Manual        |

## 9.4 Malignant Cardiac Tamponade

H. Henß

**Def:** Severe hemodynamically significant pericardial effusion caused by tumor invasion of the pericardium or myocardium. Medical emergency.

**Ep:** Invasion of pericardium or myocardium in up to 15% of patients with solid tumors.

**Pg:** Direct invasion or lymphatic / hematogenous metastasis to the pericardium or myocardium in patients with solid tumors and hematological neoplasia.

**Pp:** **Cardiac Tamponade**

Metastasis to the pericardium / myocardium

→ Pericardial effusion, arrhythmia

→ Cardiac tamponade (critical effusion volume in cases of rapid onset: 300–400 ml)

→ Diastolic dysfunction (ventricular load)

→ Cardiac insufficiency, cardiogenic shock

**Sy:** Over 65% of pericardial and myocardial metastases are clinically asymptomatic. Symptoms develop with increasing severity and due to hemodynamic consequences of malignant pericardial effusion:

- Dyspnea, cough, weakness, reduced performance
- Retrosternal pain
- Arrhythmia, tachycardia
- Signs of cardiac insufficiency (jugular venous distension, hepatosplenomegaly, cyanosis)
- Syncope

**Dg:** **Medical History, Physical Examination**

Physical examination: rise in jugular venous pressure (increased on inspiration = Kussmaul's sign), pulsus paradoxus (end-inspiratory decrease in blood pressure by > 10 mmHg), muffled heart sounds, pulmonary rales, hepatosplenomegaly, ascites, edema

**Imaging**

- Chest x-ray: enlarged heart silhouette
- ECG changes are usually unspecific, sometimes electrical alternans and/or precordial low voltage; with concurrent pericarditis: sinus tachycardia, raised ST, changes in T-wave
- Echocardiography (most important diagnostic tool)
- In selected cases: right heart catheterization, angiocardiography

**Cytology**

Diagnostic pericardiocentesis with effusion analysis:

- Total protein, LDH, glucose, triglycerides, cholesterol
- Cell count, cytology, immunocytology
- Microbiological diagnosis: cultures (including tuberculosis), Gram stain, Ziehl-Neelsen stain

**Dd:** *In cases of underlying malignancy:*

- Superior vena cava syndrome (SVCS, ► Chap. 9.2)
- Radiogenic pericarditis (as a result of radiotherapy)

**Th:** Treatment of cardiac tamponade / malignant pericardial effusion depends on symptoms, patient's performance status, and prognosis:

- Asymptomatic effusion without hemodynamic significance: treatment not indicated
- Terminal disease: individual assessment in each case

Emergency pericardiocentesis may be indicated in case of:

- Dyspnea, cyanosis, shock, altered level of consciousness
- Blood pressure decrease by > 20 mmHg
- Increase of peripheral venous pressure to > 13 mmHg

### Emergency Treatment

1. Bed rest with upper body in an elevated position
2. Where required, analgesia (paracetamol, diclofenac), mild sedation
3. Oxygen (nasal tube or mask), 2–12 l/min
4. Anticoagulation, heparin 10,000–15,000 IU/day  
*ATTENTION: discontinue before pericardiocentesis or other invasive measures*
5. Emergency pericardiocentesis  
*ATTENTION: pericardiocentesis should only be performed by an experienced cardiologist and/or in an intensive care unit, ultrasound- or echocardiography-guided. Needle is pushed (while aspirating) from below the xiphoid process in the direction of the pericardial effusion*

### Further Measures

- *Aspiration* of hemodynamically significant effusions: pericardiocentesis and pericardial drainage; if necessary, subxiphoid emergency pericardiocentesis or emergency pericardiotomy.
- *Local treatment* of confirmed malignant pericardial effusion: instillation of cytostatics (e.g., methotrexate 25 mg, cisplatin 20–200 mg, or bleomycin 30–60 mg). Pericardial fenestration, e.g., by inferior pericardiectomy. Radiotherapy: total dose of 25–35 Gy in 3–4 weeks, response rates of up to 60%.
- *Systemic treatment* of the underlying disease: chemotherapy, particularly in previously untreated patients with chemosensitive malignancies (small cell lung cancer, lymphoma, leukemia).
- *Surgery*: pleuropericardial fenestration; pericardiectomy only in selected cases (e.g., chronic radiogenic pericarditis)

