Supportive Care Practices
for
Allogeneic
Hematopoietic Stem Cell Transplantation

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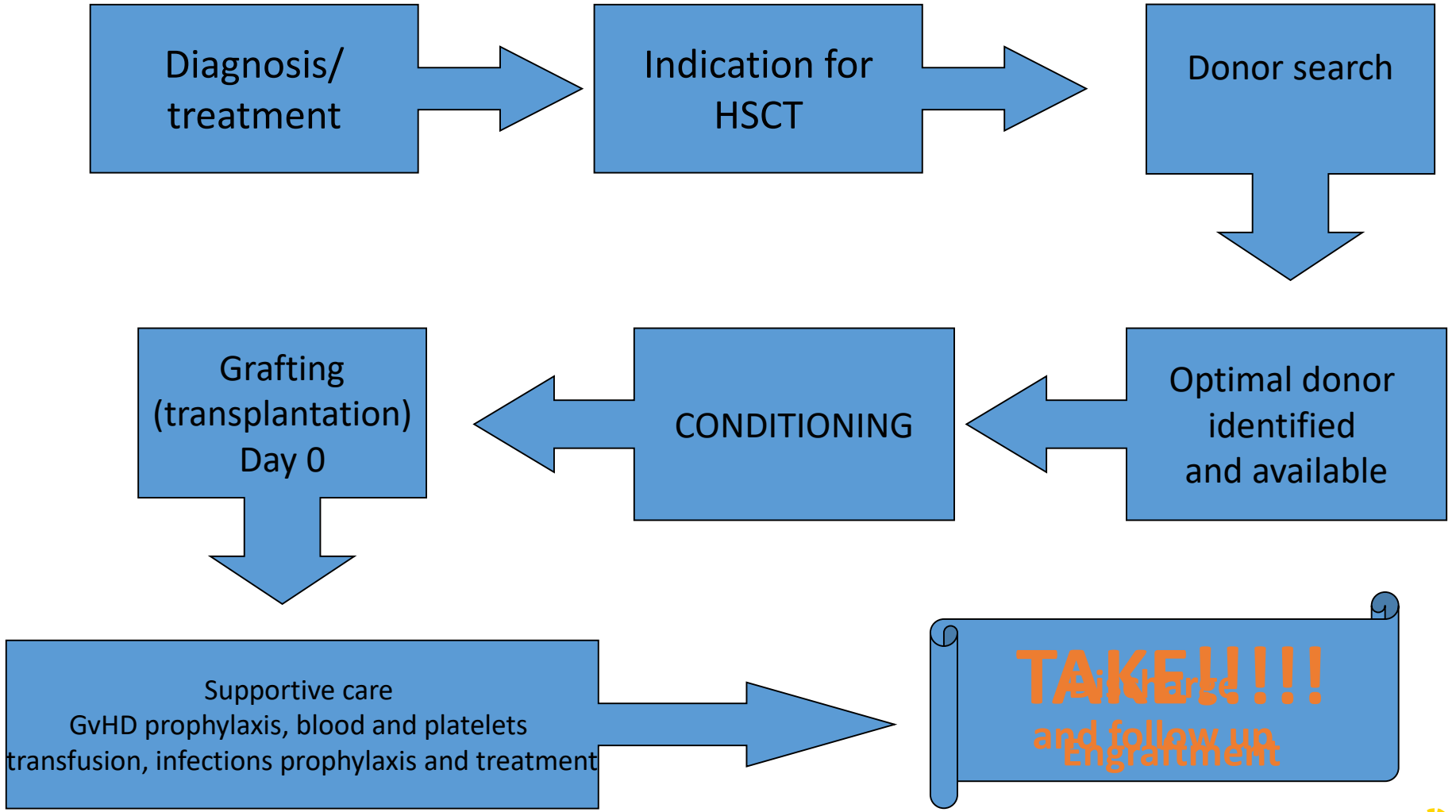
Allogeneic HSCT

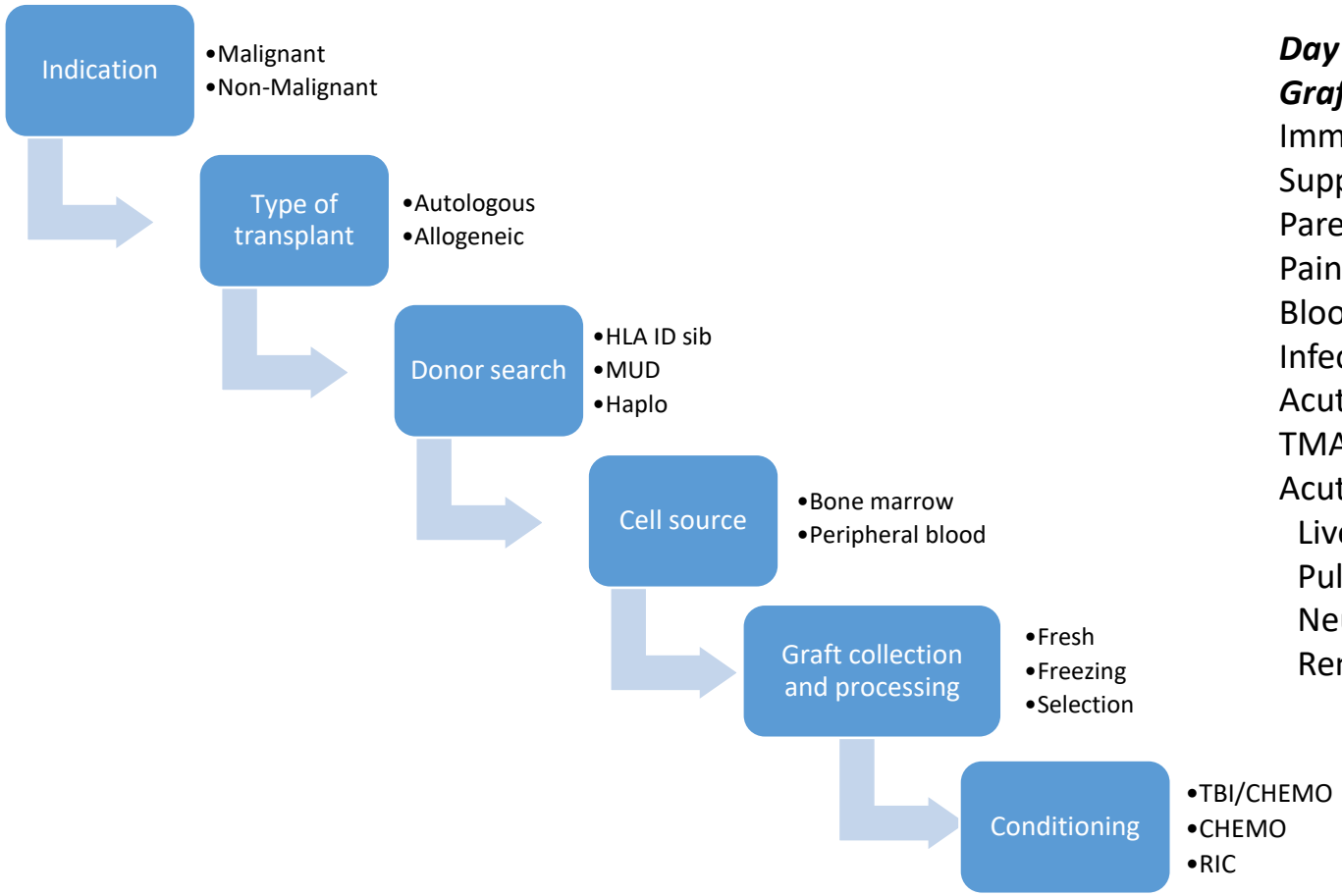
Timeline of the transplant process



Timeline of the Transplant Process

- Transplant work-up (day -100 through day -14)
- Conditioning regimen (day -21 through day +1)
- Day of graft infusion (day “0”)
- Waiting for engraftment (day 0 through day +30)
- Discharge from hospital (day +21 through day +40)
- Outpatient and home-based care (day +40 through day +365)
- Long-term follow-up care (day +365 and annually)

HSCT – complex and complicated procedure



Day "0" until +100
Graft infusion and early post-transplant
Immunosuppression
Supportive care
Parenteral nutrition
Pain management
Blood products
Infections – prophylaxis and treatment
Acute GvHD
TMA
Acute organ toxicity
  Liver toxicity – SOS
  Pulmonary toxicity
  Neurotoxicity
  Renal toxicity

Beyond day +100 –
Immunosuppression
Chronic GvHD
Sustained hematopoiesis
Immunological recovery
Still risk for infections
Risk for relapse
Long term sequelae

