

HEMATOLOGY/ONCOLOGY

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) TEACHING POINTS

Epidemiology

1. Leukemia accounts for ~31% of all childhood cancer occurring before age 15 years and about 25% of that which occurs before 20 years of age
2. Overall, ALL comprises about 75% of childhood leukemia cases
3. 3250 cases (2400 ALL) of leukemia/yr in US before age 20
4. ALL incidence peaks at 2-3 years of age in developed countries, with rate of 80 new cases/million, decreasing to 20/million at age 10 years
5. The incidence in whites is almost twice as large as that in blacks
6. There has been a modest increase in the incidence of ALL over the past 20 years
7. Little is known about the causes, but there appears to be little role of classic genetic predisposition, lifestyle factors such as diet or environmental exposures such as electric power lines

Presenting Symptoms

1. Major symptoms are those caused by bone marrow failure due to replacement of normal marrow elements with leukemia cells: pallor and fatigue (anemia); bruising, petechiae and bleeding (thrombocytopenia); and infection (neutropenia).
2. Other symptoms are due to extramedullary proliferation in lymphatic organs and include adenopathy, hepatomegaly, splenomegaly, and mediastinal masses due to thymic expansion (T-cell ALL)
3. Bone pain (general irritability in younger children) is common due to expansion of the marrow cavity
4. Fever is relatively common and is usually not due to infection and often resolves within days of beginning therapy
5. About 5% of patients have CNS involvement at diagnosis, which is most often asymptomatic. However, can have symptoms due to CSF pleocytosis (headache, neck stiffness, irritability, vomiting) and/or signs of increased intracranial pressure. Cranial nerve palsies are occasionally observed.
6. Boys can have testicular involvement (always examine testicles!)
7. Less common sites of involvement include the eye and ovaries

Diagnosis and initial evaluation

1. Differential diagnosis includes non-malignant (JRA, mononucleosis or other viral infection, ITP, pertussis/parapertussis, aplastic anemia) and malignant (lymphoma, small round blue cell tumors such as neuroblastoma, Ewing's sarcoma, etc.) disorders
2. Initial evaluation should include a careful history and PE that specifically addresses areas outlined above.
3. Laboratory evaluation should include tests needed to establish the diagnosis and define the extent of involvement: CBC with review of peripheral smear, bone marrow aspirate +/- biopsy (morphology, immunophenotype, cytogenetics, molecular genetics), LP, Chest X-ray to exclude mediastinal mass (must do prior to any general anesthesia!).
4. In addition, need to define other problems that may be present including screens for metabolic abnormalities: lytes, BUN, Cr, Ca, Mg, Phos, uric acid.
5. If febrile, culture and treat empirically with broad spectrum IV antibiotics

Detailed characterization of leukemia

1. Bone marrow morphology: ALL blasts are typically smaller than those seen in AML and do not have cytoplasmic granules. They may have cytoplasmic vacuolization (L3 morphology) and/or membrane blebbing. Cytochemical stains show +PAS, negative for myeloperoxidase
2. Leukemias must be characterized by flow cytometry to define the pattern of surface and cytoplasmic antigen expression. ALL cells are of either B- (80-85%) or T-cell (15%) lineage. Most B-lineage ALLs are derived from early precursors that can be characterized as pro-B or pre-pre-B (prior to expression of cytoplasmic immunoglobulin) or pre-B (cIg+ but no surface Ig). Mature B-cell ALL (sIg+) is quite rare and treated differently.

Most B-precursor ALLs express CD22, CD10 (common ALL antigen or CALLA), CD19, HLA-DR and TdT. T-cell ALLs, by definition, express cytoplasmic CD3 (cCD3) and most also express surface CD3 (sCD3).

3. Cytogenetics are performed to identify common non-random abnormalities that may have prognostic significance. Some of these abnormalities can also be identified by specific molecular screening tests.

Genetics of ALL

1. At least 75-80% of ALLs have identified cytogenetic abnormalities. These reflect underlying genetic changes involved in disease pathogenesis. They are somatic mutations, not germline defects so they are not present in normal cells and disappear when remission is achieved.

2. Non-random chromosome translocations (exchanges of genetic material between chromosomes) are common in ALL and define specific subtypes of disease. These commonly create fusion genes and proteins, or cause dysregulated expression of an intact protein by fusion with an immunoglobulin or T-cell receptor locus. Those with important prognostic significance include the t(12;21) and TEL-AML1 fusion (excellent prognosis) and t(9;22) or Philadelphia chromosome and BCR-ABL fusion (dismal prognosis).