**Prg:** Prognosis is determined by the underlying disease. Median survival: 6–24 months.

- Ref:**
1. Keefe DL. Cardiovascular emergencies in the cancer patient. *Semin Oncol* 2000;27:244–55
  2. Little WC, Freeman GL. Pericardial disease. *Circulation* 2006;113:1622–32
  3. Martinoni A, Cipolla CM, Civelli M et al. Intrapericardial treatment of neoplastic pericardial effusions. *Herz* 2000;25:787–93
  4. Retter AS. Pericardial disease in the oncology patient. *Heart Dis* 2002;4:387–91
  5. Soler-Soler J, Sagrista-Sauleda J, Permanyer-Miralda G. Management of pericardial effusion. *Heart* 2001;86:235–40
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## 9.5 Malignant Hypercalcemia

H. Henß

**Def:** Tumor-induced increase in serum calcium, usually paraneoplastic, with osteoclast activation.  
Types:

- *Humoral hypercalcemia of malignancy* (HHM): hypercalcemia without detectable osteolysis, e.g., multiple myeloma, pancreatic cancer, lung cancer
- Hypercalcemia in case of advanced osteolytic metastasis (tumor-induced osteolysis, TIO): detectable osteolysis, e.g., breast cancer

**Ep:** Incidence: 10–20% of all cancer patients; severe hypercalcemia requiring treatment in 1–3% of cases.

**Pg:** *Tumor entities commonly associated with hypercalcemia:* breast cancer, lung cancer, renal cell cancer, multiple myeloma

**Pp:** Secretion of osteoclast-activating factors by malignant cells

- Parathyroid hormone-related protein (PTH-RP): detectable in 75–90% of patients with tumor-associated hypercalcemia (both humoral hypercalcemia and bone metastasis)
- Interleukin-1
- Interleukin-6 (particularly multiple myeloma)
- Transforming growth factor alpha (TGF- $\alpha$ )

### Consequences

- Osteoclast activation and proliferation → increased bone destruction, calcium release
- Inhibition of osteoblast activity → reduced bone regeneration
- Glomerular filtration rate ↓, tubular calcium reabsorption ↑

**Sy:** The majority of patients with moderate hypercalcemia are asymptomatic.  
Symptoms of advanced hypercalcemia (> 2.7 mmol/l) or hypercalcemic crisis (> 3.5 mmol/l):

- *Kidney:* polyuria, polydipsia, dehydration → later anuria, acute renal damage, nephrocalcinosis, nephrolithiasis
- *Gastrointestinal tract:* nausea, vomiting, weight loss, anorexia, gastroduodenal ulcers / pancreatitis (rare)
- *Muscle:* muscle weakness, constipation, ileus
- *Cardiac:* bradycardia, atrial and ventricular arrhythmias
- *CNS:* fatigue, lethargy, impaired vision, psychosis, somnolence, coma

**Dg:**

- Routine laboratory tests including  $\text{Ca}^{2+}$ , phosphate,  $\text{K}^+$ ,  $\text{Na}^+$ ,  $\text{Cl}^-$ , urea and electrolytes, serum creatinine, bilirubin, alkaline phosphatase, albumin
- Determination of serum PTH and, where applicable, PTH-RP
- ECG: QT interval ↓, PQ interval ↓, T-wave (widened), bradycardia, arrhythmia
- Imaging: exclusion of osteolysis (skull, vertebral column, pelvis, humerus, femur); with plasmacytomas: plain x-ray (skull, axial skeleton, pelvis, thorax, humerus, femur)

**Co:** Nephrolithiasis, gastric / duodenal ulcers, pancreatitis (rare)

**Dd:** Differential diagnosis of hypercalcemia

Diagnosis	Frequency (%)
• Tumor-associated hypercalcemia	60
• Primary hyperparathyroidism	20
• Hyperthyroidism	Rare
• Adrenal failure	Rare

**Dd:** Differential diagnosis of hypercalcemia (*continued*)

Diagnosis	Frequency (%)
• Drug-induced: vitamin D, vitamin A, tamoxifen, thiazide diuretics, lithium, theophyllines	10
• Sarcoidosis, tuberculosis	< 5
• Immobilization	< 5

**Th:** Emergency Treatment

1. Hydration: NaCl 0.9%, minimum 2,000–3,000 ml/day; monitor urea, electrolytes, serum creatinine, and bilirubin; if necessary: K<sup>+</sup> / Mg<sup>2+</sup> replacement → improved renal function / calcium elimination ↑
2. Furosemide (if diuresis is inadequate) → improved renal function, calcium elimination ↑
3. Bisphosphonates, e.g., zoledronate i.v. (infusion, 1 mg/min) → inhibition of osteoclast activity  
SE: fever and/or flu-like symptoms, hypocalcemia
4. Corticosteroids, e.g., prednisolone 1 mg/kg i.v., usually 40–100 mg, particularly with hematological diseases (multiple myeloma) → cytokine release (IL-1, IL-6) ↓, intestinal calcium absorption ↓
5. If insufficient calcium level decrease: calcitonin 4–6 × 100 IU/day s.c. → osteoclast inhibition, calciuric effect
6. Dialysis in case of chronic renal failure: → calcium elimination by calcium-free dialysate

**Further Measures**

- Histology (if malignancy uncertain)
- Treatment of the underlying disease

**Prg:** Survival without treatment: < 4 weeks. After correction of electrolyte imbalance and successful antineoplastic treatment, hypercalcemia per se does not constitute an independent prognostic factor.