SCT indications in children

Hematological malignancies

Table 2. Proposed classification of transplant procedures for children—2015

Disease	*Disease status*	*Sibling donor allo-HSCT*	*Well-matched URD allo-HSCT/CBT*	*Alternative donor allo-HSCT*	*ASCT*
Haematological malignancies					
AML	CR1 (low risk[a])	GNR/II	GNR/II	GNR/III	GNR/II
	CR1 (high risk[a])	S/II	CO/II	CO/III	CO/II
	CR1 (very high risk[a])	S/II	S/II	CO/II	CO/III
	CR2	S/II	S/II	S/II	CO/II
	>CR2	S/II	CO/II	CO/II	GNR/II
ALL	CR1 (low risk[a])	GNR/II	GNR/II	GNR/III	GNR/II
	CR1 (high risk[a])	S/II	S/II	CO/II	GNR/II
	CR2	S/II	S/II	CO/II	GNR/II
	>CR2	S/II	S/II	CO/II	GNR/II
CML	Chronic Phase	CO/II	CO/II	CO/II	GNR/III
	Advanced Phase	CO/II	CO/II	CO/II	GNR/III
NHL	CR1 (low risk)	GNR/II	GNR/II	GNR/II	GNR/II
	CR1 (high risk)	CO/II	CO/II	CO/II	CO/II
	CR2	S/II	S/II	CO/II	CO/II
HL	CR1	GNR/II	GNR/II	GNR/II	GNR/II
	1st relapse, CD2	CO/II	CO/III	CO/III	S/II
MDS		S/II	S/II	CO/III	GNR/III

Abbreviations: CBT = cord blood transplant; CO = clinical option, can be carried after careful assessment of risks and benefits; CR1, 2 = First, second CR; D = Developmental, further trials are needed; GNR = Generally not recommended; HL = Hodgkin lymphoma, generally indicated in suitable patients; MDS = Myelodisplastic syndrome; MPS = Mucopolysaccaridosis; NHL = Non Hodgkin lymphoma. Well-Matched Unrelated Donor = 10/10, 8/8. 9/10 (if mismatch in DQB1). This classification does not cover patients for whom a syngeneic donor is available. [a]Categories are based mainly on number of WBCs, cytogenetics at diagnosis and molecular markers, and time to achieve remission according to international trials.

Sureda et al., BMT, 2015

SCT indications in children

Non-malignant disorders; solid tumors

Disease	*Sibling donor allo-HSCT*	*Well-matched URD allo-HSCT /CBT*	*Alternative donor allo-HSCT*	*ASCT*
Non-malignant disorders; solid tumours				
Primary immunodeficiencies	S/II	S/II	S/II	NA
Thalassemia	S/II	CO/II	CO/III	NA
Sickle cell disease (high risk)	S/II	CO/III	CO/III	NA
Aplastic anaemia	S/II	S/II	CO/II	NA
Fanconi anaemia	S/II	S/II	CO/II	NA
Blackfan-Diamond anaemia	S/II	S/II	CO/III	NA
Chronic granulomatous disease	S/II	S/II	CO/III	NA
Kostman's disease	S/II	S/II	CO/III	NA
MPS-1H Hurler	S/II	S/II	CO/II	NA
MPS-1H Hurler Scheie (severe)	GNR/III	GNR/III	GNR/III	NA
MPS-VI Maroteaux-Lamy	CO/II	CO/II	CO/II	NA
Osteopetrosis	S/II	S/II	S/II	NA
Other storage diseases	GNR/III	GNR/III	GNR/III	NA
Autoimmune diseases	CO/II	CO/II	GNR/II	CO/II
Germ cell tumour	CO/II	CO/II	CO/II	CO/II
Ewing's sarcoma (high risk or >CR1)	D/II	D/III	D/III	S/II
Soft tissue sarcoma (high risk or >CR1)	D/II	D/II	D/III	CO/II
Neuroblastoma (high risk)	CO/II	D/III	D/III	S/II
Neuroblastoma >CR1	CO/II	D/III	D/III	S/II
Wilm's tumour >CR1	GNR/III	GNR/III	GNR/III	CO/II
Osteogenic sarcoma	GNR/III	GNR/III	GNR/III	D/II
Brain tumours	GNR/III	GNR/III	GNR/III	CO/II

Abbreviations: CBT = cord blood transplant; CO = clinical option, can be carried after careful assessment of risks and benefits; CR1, 2 = First, second CR; D = Developmental, further trials are needed; GNR = Generally not recommended; HL = Hodgkin lymphoma, generally indicated in suitable patients; MDS = Myelodisplastic syndrome; MPS = Mucopolysaccaridosis; NHL = Non Hodgkin lymphoma. Well-Matched Unrelated Donor = 10/10, 8/8. 9/10 (if mismatch in DQB1). This classification does not cover patients for whom a syngeneic donor is available. [a]Categories are based mainly on number of WBCs, cytogenetics at diagnosis and molecular markers, and time to achieve remission according to international trials.

Sureda et al., BMT, 2015

Transplant evaluation

- The urgency of SCT
- Parallel treatment of the underlying disease
- Detailed timetable for the transplant process with preliminary date of transplantation (month, week)
- Donor source choice
  - Type of donor
  - Stem cell source

Transplant work-up

day -100 through day -14

- Ongoing treatment of the underlying disease
  - Conventional chemotherapy and MRD evaluation in AL
  - Treatment and prevention of infection in SCID patients
  - Blood transfusion and chelation in thalassemia patients
- Imaging scans, MIBG, X-ray
- Other provider consults
- Blood draws, infection serology, evaluation of function of critical organs – heart, kidneys, lungs
- Search for potential risk for infection during post-transplant aplasia
  - Dental status, otorhinolaryngology
- Donor work-up and preparation for stem cell harvest
- Central line placement for recipient

Potential complications after HSCT

- Direct organ toxicity (mucositis, lungs, kidney, heart, liver, gut, CNS)
- Infections
- Bleeding, Thrombotic Thrombocytopenic Purpura (TTP) Hemolytic Uremic Syndrome (HUS)
- Sinus Obstruction Syndrome (SOS) – former Veno-Occlusive Disease of the liver (VOD)
- *Graft vs Host Disease (GvHD)*
  - *Acute*
  - *Chronic*
- *Graft rejection*
- *Hemolysis – in case of blood group mismatch*
- Hemorrhagic cystitis - caused by
  - High dose chemotherapy - mainly Cyklofosfamid (Mesna prophylaxis necessary)
  - *Virus reactivation due to "immune deficiency" after transplantation*
- Psychosocial issues
- Relapse of the underlying disease
- Late effects
  - Hormonal dysfunction, sterility, short stature, bronchiolitis obliterans,

Conditioning regimen

day -21 through day +1

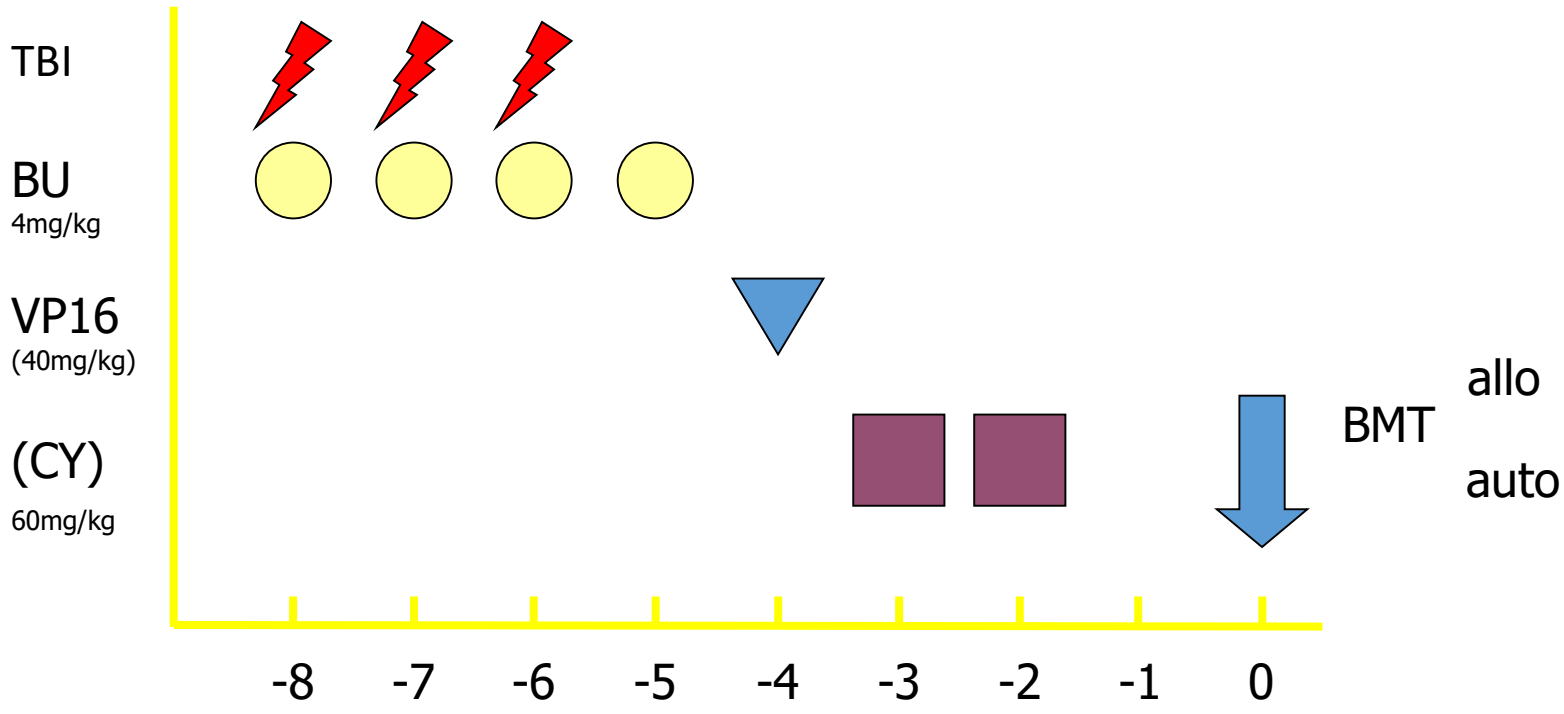
- Radiotherapy
- Chemotherapy
  - MAC
  - RIC
- Immunotherapy/serotherapy
- Immunosuppression for prophylaxis of Graft vs Host Disease