3. Another common abnormality in childhood ALL is hyperdiploidy with an increased number of chromosomes in the malignant cells. These duplications are non-random, but their pathogenesis is unknown. Hyperdiploidy and trisomy of specific chromosomes (4, 10 and 17) is associated with an excellent prognosis.

4. In contrast, hypodiploidy with chromosome number <45 is associated with a poor prognosis, with an especially bad prognosis for cases that are near haploid

Prognostic Factors

1. See above re genetic factors

2. Age and initial white blood count (WBC) are powerful predictors of outcome in all studies. Best prognosis with age 3-5 years and low WBC. Consensus (NCI/Rome) definition of risk groups for B-precursor ALL is standard (age 1.00-9.99 yrs, WBC <50,000) and high (all others with age >10 years and/or WBC >50,000). Infant (<1 year old) ALL is biologically and clinically distinct and is usually treated differently.

3. T-cell ALL is treated differently than B-precursor ALL by some, but not all, groups. T-cell ALL is associated with other adverse features (age, WBC) and may also respond differently to certain chemotherapy agents.

4. CNS disease at diagnosis requires specific therapy changes (cranial irradiation and more intensive intrathecal chemotherapy)

5. Mature B-cell (sIg+) ALL is rare (<1%) and treated very differently

6. Overall, girls fare better than boys and have more complications. Suggests differences may be due to altered metabolism of chemotherapy agents.

Treatment

1. As recently as the early 1960s, childhood ALL was incurable. Since then cure rates have steadily improved such that 80-85% of children with ALL are cured today

2. Advances have been due to optimization of multiagent chemotherapy regimens, particularly in large clinical trials by cooperative groups. Over 80% of US children with ALL are treated on clinical trials.

3. One major advance in late 60s/early 70s was the recognition of the CNS as a sanctuary site. When chemotherapy first resulted in sustained remissions, more than 50% of patients had isolated CNS relapsed because many chemotherapy agents have poor CNS penetration. This led to inclusion of presymptomatic CNS therapy into all treatment regimens. Initially, this was craniospinal irradiation. Now, the vast majority of children with ALL are treated with intrathecal chemotherapy without CNS irradiation.

4. First phase of therapy is remission induction, which generally last 4 weeks and includes 3 or 4 drugs (steroid, Vincristine, Asparaginase +/- anthracycline). With contemporary therapy, 98-99% of patients enter complete remission (CR) at end of induction. CR is defined as <5% marrow blasts by standard morphology, normalization of blood counts, and disappearance of extramedullary leukemia.

5. All therapies now include various types of post-induction consolidation or intensification regimens, CNS prophylaxis, and prolonged low intensity maintenance chemotherapy. Total duration of therapy is 2-3 years.

6. Today, most therapy is stratified on the basis of clinical and biological risk factors, with more intensive therapy for patients at higher risk. This model has defined the paradigm for modern combination chemotherapy regimens.

7. If relapse occurs, chance of salvage depends on various factors. One of strongest is the time of relapse following initial diagnosis (the sooner one relapses, the lower the chance of salvage). Relapse regimens are often much more intensive and frequently include stem cell transplantation.

Long term outlook and sequelae

1. Vast majority of patients who are cured go on to lead normal healthy lives with few serious long term morbidities
2. Risk of 2nd cancers in survivors is somewhat higher than background, and dependent on specifics of initial therapy (much higher risk of brain tumors if got CNS irradiation)
3. No appreciable increased risk of leukemia or other tumors in offspring of those cured of childhood ALL
4. No increased risk of birth defects in offspring of those cured of childhood ALL
5. Important to monitor for long-term adverse effects: growth and development, specific potential complications (anthracycline cardiomyopathy).
6. Intellectual function is monitored more closely in those at higher risk (very young age at initial diagnosis and/or cranial irradiation).
7. More and more recognition of obesity as a potential long term consequence of therapy
8. A vascular necrosis of bone is a risk as well as long term risk of alterations in bone density

SUGGESTED READING

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Brain Tumor Learning Points

Second most common (20%) pediatric cancer (after Leukemia)

Most common solid tumor in children

Hereditary Neurocutaneous Syndromes:

- a. NF-1
- b. NF-2
- c. Tuberous Sclerosis
- a. Nevoid Basal Cell Carcinoma Syndrome

Hereditary Cancer Syndromes:

- a. Von Hippel-Lindau Disease
- b. Turcot's Syndrome
- c. Li-Fraumeni Syndrome

	NF-1	NF-2
Prevalence	1:4000	1:50,000
Genetics	Chromosome 17, Autosomal dominant (50% New Mutations)	Chromosome 22, Autosomal dominant
Tumor	Neurofibromas, Café-au-lait spots	Acoustic Schwannomas, Meningiomas
Minor Tumors	Pilocytic Astrocytoma, Optic Nerve Glioma	Neurofibromas

Signs and Symptoms:

Headache

(Most common, least helpful; present at arising, relieved by vomiting, improved during the day).