- Ref:**
1. Bajorunas DR. Clinical manifestations of cancer-related hypercalcemia. *Semin Oncol* 1990;17:16–20
  2. Flombaum CD. Metabolic emergencies in the cancer patient. *Semin Oncol* 2000;27:322–34
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  4. Stewart AF. Hypercalcemia associated with cancer. *N Engl J Med* 2005;352:373–9

- Web:**
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  2. <http://www.emedicine.com/emerg/topic 260.htm> E-medicine

## 9.6 Tumor Lysis Syndrome

H. Henß

**Def:** Syndrome arising due to rapid destruction / decomposition of large amounts of tumor tissue with release of intracellular components, including  $K^+$ , phosphate, and uric acid.

**Ep:** Incidence 10% after effective treatment of acute leukemia, high-grade non-Hodgkin's lymphoma (particularly Burkitt's lymphoma), and myeloproliferative syndromes. Efficient prophylaxis (see below) can reduce the risk of tumor lysis syndrome to < 1%.

**Pg:** Effective antineoplastic treatment in patients with large tumor burden and/or rapidly proliferating malignancy:

- Leukemia, particularly acute lymphoblastic leukemia (ALL)
- High-grade non-Hodgkin's lymphomas (particularly Burkitt's lymphoma)
- Myeloproliferative syndromes (particularly chronic myeloid leukemia)
- Solid tumors (rare cases, e.g., germ cell tumors, small cell lung cancer)

### Risk Factors

- Renal failure, renal damage, dehydration
- Large retroperitoneal or mediastinal tumors, LDH ↑

**Pphys:**

- Hyperuricemia → acute urate nephropathy
- Hyperkalemia → cardiac disorders
- Hyperphosphatemia → hyperphosphaturia
- Formation / precipitation of calcium phosphate in glomeruli and tubules → additional renal damage, hypocalcemia

**Sy:** Acute disease usually occurring 12–24 h after start of chemotherapy.

- General symptoms: nausea, vomiting, malaise
- Hyperkalemia: arrhythmia, cardiac arrest, paresthesia, pareses
- Hyperphosphatemia: renal damage due to calcium phosphate precipitation
- Hyperuricemia: urate nephropathy, renal failure, lethargy, nausea / vomiting
- Hypocalcemia: muscle cramps, tetany, paresthesia, cardiac arrhythmia, diarrhea

**Dg:** **Medical History, Physical Examination**

- Medical history including chemotherapy, malignant diseases
- Physical examination including cardiovascular function, renal function, neurological status

### Laboratory Tests

- Blood count, liver and renal function parameters, including  $K^+$ ,  $Ca^{2+}$ , phosphate, urea, serum creatinine, bilirubin, uric acid, LDH

### ECG

- Signs of hyperkalemia (prolonged PQ interval, P amplitude ↓, QRS complex widened, shortened QT, tall peaked symmetrical T-wave, ultimately “sinus wave”) and signs of hypocalcemia (arrhythmia, impaired conduction, QT interval ↑)

**Dd:**

- *Acute tissue destruction:* rhabdomyolysis, burns, trauma, hemolytic crisis
- *Hyperuricemia:* metabolic syndrome
- *Electrolyte imbalance:* renal failure, hypoparathyroidism, pancreatitis, sepsis, acidosis, paraneoplastic syndromes, potassium-sparing diuretics

**Th: Emergency Treatment**

1. Regular ECG monitoring; cardiac function monitoring if necessary
2. Hydration: NaCl 0.9%, minimum 2,000–3,000 ml/day
3. Hyperkalemia (> 5 mg/dl):
  - Cation exchange resin p.o. or enema every 6 h
  - Glucose plus insulin (1 U per 2 g of glucose). *ATTENTION*: rebound effect when discontinued, as K<sup>+</sup> is not fully eliminated but bound intracellularly
  - If necessary, dialysis to eliminate calcium
4. Hypocalcemia (< 2 mmol/l or < 8 mg/dl):
  - Calcium gluconate 10% i.v. 10–40 mg, repeat every 12 h if necessary
  - In mild cases: calcium 500–1,000 mg p.o.
5. Hyperuricemia:
  - Rasburicase (recombinant urate oxidase) 0.2 mg/kg/day, for 5–7 days. *ATTENTION*: for measurement of uric acid during treatment with rasburicase use cooled serum; otherwise inaccurate (low) readings.
6. Renal dysfunction / acute oliguria:
  - Dopamine 100–200 mg/24 h (infusion pump); benefit not fully established.
  - Dialysis (after exclusion of urinary tract obstruction)