Conditioning makes the patient very sensitive to infection both endogenous (reactivation) and exogenous.

Conditioning regimen - TBI

- **Total Body Irradiation (TBI) 12 -14,4 Gy**
  - Given in a single dosee or fractionated up to sixdoses adjusted (reduced) for radiosensitive tissue – lower dose toward lungs
  - Total Marrow Irradiation – a new approach
  - Children < 3 years should not receive TBI
  - High risk for severe late effects including secondary malignancies

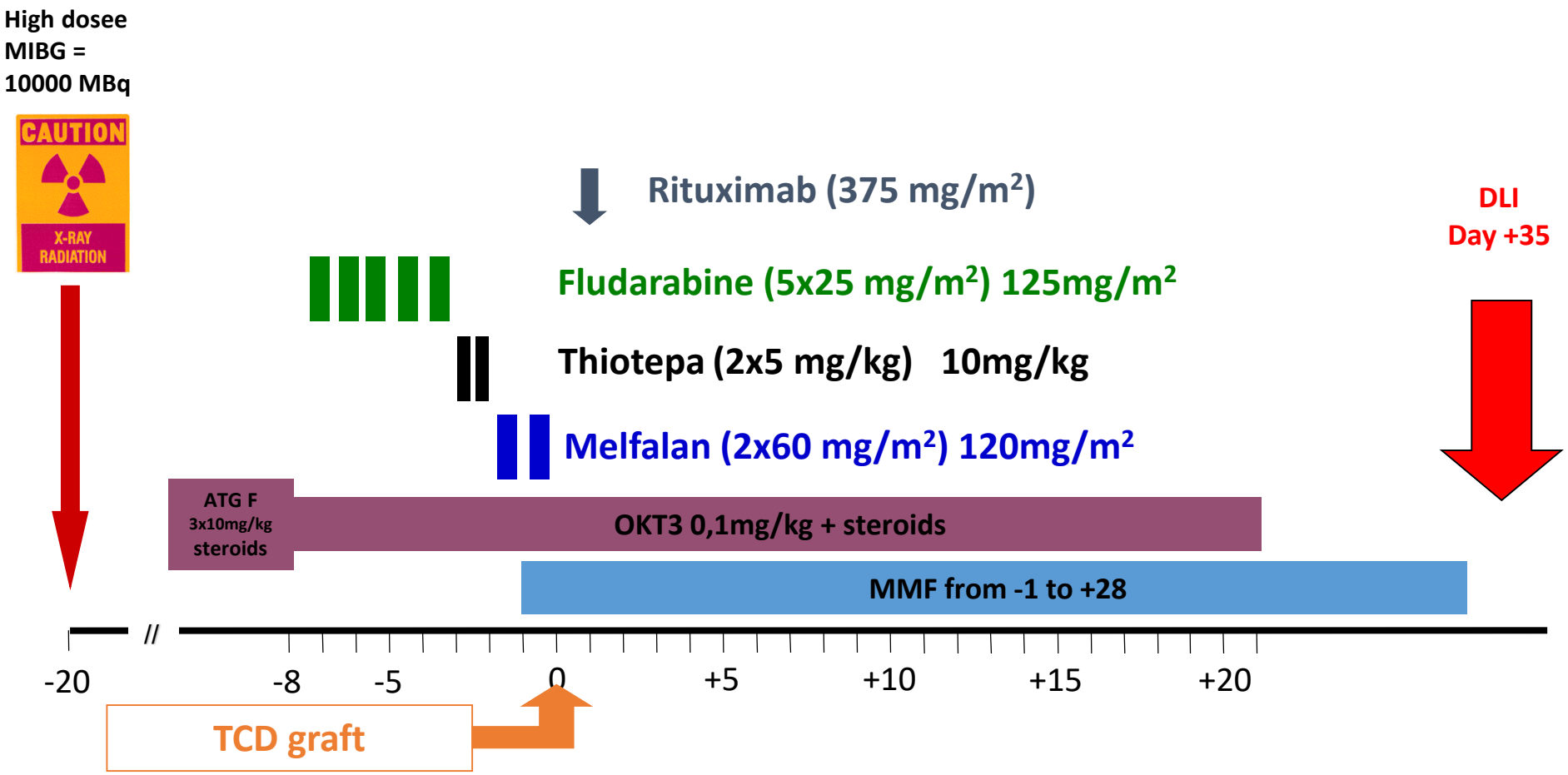
Example of conditioning



ATG for MUD day -3, -2, -1

Conditioning before haploidentical SCT for neuroblastoma

RIC ± mega dose of ^{131}I-MIBG



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Supportive care measures related to SCT

- Supportive care during conditioning
- Infections, neutropenic fever
- GvHD
- VOD/SOS
- Transfusion support
- Nutritional support
- Thrombotic microangiopathy
- Long-term post-transplant supportive care
  - Follow up
  - Vaccination
  - Hormonal substitution
  - Functional tests
  - Transfer to late effect outpatient clinic when older than 18 yr