Vomiting

(Frequently in the morning, relieves headache, no nausea or anorexia, hunger soon after).

Visual Difficulties

(Blurred vision common complaint in the young child; double vision common complaint in the older child; due to inability to deviate eye laterally-stretching/paresis of abducens).

Seizure

Neurological Deficit

Alteration in Consciousness

Academic Deterioration

Diagnostic Evaluation:

Either computed tomography (CT) or magnetic resonance imaging (MRI) should be performed with and without intravenous contrast. MRI is preferred since it provides superior resolution and multiplanar imaging capabilities. It avoids the “spray” artifact from the petrous ridge that may obscure CT images of the base of the brain. A repeat MRI should be done as soon as possible after surgery (within 72 hours) to evaluate residual disease. If not done within that period of time, it should be performed 2 weeks later. (When surgery related changes have stabilized).

For lesions with a high frequency of CSF dissemination, such as PNET, medulloblastoma, ependymoma and germ cell tumors, MRI of the whole spine should also be done. Lumbar CSF should be obtained in these tumors for cytology, and in germ cell tumors also for alpha-fetoprotein and beta-HCG. Because brain tumors rarely have disseminated extra-neurally at the time of diagnosis, a bone scan and a bone marrow biopsy are seldom indicated initially. (Unless required for a study). They are indicated for recurrent medulloblastoma.

A hearing test should be done in all patients with a brain tumor since either the tumor itself, or radiation therapy or some chemotherapeutic agents (like cisplatin and carboplatin) can cause hearing loss.

Diagnosis:

Histologic diagnosis is done on a resection or a biopsy specimen. When resection is not feasible, the neurosurgeon can do a stereotactic biopsy. Stereotactic biopsy is the precise (CT guided) introduction of a metal probe into the brain tumor and removal of a small piece of it.

Common Childhood Brain Tumors:

Low-grade astrocytoma 49%

Medulloblastoma 21%

High-grade glioma 15%

Ependymoma 9%

Germ Cell tumor 3%

Brainstem Glioma 3%

Grading of Astrocytoma

The grading of Astrocytoma is based on the specific combination of the following histological criteria: Nuclear atypia, mitotic activity, endothelial proliferation and necrosis. The more criteria present, the higher the grade.

GLIOMA	WHO GRADE
ASTROCYTOMA	
Pilocytic	I
Fibrillary	II
Anaplastic	III
Glioblastoma Multiforme	IV
OLIGODENDROGLIOMA	I
Anaplastic	II
EPENDYMOMA	I
Anaplastic	II

Treatment:

Surgery is the mainstay of treatment. Whenever possible the tumor should be removed or debulked surgically, either at diagnosis or after response to radiation or chemotherapy. Unfortunately, this is not possible in many cases because of the location of the tumor.

Radiation therapy involves aiming beams of x-rays or gamma rays at the tumor in exactly prescribed dose over a scheduled period of time. The radiation volume is calculated with the aid of a computer and using MRI and CT scan information. Conformal radiation therapy uses computers to create a 3-dimensional picture of the tumor so that multiple radiation beams can be shaped exactly (conform) to the contour of the treatment area. It spares normal tissue.

Radiosurgery is an even more precise technique. It uses a large number of narrow, highly focused beams of ionizing radiation. It can be given in one treatment using a high dose, or divided into daily fractions (so called fractionated radiosurgery). Radiosurgery is used for small tumors.

Because of the risks of radiotherapy to the developing brain there is a growing trend to defer radiation in young children (especially those below 3 years of age), by using chemotherapy as the initial treatment. In addition, ongoing studies in older children with selected lesion, such as "standard risk" medulloblastoma and germinoma, use reduced doses of radiation in conjunction with chemotherapy to minimize radiation-induced neurotoxicity.

Chemotherapy can be given in conventional doses and schedules. It can also be given in high-dose with stem-cell support, either as an autologous stem cell transplant, or as consecutive high-dose chemotherapy with stem-cell support.