**Further Measures**

Close monitoring: ECG, central venous pressure (CVP, target: > 5), routine laboratory tests (urea + electrolytes, serum creatinine, bilirubin, uric acid)

**Px:** *Most important: detection of risk factors and appropriate prophylaxis prior to initiation of treatment in high-risk patients:*

- Identification of high-risk patients (acute leukemias, Burkitt's lymphoma, high-grade non-Hodgkin's lymphomas, high tumor burden)
- Sufficient rehydration (target: > 2.5 l urine daily) while monitoring CVP
- Alkalinization (target: urinary pH > 7) with NaHCO<sub>3</sub> p.o. or citrate p.o., intravenous bicarbonate (if required)
- Xanthine oxidase inhibitors (allopurinol 300 mg/day) → if not tolerated: benzbromarone (uricosuric agent)

**ATTENTION:** allopurinol inhibits the metabolism of 6-mercaptopurine, azathioprine, theophylline, and phenprocoumon → if given with allopurinol, the dose of 6-mercaptopurine must be lowered to 25%.

- Ref:**
1. Cairo MS, Bishop M. Tumor lysis syndrome: new therapeutic strategies and classification. *Br J Hematol* 2004;127:3–11
  2. Del Toro G, Morris E, Cairo MS. Tumor lysis syndrome: pathophysiology, definition and alternative treatment approaches. *Clin Adv Hematol Oncol* 2005;3:54–61
  3. Nicolin G. Emergencies and their management. *Eur J Cancer* 2002;38:1365–77

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1. <http://www.emedicine.com/MED/topic2327.htm> E-medicine
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## 9.7 Hemorrhagic Complications / Malignant Vascular Erosion

H. Henß

- Def:** Hemorrhagic complications associated with malignant diseases.
- Ep:** Of patients with solid tumors, 10% die due to hemorrhagic complications caused by vascular invasion / erosion or ischemic tumor lysis.
- Pg:** Often combination of several pathogenetic factors:
- Thrombocytopenia, thrombopathy
  - Disseminated intravascular coagulopathy, hyperfibrinolysis, coagulation inhibitors
  - Decrease in plasmatic coagulation factors / hepatic dysfunction
  - Treatment-induced hemorrhage (hemorrhagic cystitis, mucositis, asparaginase therapy)
  - Surgery-induced hemorrhage (biopsy, centesis, etc.)
  - Tumor-induced hemorrhage: bleeding from tumor (gastrointestinal tumors, lung cancer) or malignant vascular erosion (head and neck tumors)
- Sy:**
- Hemorrhage (acute bleeding), e.g., hematemesis, hemoptysis, melena, hematuria
  - Anemia (chronic bleeding)
  - Signs of shock (tachycardia, hypotension)
- Th:** Treatment is determined by the severity of the hemorrhage.

### Emergency Treatment

1. Bed rest
2. Rehydration
3. Oxygen (nasal tube or mask), 3–12 l/min
4. Blood typing, ordering of blood products

### Further Measures

- Where applicable, red blood cell (RBC) transfusion; thrombocytopenic patients: platelet transfusion (► Chap. 6.3)
- Specification of the hemorrhage: local / punctate / diffuse / generalized
- Specific hemostatic measures: endoscopic obliteration; where applicable: surgical intervention (vascular ligation, tumor extirpation), transarterial embolization (angiography and subsequent embolization)

## Specific Types of Hemorrhage

### Hemorrhagic Cystitis

- Def:** Acute or subacute hemorrhagic inflammation of the mucous membrane of the urinary bladder, usually treatment-induced (cyclophosphamide, ifosfamide, radiotherapy)
- Sy:** Hematuria, pollakiuria, pain
- Th:** *Mild Hemorrhage*  
Bladder irrigation; often spontaneous cessation.

### Severe Bleeding

- Irrigation with large urinary catheter
- Removal of blood clots (if required, cystoscopically)
- Intravesicular treatment, e.g., 1% alum or prostaglandin E2 and F2
- With circumscribed hemorrhage: possibly cystoscopic obliteration of the source of bleeding

**Px:** *Prophylactic treatment with mesna after cyclophosphamide / ifosfamide therapy. Severe hemorrhage may require surgery.*

### Severe Hemoptysis

**Def:** Coughing up of large quantities of blood (bright red and foamy = arterial, dark = venous), usually vascular erosion by malignant tumor.