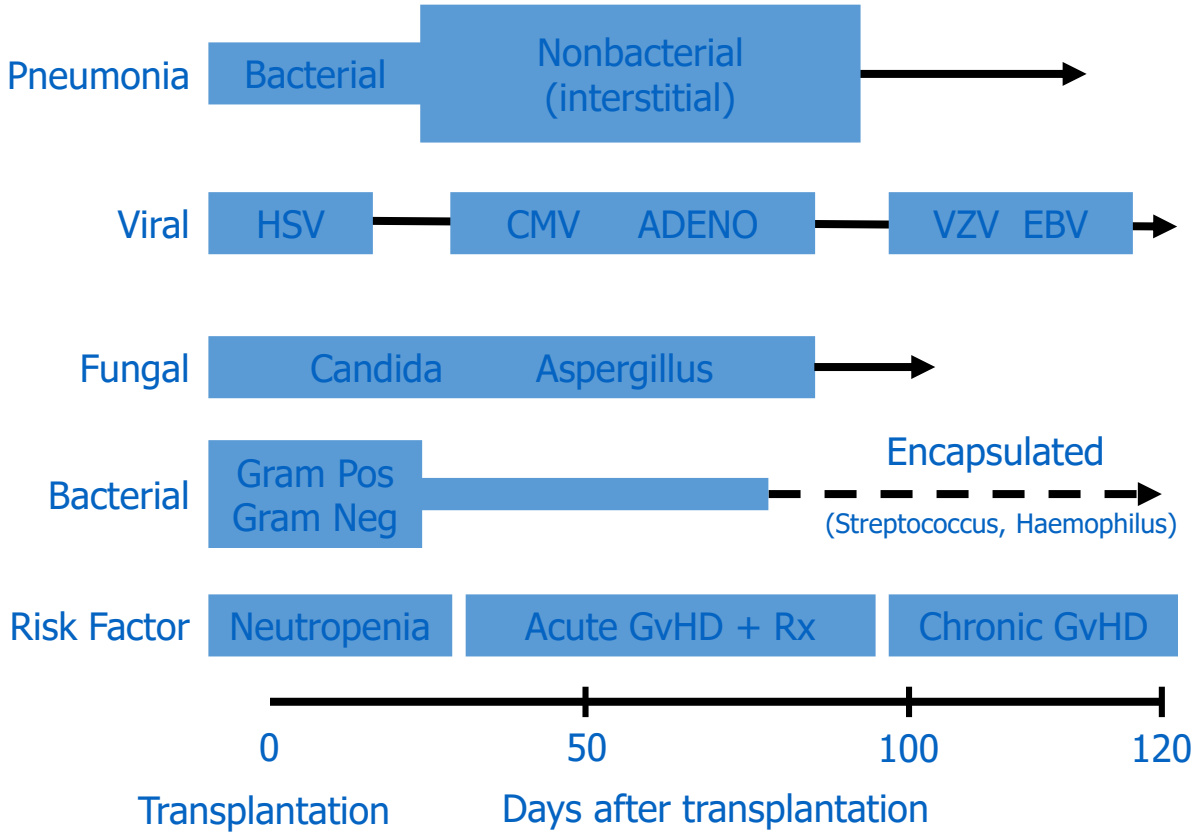
Supportive care during conditioning

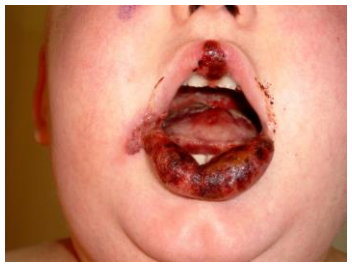
- Chemotherapy
  - Antiemetic prophylaxis
  - Mesna (if Cyclophosphamide)
  - Hyper-hydration
  - Forced diuresis
  - Anti-epileptic prophylaxis (if Busulfan)
  - BU dose adjustment
  - Enteral/parenteral nutrition
- TBI
  - Antiemetic prophylaxis
  - Hb concentration >100g/L
  - Anesthesia in younger children
  - Pain management

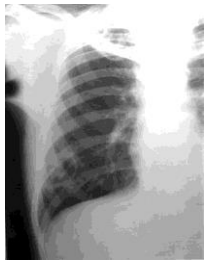
- Serotherapy (ATG)
  - Premedication – steroids, antihistamine, paracetamol
  - Infusion time (from 2 to 12 hours)
  - Careful monitoring of vital function in order to early detect anaphylaxis or infusion reactions (SIRS)
    - Fever, chills, erythema, dyspnea, oxygen desaturation, nausea/vomiting, diarrhea, abdominal pain, hyperkalemia, tachycardia, hypo- or hypertension, malaise, rash, urticaria, headache, arthralgia, myalgia (serum sickness, after 5–15 days from infusion), hepatic cytolysis, and even systemic anaphylaxis
  - Systemic Inflammatory Response Syndrome (SIRS) → CRS = cytokine release syndrome is a form of SIRS
    - Treatment with steroids, symptoms pronounce on the 1st day of serotherapy

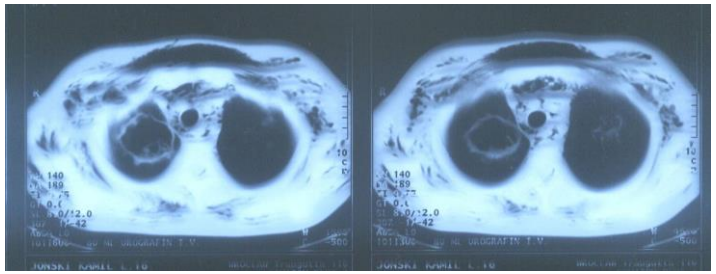
Infections following allogeneic SCT

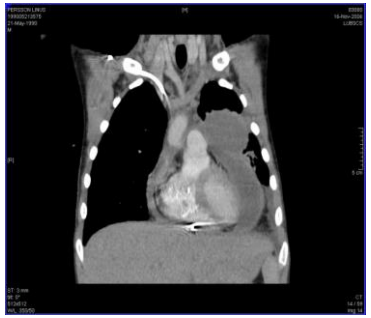
Allogeneic SCT continues to be associated with a profound humoral and cellular immune deficiency, predisposing patients to the development of opportunistic infections,

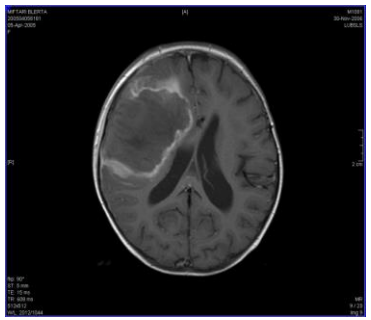












Infections following allogeneic SCT

- Transmission
  - Contact
    - Cl. difficile
    - MDR pathogens
    - EBV
    - Salmonella, Rotavirus, Norovirus
    - Blood transfusion related
      - CMV, hepatitis, malaria,
  - Droplet
    - Influenza
    - Respiratory viruses (RSV, AdV,)
  - Airborne
    - Pneumocystis jiroveci
    - TBC
    - Chickenpox
    - Measles
    - Generalized herpes zoster
    - Fungal infection
      - Aspergillus, Mucor,

- Endogenous pathogens
  - Bacterial
    - MDR – previous colonization,
    - Central line related
  - Fungal
    - Candida
    - Aspergillus
  - Viral
    - CMV
    - HZV, VZV
    - EBV
    - AdV

Prevention is better than cure

Standard precautions

- Proper hand hygiene
- Protective environment
- Single room
  - Ventilation with HEPA filters
  - positive air pressure
- Use of standard personal protective equipment
- Cleaning and disinfection protocols
  - (including those for shared equipment or toys and play areas in pediatric units)
- Safe injection practices
- Infection control practices for special procedures
  - (e.g. surgical masks for lumbar puncture)
- Prophylactic, empiric, preemptive medication
  - Acyclovir, Gancyclovir,
  - Trimetorim/Sulphametoxazole
  - Antifungal prophylaxis
  - Ciprofolxacin

Avoid high risk food

- Raw or undercooked meat, poultry, fish or shellfish
- Refrigerated smoked fish
- Unpasteurized milk
- Foods with raw or undercooked eggs
- Unwashed fruits and vegetables
- Raw sprouts
- Soft cheeses made from unpasteurized milk like brie, camembert and blue-veined andfresh cheese (can be eaten if cooked)
- Hot dogs, deli meats and luncheon meats that have not been reheated to steaming hot or to 75°C
- Unsafe water and ice made of it

Neutropenic fever

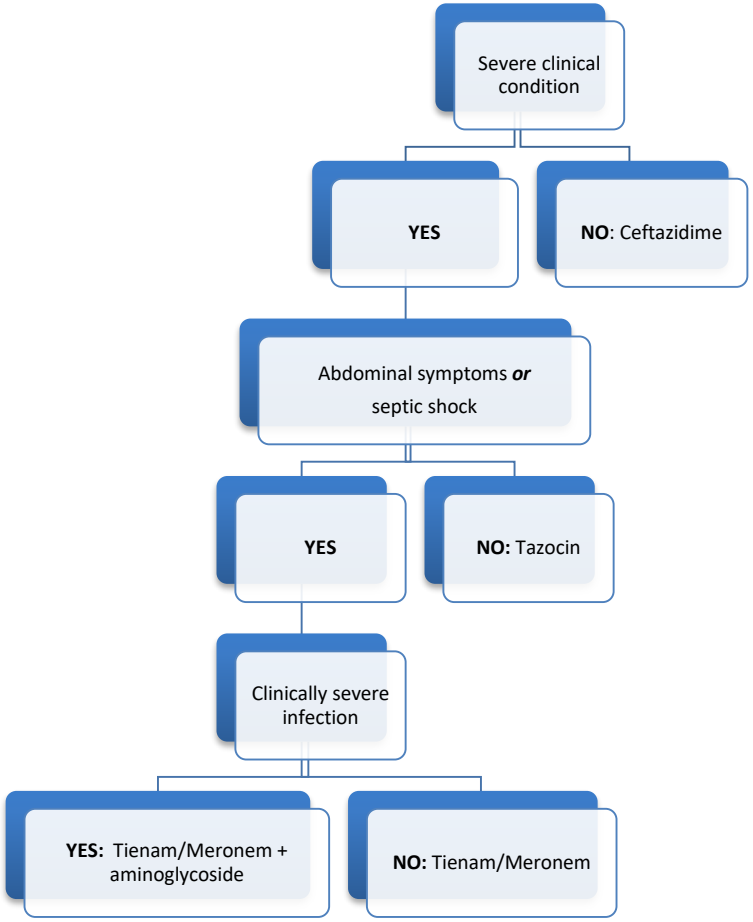
Fever is a highly unspecific sign of numerous causes

- Bacterial
- Viral infections
- Fungal infections
- Drug reactions (e.g. ATG)
- Transfusion reactions
- Mucositis
- Underlying disease
- Engraftment syndrome
- GvHD
- Cytokine release syndrome
- Rejection
- Hemophagocytosis

1. Aerobic & anaerobic blood culture x2
2. Clinical examination
    1. Central line
    2. Perineal pain
    3. Abdominal pain
    4. Respiratory tract symptoms
    5. Skin lesion
    6. Mucosal lesion
    7. CNS signs and symptoms
3. Microbiology test based on the anamnesis and previous history
    1. CMV, Clostridium galaktomannan, urine arabinitol, β-D-glucan, EBV
    2. Direct microscopy
4. X-ray, CT
5. Immediate start of empiric treatment