**Th:** Emergency bronchoscopy, if possible: local coagulation, blockade / tamponade with balloon-tipped catheter

### Severe Hematemesis

**Def:** Vomiting of large quantities of blood, due to a bleeding malignant tumor, hemorrhagic gastritis / mucositis, vascular erosion.

**Th:** Endoscopy, local coagulation, if necessary: emergency surgery

### Melena (Tarry Stools) / Hematochezia (Perianal Hemorrhage)

**Def:** Hemorrhage in the upper gastrointestinal tract (melena) or lower gastrointestinal tract (bright red blood in stools).

**Pg:**

- *Melena:* occurring in cases of hemorrhage > 100–200 ml from upper GI tract and slow passage (> 8 h) through the intestine. Bacterial fermentation of the blood in the intestine.
- *Hematochezia:* usually colorectal hemorrhage; in rare cases: massive bleeding in the upper GI tract and rapid passage through the intestine.

**Sy:**

- Melena: black tarry stools
- Hematochezia: symptoms depend on severity and location of the bleeding → rectal hemorrhage: blood covering the stools, bleeding from colon: bloody diarrhea or visible traces of blood in the stools

**Dg:**

- If necessary, fecal occult blood test to confirm presence of blood in stools
- Investigation of the cause of hemorrhage: esophago-gastro-duodenoscopy, rectoscopy, colonoscopy, possibly radionuclide scintigraphy (<sup>99</sup>Tc-marked erythrocytes) or selective arteriography
- Monitoring of blood quantity and cardiovascular parameters, renal function, coagulation

**Th:** Specific hemostatic measures (endoscopic or surgical).

**Ref:**

1. British Committee for Standards in Haematology. Guidelines on the management of massive blood loss. *Br J Haematol* 2006;135:634–41
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3. Mannucci PM, Levi M. Prevention and treatment of major blood loss. *N Engl J Med* 2007;356:2301–11
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5. Reimann T, Butts CA. Upper gastrointestinal bleeding as a metastatic manifestation of breast cancer: a case report and review of the literature. *Can J Gastroenterol* 2001;15:67–71

**Web:**

1. <http://www.cancernetwork.com/textbook/morev42.htm#Cardiovascular%20Emergencies>
2. <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=cmed6.section.43920>

## 9.8 Transfusion Reactions

H. Bertz

**Def:** Complications occurring after transfusion of cellular blood products (packed red cells and platelet concentrates), fresh frozen plasma (FFP), coagulation factors, immunoglobulins, or human albumin. Transfusion reactions are classified according to pathogenesis, type of blood product, time of occurrence, and clinical picture.

### Acute Transfusion Reactions

**Ep:** Incidence: approximately 1–10% of all transfusions.

**Pg:** **Acute Hemolytic Transfusion Reaction (AHTR)**

- Most dangerous form of acute transfusion reactions, incidence 1:6,000 to 1:25,000 transfusions, 0.75 deaths per 100,000 transfusions
- Major ABO incompatibility → severe acute intravascular hemolysis with complement activation and cytokine release
- In rare cases, irregular preformed antierythrocytic allo- or autoantibodies in the recipient (Kell system, Kidd system, Duffy system, etc.)

**Febrile Non-hemolytic Transfusion Reaction (FNHTR)**

- Most common transfusion reaction, 5% of all transfusions
- Post-transfusion temperature increase by  $\geq 1^\circ\text{C}$  with no signs of hemolysis or other transfusion-induced reactions
- *Pathogenesis:* antibodies against platelets or leukocytes, active mediator release from viable leukocytes contained in the blood product (e.g., cytokines), bacterial contamination (very rare)

**Urticarial Reaction**

- Local or generalized allergic reaction to plasma proteins
- In case of *local urticarial reaction*: transfusion may be continued after antihistamine treatment (all other cases of transfusion reactions: stop the transfusion, return blood product to blood bank, see below)

**Anaphylactic Reaction to Plasma-containing Products (Platelet Concentrates, FFP)**

- Patients with congenital IgA deficiency (incidence 1:700) and presence of IgA antibodies. In the majority of cases, pathogenesis not clear.

**Transfusion-related Acute Lung Injury (TRALI)**

- Granulocyte- or monocyte-specific antibodies (HLA class I or II) in the donor plasma react with leukocyte antigens in the recipient (in rare cases, reverse antibody constellation) → agglutination and activation of granulocytes and monocytes, especially in the lungs
- Rare and potentially fulminant ARDS-like reaction occurring 1–6 h after transfusion; lethal in approximately 15%

**Non-immunological Side Effects (esp. with Massive Transfusions)**

- Citrate intoxication (platelet concentrates, FFP) and alkalosis
- Hypothermia, hypovolemia
- Hyperkalemia (neonates, anuric patients), hypocalcemia
- Embolism (rare), bacterial contamination (rare)

**Sy:** *Rapid onset after start of transfusion:*

- Shivers, fever, sweating, nausea, vomiting
- Skin reactions, urticaria, flush, pruritus (particularly with allergic transfusion reactions)

- Restlessness, drop in blood pressure, tachycardia, dyspnea, tachypnea
- Headache, back pain
- Hemolytic transfusion reactions: red-brown urine (hemoglobinuria), later: jaundice
- **ATTENTION: in anesthetized patients, symptoms may be masked**

**Dg:** **Medical History, Physical Examination**

- Medical history including specifics of the transfusion, risk factors
- Physical examination including blood pressure, pulse, respiratory rate, cardiopulmonary auscultation; close monitoring

**Laboratory Tests**

- Blood count, hemolysis parameters (haptoglobin, bilirubin, LDH, free plasma hemoglobin) → ideally compared to pretransfusion sample
- Urine sample (hemoglobinuria)
- Blood culture (exclusion of bacterial contamination)

**Notification of the Blood Bank (Side Effects of Medicinal Products)**

- Retain blood bag (forensic reasons)
- Return blood bag and a recent blood sample of the patient to the blood bank  
→ Retesting of serological compatibility (before/after reaction), ABO compatibility between blood product and patient's blood, direct antiglobulin test, screening for irregular antibodies, bacteriological examination of the blood product

**Co:**

- AHTR: shock, disseminated intravascular coagulation (DIC), acute renal failure
- FNHTR, urticaria: usually self-limiting without serious complications
- TRALI: acute respiratory insufficiency, cardiopulmonary failure. Urgent indication for intensive medical care
- *Anaphylaxis*: shock

**Th:**

**Emergency Treatment**

1. **Stop transfusion immediately** (most important measure)
2. Save the intravenous line or insert a new access
3. Diagnostic measures (see above), close monitoring (blood pressure, pulse, respiratory rate, urinary output, clinical examination)
4. Supportive treatment (depending on the severity / cause of the reaction): oxygen, blood pressure, stabilization, diuresis maintenance with fluids and/or osmotic diuretics (mannitol); TRALI: early ventilation support may be required
5. Prednisolone 100 mg i.v., alternatively: dexamethasone 8 mg i.v.
6. Allergic reactions: antihistamines

**Further Measures**

- Volume substitution, alkalization, monitoring of urinary output to prevent acute renal failure; with impending acute renal failure: hemodialysis; **ATTENTION**: hyperkalemia due to potassium release from erythrocytes
- Continued antiallergic treatment: steroids, antihistamines
- Close monitoring of coagulation parameters, exclusion of DIC (► Chap. 6.5.5)

**ATTENTION: do not underestimate the dynamics of acute transfusion reactions. Patients may require intensive care from an early stage.**



## Subacute Transfusion Reactions

### **Pg:** *Post-transfusion Purpura (Packed Red Cells or Platelet Concentrates)*

- Development of platelet-specific alloantibodies → severe thrombocytopenia approximately 5–9 days after transfusion involving the patient's own platelets (“innocent bystander”), usually occurring in women between 50 and 70 years of age
- *Treatment:* intravenous IgG (avoid platelet transfusion)

### *Delayed Hemolytic Transfusion Reaction (DHTR)*

- Primary immunization or boosting of alloantibodies → delayed hemolysis, usually few clinical symptoms
- *Diagnosis:* immunohematological re-examination, hemolytic parameters

### *Transfusion-associated Graft-versus-Host Reaction (tGvHR)*

Reaction of proliferating donor T-lymphocytes to the recipient; occurring with transfusion of immunosuppressed patients and transfusion of blood relatives (“one-way HLA match”)

- Engraftment of transfused cells
- Later: transfusion-associated graft-versus-host disease (tGvHD)
- After latent period of 20–60 days, skin manifestations (dermatitis), intestinal symptoms (gastroenteritis), hepatitis; often not associated with transfusion due to latency period, mortality rate of up to 90%
- *Diagnosis:* detection of donor lymphocytes, DNA fingerprinting, skin biopsies
- *Prophylaxis:* irradiation of blood products (indications: ► Chap. 4.9.1)

## Hemosiderosis

**Pg:** Iron deposition in the tissue due to iron overload by a factor of  $\geq 5$  (normal iron level: men 3.5 g, women 2.2 g).

*Rule of thumb:* in chronically transfused patients risk of hemosiderosis after  $\geq 100$  packed red cell transfusions (approximately 250 mg iron per transfusion).