Empiric treatment of neutropenic feber

(Lund Pediatric Hematology/Oncology)



Doses for *i.v.* anibiotics

• Ceftazidime (Fortum®)	>2 mo	35mg /kg x 4	Max 1-2g x 4
• Piperacillin-tazobactam (Tazocin®)	≥2 yr	100mg/kg x 4	Max 4g x 4
• Imipenem-cilastatin (Tienam®)	>mo	25mg/kg x 4	Max 0,5 g x 4;
• Pseudomonas infection			Max 1g x 4.
• Meropenem (Meronem®)	≥3 mo	20mg/kg x 4	Max 1g x 4
• Trimetoprime-sulfa (Bactrim) vid PCP		5-6,6mg/kg x 3 (Trimetoprim)	
• Trimetoprim-sulfa (Bactrim) PCP-profylax		2,5mg/kg x 2 x II	
• Clindamycin (Dalacin®)	>1 mo	6-13mg/kg x3	Max 600mg x 3
• Gentamycin (Garamycin®)	>3 mo	8mg/kg x 1	
• Ciprofloxacin		10mg/kg x 2	Max 400mg x 2

Fever persistent over >72-96 hours after start of empiric antibiotics and negative blood culture

1. Reassessment
2. Chest X-ray, or better CT (HRCT)
3. Blood culture → fungal infection
4. (U-arabinitol, Galaktomannan, β-D-glucan)
5. Urine, faeces culture, NPX
6. Broad viral diagnostic if not done before
7. Consider use glycopeptides against Gram-positive strains (Vancomycin, 4x10mg/kg
   - Through level → 15 – 20 mg/L
8. Consider anti-fungal treatment (No Vfend i.v. if renal insufficiency)
   - Voriconazol (Vfend®), Caspofungin(Cancidas®) orAmbisome®
     - Candida → Cancidas®
     - Aspergillus → Vfend®
     - CNS FI → AmBisome®

Virus reactivation and treatment

Weekly virus screening (plasma, urine faeces – DNA, quantitative) for:

- Adenovirus
- Cytomegalovirus
- Ebstein-Barr virus
- BK virus – human polyoma virus (HPV)
- Herpes simplex och Varicella-Zoster – after indications
- Airways panel if clinical symptoms of infection

Donor recipient viral status is important in order of assessment risk for reactivation as well as choosing an appropriate prophylaxis strategy

Prophylaxis in risk patients, preemptive treatment, or treatment of overt infection:

- Acyclovir → HSV, VZV
- Valtrex → HSV, VZV
- Cymevene → CMV,
- Valcyte → CMV,
- Foscavir → CMV,
- Cidofovir → CMV, AdV, BK
- Brincidofovir → CMV, AdV
- Famciclovir → CMV, HSV, VZV
- Ribavirine → RSV, AdV
- Oseltamivir (Tamiflu) → Influenza
- Rituximab → EBV (PTLD)
- Reduction/withdrawal of immunosuppression
- IVIG
- Virus specific T lymphocytes

Graft versus Host Disease

- The major cause of short-term mortality after allo-HSCT
- Pathophysiology
  - Tissue damage caused by conditioning
  - Activation of host antigen presenting cells
  - Activation and proliferation of donor T cells
  - Cytotoxic cell damage and release of inflammatory cytokines (IL-1, TNF-alfa) causing tissue necrosis

Classification	Day after SCT	Features of acute GvHD	Features of chronic GvHD
Acute GvHD			
Classic acute Persistent, recurrent, or late onset	<100 days >100 days	YES YES	NO NO
Chronic GvHD			
Classic chronic Overlap syndrome	No time limit No time limit	NO YES	YES YES

Manifestations of acute GvHD

SKIN

Erythematous maculopapular rash, often initially involving the palms, and soles. May progress to involve the entire body surface and may be pruritic and/or painful

LIVER

Cholestasis with or without frank jaundice

Cholestatic enzymes comparatively more deranged than transaminases

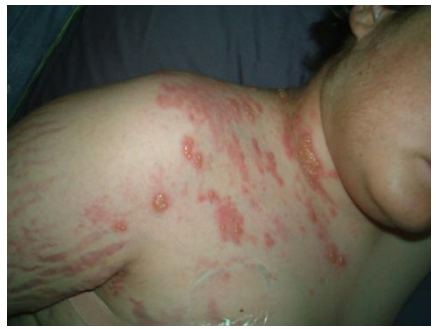
Gastrointestinal tract

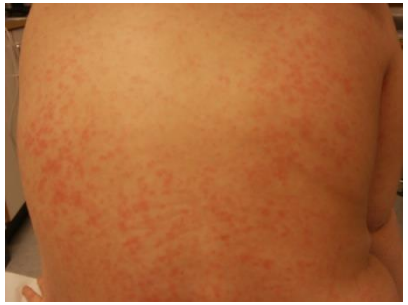
Upper

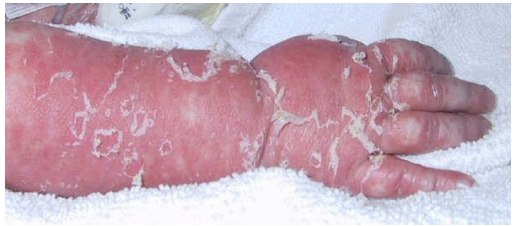
Anorexia, nausea, and vomiting

Lower

Diarrhea, typically green and watery; in severe case diarrhea contains fresh blood and mucosa and is accompanied by abdominal cramps and, on occasion, paralytic ileus







GvHD prophylaxis – prevention is better than cure

- Gold standard - combination of calcineurine inhibitor (Cyclosporine A or Tacrolimus) and Methotrexate after MAC (myeloablative conditioning)
- Cyclosporine A ± Mycofenolat mofetil (CellCept) after RIC (reduced intensity conditioning
- Serotherapy with ATG after unrelated transplants
- T-cell depletion in vitro in haploidentical setting
- Post-transplant Cyclophosphamide in haploidentical setting

	Cyclosporine	Methotrexate
Drug posology	3 mg/kg/day IV till engraftment Then orally	15 mg/m^2 day +1 10 mg/m^2 day +3, +6, +11
Adjusting dose	Target dose to 150–200 ng/mL; adjust to renal function	Day 11 may be omitted if grade III/IV mucositis
Interaction	Numerous; ++ with azoles	
Secondary effects	Numerous: Renal insufficiency, CNS, and endothelial toxicities	Mucositis

Acute GvHD staging and grading

Stage	Skin	Liver (based on bilirubin)	GI* children	GI adults
0	No rash	<34 µMol/L	Diarrhea < 10mL/kg/day	
1	Maculopapular rash on <25% of surface	34-50 µMol/L	Diarrhea >10 - ≤15mL/kg/day or persistent nausea, vomiting, or anorexia with positive pathology (biopsy)	500–1000 mL
2	Maculopapular rash on 25-50% of surface	51-102 uMol/L	Diarrhea >16 - ≤20mL/kg/day	1001–1500 mL
3	Generalized erythroderma	103-255 µMol/L	Diarrhea >21 - ≤25mL/kg/day	>1500 mL
4	Generalized erythroderma with bullae and desquamation	>255 µMol/L	Diarrhea >26mL/kg/day Blood per rectum, abdominal pain, ev. ileus	Severe abdominal pain with and without ileus

* For children over 40kg bw use criteria for adults

Grade	Skin- stage	Liver - stage		GI- stage	Decrease in clinical performance
I	1 to 2	0		0	no
II	1 to 3	1	and/or	1	mild
III	2 to 3	2 to 3	and/or	2 to 3	marked
IV	2 to 4	2 to 4	and/or	2 to 3	extreme

eGVHD

The eGVHD app is developed by the **UZ Leuven** (Belgium) in collaboration with the **EBMT** (European Bone Marrow Transplantation Society) Transplantation Complications Working Party and the **National Institute of Health** (Bethesda, USA).

It is an electronic tool designed as an algorithm-driven application, to help clinicians apply the internationally recognized criteria for the assessment of graft versus host disease (GVHD), a pleiotropic disease affecting allogeneic stem cell transplantation recipients when their transplanted stem cells react against their own body.

GET IT ON Google Play Available on the App Store

This app is not a medical tool aiming at replacing the diagnosis of a clinician, but **a user-friendly educational tool**. It helps health care professionals improve their ability to diagnose and score the severity of GVHD by showing the user **differential information** and **making an automatic summary** of what has been filled in.