**Sy:** Symptoms depending on the affected organs:

- Hepatic dysfunction, diabetes mellitus, endocrine disturbances
- Dark pigmentation of the skin (“bronze diabetes”)
- Cardiomyopathy, arrhythmia

### **Dg:** *Medical History, Physical Examination*

- Medical history
- Physical examination including skin pigmentation, cardiopulmonary status

### *Laboratory Tests*

- Serum iron  $\uparrow$ , ferritin  $\uparrow$ , transferrin saturation  $\uparrow$

### *Histology*

- Detection of iron in the bone marrow (bone marrow biopsy / smear) or in the liver (ultrasound-guided liver biopsy)

**Dd:** Primary iron storage disease: hemochromatosis

**Th:**

- Chelators, e.g., desferrioxamine: 2,000 U/day s.c. long-term therapy via pump or weekly bolus s.c.
- Oral therapy with deferasirox: 20–30 mg/kg body weight/day or deferiprone, 25mg/kg body weight,  $\times 3$ /day

## Infectious Complications

### **Pg:** *Human Immunodeficiency Virus (HIV)*

Risk with cellular products: < 1: 1,000,000 → further minimized due to introduction of HIV genome testing of donors by nucleic acid amplification; significantly lower risk with cell-free products (FFP, immunoglobulins, and coagulation factor products) due to quarantine or virus inactivation.

### *Hepatitis B Virus (HBV)*

Risk with cellular products: 1:50,000 to 1:200,000; significantly lower risk with cell-free products (due to quarantine or virus inactivation).

### *Hepatitis C Virus (HCV)*

Risk with cellular products: < 1:500,000; risk minimization possible by statutory nucleic acid amplification testing (HCV-NAT) of cellular blood products; significantly lower risk with cell-free products (due to quarantine or virus inactivation).

### *Cytomegalovirus (CMV)*

- Leukocyte-depleted cellular blood products are equally low risk as anti-CMV-negative blood products (according to guidelines). However, high-risk patients (e.g., anti-CMV-negative recipient of allogenic stem cell transplant, intrauterine transfusion) should strictly receive anti-CMV-negative blood products
- CMV reactivation / CMV coinfection in anti-CMV-positive immunosuppressed recipients by administration of blood products is unlikely (general leukocyte depletion)

### *Other Transfusion Relevant Viruses*

- Parvovirus B19 (PV-B19): transfusions from PV-B19-IgG-positive donors recommended in patients needing regular transfusions
- HTLV I/II: risk identification and sequential testing of donors for HTLV I/II is recommended
- EBV (Epstein-Barr virus), HHV-6, HAV (hepatitis A virus)
- HGV (hepatitis G virus): relevance in relation to transfusions as yet uncertain
- TTV (transfusion-transmitted virus): isolated in 1998, significance as yet uncertain

### *Other Transfusion Relevant Infectious Agents*

- *Bacteria*: bacterial contamination is rare with sterile preparation and use of single-use materials.
- *Parasitic diseases*: malaria, babesiosis, Chagas' disease etc; preventable by temporary abstinence from blood donation after travel to affected regions.
- *Creutzfeldt-Jakob disease (CJD) / new variant CJD (vCJD)*: so far, no scientific data on transmission through blood products, however this possibility can not be definitively excluded. Individuals potentially at risk of CJD infection due to their medical history (e.g., treatment with human growth hormone derived from pituitary glands of corpses, > 6 month stay in Great Britain between 1980 and 1996) are excluded from donation.

- Ref:**
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  2. Dzik WH. New technology for transfusion safety. *Br J Haematol* 2006;136:181–90
  3. Pomper GJ, Wu Y, Snyder EL. Risks of transfusion-transmitted infections 2003. *Curr Opin Hematol* 2003;10:412–8
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  6. Sillmann CC, Ambrusi DR, Boshkov LK. Transfusion-related acute lung injury. *Blood* 2005;105:2266–73

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  2. <http://www.nlm.nih.gov/medlineplus/ency/article/001303.htm> Medline Plus
  3. [http://www.psbcc.org/medical/transfusion/bcrm/section\\_c/default.ht](http://www.psbcc.org/medical/transfusion/bcrm/section_c/default.ht) Puget Sound Blood Ctr
  4. <http://www3.mdanderson.org/~citm/> MD Anderson, Transfusion Reactions

## 9.9 Extravasation of Cytostatic Drugs

B. Lubrich, H. Henß

**Def:** Extravasation / paravascular administration of cytostatic drugs.

**Ep:** Extravasation in 0.1–0.5% of all cases of intravenous administration of cytostatic drugs.

**Pp:** Classification of cytostatic drugs according to local toxicity

### *Severely necrotizing compounds*

Amsacrine	Mitomycin
Cisplatin (> 0.4 mg/ml)	Mitoxantrone
Dactinomycin	Paclitaxel
Daunorubicin	Vinblastine
Docetaxel	Vincristine
Doxorubicin	Vindesine
Epirubicin	Vinorelbine
Idarubicin	

### *Moderately toxic compounds*

Bendamustine	Estramustine
Carmustine	Etoposide
Cisplatin	Fotemustine
Dacarbazine	Melphalan
Daunorubicin liposomal	Oxaliplatin
Epirubicin liposomal	Treosulfan

### *Compounds of low local toxicity*

Alemtuzumab	Irinotecan
Asparaginase	Methotrexate
Carboplatin	Nimustine
Cladribine	Pegaspargase
Cyclophosphamide	Pentostatin
Cytarabine	Raltitrexed
Etoposide phosphate	Rituximab
Fludarabine	Thiotepa
Fluorouracil	Topotecan
Gemcitabine	Trastuzumab
Ifosfamide	

**Sy:** *Acute Reaction*

- Edema, erythema, pain, hyperthermia
- Potential systemic reactions: vasovagal reaction, nausea, vomiting

*Delayed Symptoms*

- Compounds of severe local toxicity: tissue necrosis / ulceration from day 7
- Superinfection of skin lesions

**Dd:** Local allergic reactions (→ topical corticoid treatment is advisable)

**Th: Emergency Treatment**

*Check pulse, local symptoms, and vital signs every 30 min*

*Immediate therapy—even if no symptoms*

1. *Basic measures:*
  - Stop infusion immediately, leave i.v. line, replace infusion set.
  - Place 5-ml syringe on i.v. access and extract extravasated fluid if possible, then remove needle.
  - In case of blistering or extensive extravasation: transcutaneous aspiration.
2. *Substance-specific measures:*
  - Anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin), anthracenediones (mitoxantrone), platinum compounds (cisplatin, carboplatin), and mitomycin C: DMSO 99% every 3–4 h for at least 3 days (up to 14 days) → apply with swab to the entire extravasation area and leave to dry.
  - Anthracyclines: dexrazoxane hydrochloride 1000 mg/m<sup>2</sup>/d i.v. 24 h and 48 h after extravasation, 500 mg/m<sup>2</sup> at 72 h.
3. *Other measures:*
  - In the first 24–48 h: elevate legs.
  - Cool local areas as required (to alleviate pain).
  - *Exception:* etoposide, teniposide, vinblastine, vincristine, and vindesine: mild dry warmth (use blanket to keep extravasation site warm).
  - Avoid exposure to light (dacarbazine).
4. *Surgical measures:*
  - Progressive necrosis / ulceration: surgical debridement / removal of necrotic tissue / plastic surgery (flap).
5. *Documentation:*
  - All cases of extravasation as well as management and treatment must be accurately documented.
6. *Observation of the patient for at least 6 weeks:*
  - Necrosis may occur weeks or months after the incident

**Further Measures (Optional)**

A number of therapies have been reported to be effective in the treatment of extravasation of various cytostatic drugs. These reports are usually based on individual case studies or studies with small groups of patients rendering a comprehensive assessment impossible. The therapies described in the following lack proof of efficacy and may even cause additional toxicity:

- Local application of corticosteroids, topical or subcutaneously (highly controversial, potential increase in skin toxicity)
- Local infiltration of hyaluronidase
- Local infiltration of NaHCO<sub>3</sub> 8.4%, sodium thiosulfate, or heparin (particularly with vinca alkaloids)
- Local dilution by subcutaneous installation of NaCl 0.9% or glucose 5%

**F/U:** Close monitoring for 6 months

**Px:** *Prevention of extravasation by correct administration of cytostatic drugs:*

- For peripheral line: only use veins on the dorsum of the forearm, ensure good flow
- Only use intravenous catheters
- In patients with history of mastectomy, use contralateral arm for infusion (due to impaired lymph drainage and venous congestion after axillary dissection)

- Ensure correct position of the intravenous line (erythema, swelling, induration, local pain); if in doubt: resite the i.v. line
- Reliable fixation of the extremity, leave access visible
- If placement of intravenous line was unsuccessful at first attempt, avoid puncturing the same vein distal to the original access point
- Cytostatic drugs should only be added to a freely running infusion (NaCl 0.9% or glucose 5%); consider possible incompatibilities (► Chap. 3.2.6)
- Always administer cytostatic drugs with severe local toxicity as infusion via a central venous line
- Administration of cytostatic drugs of severe local toxicity via peripheral line: only as bolus by experienced physician / nurse

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**Web:**

1. <http://www.extravasation.org.uk/home.htm> Natl Extravasation Info