The eGVHD app has been developed according to a human centered design, to ensure optimal usability. It offers several features:

1. An interface to give health care professionals assistance with diagnosing GVHD (making the difference between classic acute, late acute, classic chronic and overlap chronic GVHD), including optional fields reserved for research use
2. An interface to give health care professionals assistance with scoring acute GVHD (three organs involved), including optional fields reserved for research use
3. An interface give health care professionals assistance with scoring chronic GVHD (eight organs

aGvHD treatment guidelines

- Grade I
  - Consider topical treatment with steroids alone
  - If persistent/exaggerating a short systemic treatment with maximal dose of 1mg/kg/day prednisolone with subsequent tapering with response might be considered.
- Grade II
  - Has to be treated in most of the cases, prednisolone p.o. or methylprednisolone i.v. 1-2 mg/kg/day bid, with subsequent tapering over 4-5 days with response.
- Grade III –IV
  - Has to be treated with methylprednisolone i.v. 1-2 mg/kg/day bid, with subsequent tapering over 4-5 days with response.

Additionally with Grade II-IV CNI (cyclosporine A) dose has to be escalated up to the maximum tolerated concentration.

With GI aGvHD additional treatment with budesonid (Entocort, Cortiment) p.o. 9mg/dose/day can be considered.

Treatment of steroid resistant aGvHD

Definition →

- progression of symptoms after 3 days of steroid treatment OR
- no improvement after 5-7 day steroid treatment OR
- no remission after 14 days of full dose steroid treatment

Treatment →

Empiric, drugs registered for this indication, institutional guidelines

MMF (CellCept) 30mg/kg/day and/or infliximab (Remicade) 5mg/kg once per week until response

OR ruxolitinib (Jakavi) 5 mg bid p.o. OR vedolizumab (Entyvio) 300mg i.v.

Alemtuzumab; ATG; Pentostatin; Ibrutinib; mesenchymal stem cells; ECP

Important!!

- reduction of steroid dose down to max. 1mgh/kg/day
- increased risk for infections and necessary prophylaxis against gram-negative bacteria, HSV/VZV, pneumocystis angd fungal infection

Chronic GvHD

<u>cGvHD is the most relevant cause of late non-relapse morbidity and subsequent mortality</u>

- Lower incidence in children 20 -40 %
- Onset 3 months up to 2 years after SCT
- Can imitate almost any autoimmune disease
- Pathophysiology related to impaired immune tolerance
  - Both auto- & allo-reactive donor deriver T and B lymphocytes involeved
  - Characterized by chronic inflammation, scare formation and fibrosis
- Increased incidence when HLA mismatch, PBSC a graft source, older patients, history and severity of preceding acute GvHD
- Mild cGvHD → protective effect towards relapse
- Long-term mortality of pateints with cGvHD up to 50 % especially when
  - Low PLT counts at the diagnosis of cGvHD
  - Direct progression from acute to chronic GvHD
  - Organ manifestation as lung, GI and cholestatic liver involvement
  - Non-malignant underlying disease in children

Clinical manifestations of cGvHD

- Skin
- Eyes
- Oral mucosa
- Liver
- Gastrointestinal tract
- Genitals
- Lung
- Joints and fasciae
- Other

Overall severity	Mild	Moderate	Severe
Number of organs involved	1-2	≥ 3	≥ 3
Severity of involved organs	Mild (excluding lung)	Mild–moderate (lung only mild)	Severe (lung moderate or severe)

First line treatment cGvHD

- Skin
- Eyes
- Oral mucosa
- Liver
- Gastrointestinal tract
- Genitals
- Lung
- Joints and fasciae
- Other

Drug	Recommendation		Side effects In 25 % pts	Response rate	Comments
	Grad	Evidence			
Steroids	A	I	Osteoporosis, osteonecrosis, diabetes mellitus	~30–50% CR	Main drug; strategies to reduce use due to SEs very important
CNI + steroids	C-1	II	Renal toxicity, hypertension	~30–50% CR	Reduces steroid use, reduced incidence of osteonecrosis
Rituximab + steroids/CNI	C-1	III [12]	Increased risk for late infectious complications	~75%	Randomized data are lacking
MMF + CNI/ steroids	D	II	GI complaints, infections		No increased efficacy compared to CNI and steroids, increased risk of relapse of malignancy
Azathioprine	D	II	Cytopenia, risk of infection		Increased mortality
Thalidomide	D	II	Neurotoxicity, drowsiness, constipation		Very little effect in first-line therapy

A: should always be used;
C-1: use in first-line therapy justified,
D: moderate evidence of lack of efficacy or unacceptably high risks, should generally not be offered

I: evidence from ≥1 properly randomized, controlled trials,
II: evidence from more than one well-planned non-randomized clinical trial, from cohort or case-controlled, analytic studies (preferably at several sites),
III-1: only one non-controlled study,
III-2: only one retrospective, non-controlled study or retrospective evaluation.

(Evidence and recommendations graded according tothe 2005 NIH Consensus)
SE side effect,
NIH US National Institutes of Health,
MMF mycophenolate mofetil

First line treatment cGvHD – specific issues

- Side effects of long term steroid therapy in children → consider topical drugs
  - Growth, bone density, osteonecrosis, organ development, hormonal dysfunction, diabetes
- cGvHD is by definition an immuno-deficient condition intensified by immunosuppressive treatment
- Increased risk for severe (systemic) infections
  - Viral reactivation - CMV, AdV, EBV
  - Fungal infection – aspergillosis, candida
- Functional asplenia with higher risk for pneumococcal sepsis – prophylaxis with penicillin, vaccination
- Revaccination with inactivated polyvalent vaccines
- No live vaccines
- IVIG replacement if IgG <400mg/dL or recurrent infections

Second line treatment cGvHD

Drug	Recommendation		Response rate	Side effects in >25% of patients	Comments
	Grade	Evidence			
Steroids	B	III-1	n.a.	Osteoporosis, osteonecrosis, diabetes mellitus	Main drug, strategies to reduce use due to SEs very important
Ibrutinib	C-1	III-1	~50–75% ~16–25% CR	Bruising, diarrhea, infections	FDA approved in second-line treatment of cGVHD
Photophereses	C-1	II	~60–70% ~30% CR	Infections of the CVC (if applicable)	Venous access required, steroid-saving effect, good tolerability
mTOR-inh (sirolimus, everolimus)	C-1	III-1	~60% ~20% CR	TMA, hyperlipidemia, cytopenia	Increased risk of TMA when combined with CNI, regular blood levels required
MMF	C-1	III-1	~50% ~10% CR	GI SEs, risk of infection (viral) and increased risk of relapse	Steroid sparing activity
CNI	C-1	III-1	n.a.	Renal toxicity, hypertension	Reduces steroid use, regular blood levels required
MTX	C-2	III-1	~50% ~10–20% CR	Cytopenia	Best results in mucocutaneous cGVHD, reduces steroid use, contraindicated in the presence of pleural effusions or ascites
IL-2	C-2	III-1	~65% (only PR)	Fever, malaise, and fatigue	Applied in sclerodermoid skin disease
Ruxolitinib	C-2	III-1	n.a. (retrospective analysis)	Increased risk for viral reactivation, bacterial infection, hepatotoxicity	Prospective data pending
Bortezomib	C-2	III-1	n.a. for second-line Tx	Cytopenia, neuropathy	Trial was performed in first-line treatment
High-dose steroids	C-2	III-2	50–75% (only PR)	Infections	Rapid control of cGVHD
Total nodal irradiation	C-2	III-2	~50% ~25% CR	Cytopenia	Best results for fasciitis and mucocutaneous cGVHD
Hydroxychloroquine	C-2	III-2	~25% ~10% CR	GI side effects	Best results for mucocutaneous and hepatic cGVHD
Pentostatin	C-2	II	~50% ~10% CR	Cytopenia, risk of infection	Best results in children
Rituximab	C-2	II	~50% ~10% CR	Risk of infection	Effective in manifestations associated with autoAb and sclerodermoid cutaneous involvement
Imatinib	C-2	III-1	~50% ~20% CR	Fluid retention	Efficacy demonstrated mainly in sclerodermoid cGVHD and bronchiolitis obliterans
Thalidomide	C-3	II	~20–30% (only PR)	Neurotoxicity, drowsiness, constipation	Treatment for simultaneous cGVHD and recurrent multiple myeloma
Azathioprine	C-3	III-1	n.a.	Cytopenia, risk of infection, secondary malignancies	Increased risk of malignant disease of the oral mucosa
Retinoids	C-3	III-2	~60% (only PR)	Skin toxicity, hyperlipidemia	Effective in sclerodermoid cutaneous involvement
Abatacept	C-3	III-2	~40%		Effective in mucocutaneous and pulmonary involvement
Regulatory T cells	C-4				Currently explored in several clinical trials
Mesenchymal stem cells	C-4	III-2	n.a.		Repetitive application required
Alemtuzumab	C-4	III-3	n.a.	Infectious risks	Last resort for refractory cGVHD
Etanercept	C-4	III-3	n.a.	Infectious risks	May be used to treat mixed acute and chronic GVHD or pulmonary or GI manifestations of cGVHD

Adapted from Wolff et al. (2011), B: should generally be used, C-1: use in second-line therapy justified, C-2: use after failure of second-line therapy justified, C-3: should only be used in specific circumstances, due to unfavorable risk profile, C-4: experimental, should only be used in clinical trials and individual cases, II: evidence from >1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferable from >1 center) or from multiple time series, III-1: several reports from retrospective evaluations or small uncontrolled clinical trials, III-2: only one report from small uncontrolled clinical trial or retrospective evaluations, III-3: only case reports available, SE: side effect, n.a.: not available

- No consensus
- Second-line therapy mostly is based on phase II trials, and retrospective analyses
- No more than three IS agents should be combined,
- No predictors of response for a single agent in individual patients are yet available,

SOS/VOD

- SOS/VOD is an unpredictable and potentially life-threatening complication
- injury to both sinusoidal endothelial cells and hepatocytes triggered by
  - toxicity of the conditioning regimen
  - release of cytokines due to inflammation and engraftment
  - release of endotoxins
  - phenomena of alloreactivity
  - protein C anticoagulant pathway abnormalities
  - use of calcineurin inhibitors.
  - use of monoclonal antibodies tagged with calicheamicin derivatives
    - gemtuzumab ozogamicin
    - inotuzumab ozogamicin
- triggers of SOS/VOD and onset can occur after Ab administration

SOS/VOD risk factors

- Conditioning known to be toxic to the endothelium
  - high-dose busulfan,
  - single-fraction or high-dose fractionated (⩾12 Gray) TBI-based conventional MAC,
  - Combination of busulfan and cyclophosphamide and/or melfalan
  - Infants
  - Pediatric/genetic diseases with incidences above average
  - Previous incidents of hepatotoxicity
  - Irradiation towards abdomen/right flank prior to SCT

Table 2. EBMT diagnostic criteria for hepatic SOS/VOD in children

- No limitation for time of onset of SOS/VOD

The presence of two or more of the following[a]

- Unexplained consumptive and transfusion-refractory thrombocytopenia[b]
- Otherwise unexplained weight gain on three consecutive days despite the use of diuretics or a weight gain >5% above baseline value
- [c]Hepatomegaly (best if confirmed by imaging) above baseline value
- [c]Ascites (best if confirmed by imaging) above baseline value
- Rising bilirubin from a baseline value on 3 consecutive days or bilirubin ⩾2 mg/dL within 72 h

Abbreviations: CT = computed tomography; HCT = hematopoietic cell transplantation; MRI = magnetic resonance imaging; SOS/VOD = sinusoidal obstruction syndrome/veno-occlusive disease; US = ultrasonography. [a]With the exclusion of other potential differential diagnoses. [b]⩾1 weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines. [c]Suggested: imaging (US, CT or MRI) immediately before HCT to determine baseline value for both hepatomegaly and ascites.

Table 3. EBMT criteria for grading the severity of suspected hepatic SOS/VOD in children[a]

CTCAE	*Mild*	*Moderate*	*Severe*	*Very severe MOD/MOF*
	1	*2*	*3*	*4*
LFT[b] (ALT, AST, GLDH)	⩽2×normal	>2 and ⩽5×normal	>5	
Persistent RT[b]	<3 days	3–7 days	>7 days	
Bilirubin (mg/dL)[b, c]	<2		⩾2	
Bilirubin (μmol/L)	<34		⩾34	
Ascites[b]	Minimal	Moderate	Necessity for paracentesis (external drainage)	
Bilirubin kinetics				Doubling within 48 h
Coagulation	Normal	Normal	Impaired coagulation	Impaired coagulation with need for replacement of coagulation factors
Renal function GFR (mL/min)	89–60	59–30	29–15	<15 (renal failure)
Pulmonary function (oxygen requirement)	<2 L/min	>2 L/min	Invasive pulmonary ventilation (including CPAP)	
CNS	Normal	Normal	Normal	New onset cognitive impairment

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; CNS = central nervous system; CPAP = continuous positive airway pressure; CTCAE = Common Terminology Criteria for Adverse Events; GFR = glomerular filtration rate; GLDH = glutamate dehydrogenase; LFT = liver function test; MOD/MOF = multi-organ dysfunction/multi-organ failure; RT = refractory thrombocytopenia; SOS/VOD, sinusoidal obstruction syndrome/veno-occlusive disease. [a]If patient fulfills criteria in different categories they must be classified in the most severe category. In addition, the kinetics of the evolution of cumulative symptoms within 48 h predicts severe disease. [b]Presence of ⩾2 of these criteria qualifies for an upgrade to CTCAE level 4 (very severe SOS/VOD). [c]Excluding pre-existent hyperbilirubinemia due to primary disease.

SOS/VOD prophylaxis

- Ursodeoxycholic acid (UDCA) prophylaxis - 12 mg/kg daily, divided in two doses, started from the day preceding the preparative regimen and continued for the first three months of transplantation

- Defibrotide in high risk children
    - From conditioning start until day +30
    - 25mg/kg/day divided into 4 doses (6.25mg/kg/dose)

- High risk of developing SOS/VOD
    - Pre-existing hepatic disease (elevated serum aspartate aminotransferase, AST)
    - Second myeloablative transplant
    - Allogeneic transplant for leukemia beyond second relapse
    - Conditioning with busulfan-containing regimen
    - Prior treatment with gemtuzumab ozogamicin
    - Diagnosis of primary hemophagocytic lymphohistiocytosis, adrenoleukodystrophy, or osteopetrosis

SOS/VOD treatment - supportive care

- Euvolemia
  - Daily weights and measures of fluid intake and output are critical to maintaining euvolemia. Fluid restriction and diuresis should be initiated when intake exceeds output. A reasonable weight goal would be -2 percent to 5 percent from baseline by the day of stem cell infusion
- Natrium restriction
- Minimizing exposure to hepatotoxic agents
- Pain control – may require narcotics
- Paracentesis – Patients may require serial paracentesis for ascites that is associated with discomfort or pulmonary compromise. The amount of fluid removed at each session should be limited to maintain renal perfusion
- Avoid lipids in TPN

SOS/VOD treatment - DEFIBROTIDE

- For patients with severe SOS (e.g. with pulmonary and renal dysfunction)
- From the onset of SOS
- 25mg/kg/day divided into 4 doses (6.25mg/kg/dose)
- For a minimum 21 days
- If SOS not resolved treatment is continues until resolution
- Expensive approach
- Toxicities
  - Hypotension
  - Diarrhea
  - Nausea/vomiting
  - Epistaxis
  - Contraindicated in children with significant bleeding
  - Defibrotide should be discontinued at least 2 hours prior to invasive procedures
  - Defibrotide should be permanently discontinued in case of life-threatening hypersensitivity reaction

Transfusion support

- RBC
  - 8g/dL
- Platelets
  - ≤$10x10^9$/L – non-bleeding, non-febrile
  - ≤$10x10^9$/L – otherwise
  - Platelets refractoriness
    - Immune mediated (anti-HLA ab
    - Non-immune mediated
      - Fever
      - Sepsis
      - DIC
      - VOD/SOS
      - GvHD
      - ATG treatment
      - Heparin induced
      - Splenomegaly
- Granulocytes
- Plasma

- All transplanted children should receive leukocyte depleted and irradiated RC and PT
  - Risk for febrile reactions
  - Risk for allo-immunization
  - Risk for CMV transmission
  - Risk for transfusion associated aGVHD
  - Additionally granulocyte concentrates must be also irradiated
- Additionally patients receiving lymphodepleting agents (Fludarabine, Clofarabine) shouls receive irradiated blood products prior to transplantation
- Duration of the use of irradiated blood products
  - No clear guidelines
  - Start with conditioning
  - Until 6 months after transplantation
  - Or until immuno-reconstitution
  - As long as ongoing immunosuppression

RBC, platelet, and plasma transfusion support

for patients undergoing ABO-incompatible SCT

			Phase I[c]	Phase II & Phase III[c]				
				RBC	Platelets		Plasma	
ABO incompatibility	Recipient	Donor	All products	Choice [a]	First choice	Second choice [a]	First choice	Second choice
Major	0	A	Recipient	0	A	AB, B, 0	A	AB
	0	B	Recipient	0	B	AB, A, 0	B	AB
	0	AB	Recipient	0	AB	A, B, 0	AB	-
	A	AB	Recipient	A, 0	AB	A, B, 0	AB	-
	B	AB	Recipient	B, 0	AB	B, A, 0	AB	-
Minor	A	0	Recipient	0	A[b]	AB, B, 0	A	AB
	B	0	Recipient	0	B[b]	AB, A, 0	B	AB
	AB	0	Recipient	0	AB [b]	A, B, 0	AB	-
	AB	A	Recipient	A, 0	AB [b]	A, B, 0	AB	-
	AB	B	Recipient	B, 0	AB [b]	B, A, 0	AB	-
Bidirectional	A	B	Recipient	0	AB	B, A, 0	AB	-
	B	A	Recipient	0	AB	A, B, 0	AB	-

- not applicable

[a] choices are listed in the order of preference

[b] for practical reasons, the use of donor type platelets might be defined as first choice, in phase III, i.e., after complete engraftment

[c] phase I until preparative regimen, phase II until complete engraftment, phase III after complete engraftment.

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Nutritional support – general considerations

- There is high risk for malnutrition upon HSCT treatment
- Malnutrition is an independent risk factor
- The potential benefit of all nutritional interventions remains largely unproven
- Oral and enteral nutritional support is recommended over parenteral support in case of functioning gastrointestinal tract
- A minimal oral or enteral food intake is beneficial for recovery of mucosa and microbiome
- Neutropenic diets did not show a benefit over safe food handling approaches
- Acute and chronic GvHD
- Infections – viral, bacterial (Cl. difficile)

Recommendation for nutritional support

Screening for malnutrition	
Indication	All patients to estimate risk for pre-existing malnutrition
Tools	NRS 2002
Nutritional support	
General management	1. Early involvement of dietitians 2. Consider placement of nasogastric tube on day +1 3. Standardized monitoring of nutritional intake 4. Nutritional reassessment every 3 days using the NRS 2002
Indication of intervention	1. Oral intake <60% for 3 days consecutively 2. Consider nutritional support in all patients with preexisting malnutrition and/or BMI < 18
Discontinuation	Oral intake >50% for 3 days consecutively
Estimation of caloric needs	According to Harris Benedict formula (ideal body weight) OR BASA-ROT table/(25–30 kcal/kg ideal body weight)
Route of nutritional support	1. Intensification of oral nutrition 2. Enteral nutrition 3. Parenteral nutrition

https://www.mdcalc.com/nutrition-risk-screening-2002-nrs-2002

Recommendation for nutritional support

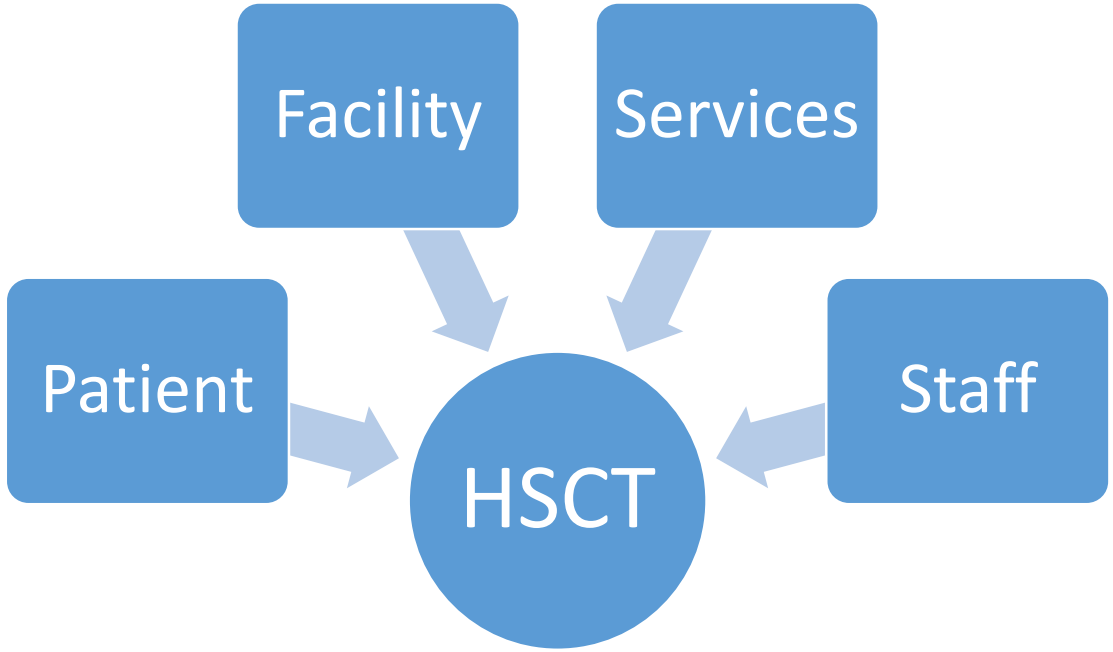
Forms of nutritional support	
Intensified oral nutrition	***Indication***: Malnutrition or underweight (BMI < 18 kg/m2) and preserved oral intake ***Options***: Additional snacks rich in proteins and energy, protein or calorie enrichment of main courses, additional protein and energy drinks (ONS) ***Standardized supplementation***: None
Enteral nutrition	***Indication***: If nutritional goals cannot be reached by oral support alone ***Standardized*** *supplementation:* Vitamin K once weekly
Parenteral nutrition	***Indication***: If nutritional goals cannot be reached in patients with gastrointestinal failure and/or intolerance for NGT ***Standardized supplementation:*** Lipid-soluble vitamins (ADEK), Water-soluble vitamins, Trace elements
Vitamin and trace elements	Multivitamin generally recommended Vitamin D: Supplementation recommended (Bolus of 40000E at admission, maintenance therapy with 1500E orally per day Other vitamins or trace elements if overt deficiency

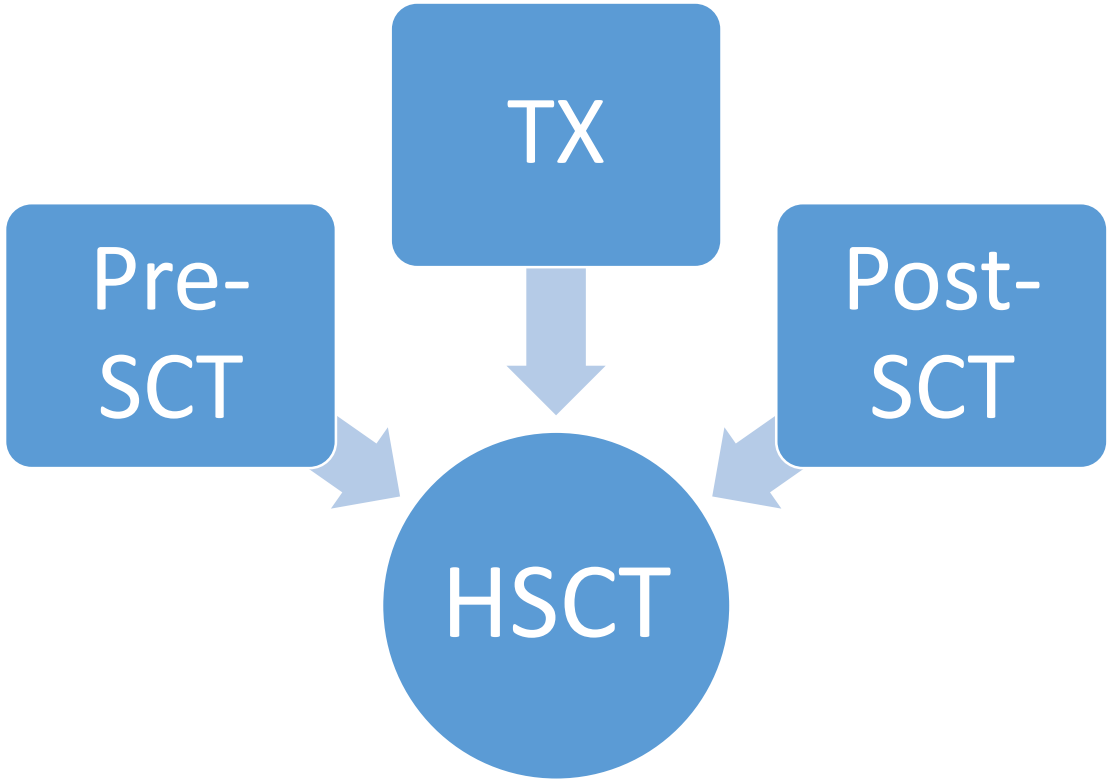
https://www.mdcalc.com/nutrition-risk-screening-2002-nrs-2002

Life-threatening acute symptoms that require immediate action

- Infection
  - Fever >38,5°C
  - Impaired general condition
  - Respiratory/circulatory dysfunction
  - Suspected septicemia
- Seizures and other neurological symptoms
  - Often related to Cyclosporine and concomitant use of steroids
  - Inclusive convulsive status epilepticus
  - Malignant hypertonia
  - Electrolyte imbalance
- Bleeding
  - Generalized bleeding
  - Intracranial bleeding
- Renal dysfunction

HSCT – complex and complicated ~~procedure~~ process





Thank your for your attention

Tack för uppmärksamheten

از توجه شما متشکرم