TYPE OF TUMOR	5 YEAR SURVIVAL
Medulloblastoma	
Local	90%
Metastatic	67%
Ependymoma	
Less than 3 years of age	22%
Older children	75%
Cerebellar Astrocytoma	
Pilocytic (resected)	90%-100%
Brain Stem Glioma	
Focal (midbrain, medulla)	
Completely resected	94%
Partially resected	52%
Cervicomedullary	70%
Diffuse (intrinsic, pontine)	< 20% 2 year survival

Late Effects

Many of the sequelae of treating childhood brain tumors manifest several years after diagnosis, which mandates long-term multidisciplinary follow-up.

Loss of IQ: Children younger than 7 years of age who receive whole brain radiation demonstrate progressive deterioration of intelligence. In one study the average loss of IQ was 27 points and all patients required special education.

Endocrine Deficiencies are extremely common in children who have been treated. Growth hormone deficiency is seen in the majority of children who have received whole brain radiation. Growth may also be stunted from irradiation of the spine. In addition patients may have thyroid and gonadal dysfunction.

Hearing Loss: Either the tumor itself, or radiation therapy or some chemotherapeutic agents (like cisplatin or carboplatin) can cause hearing loss, partial or complete.

Second malignancy is another concern in long term survivors. It ranges from 1% to 3% and may include secondary brain tumors (usually more malignant than the primary), sarcomas and hematological malignancies.

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Chemotherapy Teaching Points

1. Antimetabolites - These drugs are analogs of vital co-factors in DNA or RNA synthesis. They competitively inhibit DNA or RNA production, or are directly incorporated into the DNA/RNA yielding a defective product. These drugs require that cells are in a phase when they are preparing to divide (S-phase specific).
 - a. Methotrexate – A structural analog to folic acid, a required cofactor for purine and thymidine synthesis. Methotrexate blocks dihydrofolate reductase which converts folic acid to its active form which is necessary for DNA synthesis.
 - i. Methotrexate is active in leukemias, lymphoma, histiocytosis, and osteosarcoma.
 - ii. Common toxicities include myelosuppression and mucositis both of which are preventable with leukovorin rescue
 - iii. Other toxicities include hepatitis, pneumonitis, dermatitis, and arachnoiditis.
 - iv. Methotrexate is contra-indicated if effusions are present because it will tend to concentrate there and be released slowly, increasing patient's overall exposure to the medication.
 - b. Ara-C or Cytarabine- A structural analog to cytosine, this drug is converted to Ara-CTP which is incorporated into newly synthesized DNA strands. The abnormal nucleotide blocks the advancing DNA polymerase, which blocks chain elongation.
 - i. Ara-C is active in most leukemias
 - ii. Side effects include: Myelosuppression, GI – nausea, vomiting, mucositis, pancreatitis, Neurologic – cerebellar toxicity, Ocular – conjunctivitis, Dermatologic – palmar/plantar erythema, Pulmonary – edema
 - c. Mercaptopurine (6-MP) and Thioguanine (6-TG). Analogs of purines, these compounds are incorporated in to DNA like Ara-C, but also inhibit de novo purine synthesis.
 - i. Useful in ALL, AML, and histiocytosis.
 - ii. Side effects include myelosuppression and hepatitis. 6-TG can cause hepatic veno-occlusive disease.
 - d. Hydroxyurea: This drug inhibits the conversion of ribonucleotides to deoxyribonucleotides
 - i. Hydroxyurea is useful in chronic myelogenous leukemia, some solid tumors – melanoma, head and neck tumors, and myeloproliferative disorders.
 - ii. Side effects include neutropenia, diarrhea, mucositis, and skin rash

2. Alkylating Agents – These agents bind irreversibly to DNA and RNA. These drugs are not S-phase specific (cells do not need to be in act of dividing at time of exposure), and so can be used in combination with the antimetabolites for synergistic tumor kill. Alkylating agents include:
 - a. Cisplatinum/Carboplatin
 - i. Active in multiple solid tumors, especially germ cell tumors, hepatoblastoma, neuroblastoma, Ewings sarcoma
 - ii. Side effects include: severe nausea and vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy, and myelosuppression
 - iii. Secondary malignancy and sterility are serious long-term side effects seen as a result of these drugs.
 - b. Cyclophosphamide(Cytoxan)/Ifosfamide
 - i. Useful in a wide variety of malignancies
 - ii. Side effects include:
 - iii. Hemorrhagic cystitis is a toxicity unique to these two drugs, and is preventable with hydration and MESNA,
 - iv. SIADH is another idiosyncratic side effect of these two drugs. Watch urine output and serum sodium closely, and if urine output decreases, use furosemide and not fluid restriction.
 - v. Cardiotoxicity is a rare side effect following use of these drugs.
 - vi. Renal dysfunction, especially Fanconi’s syndrome, is associated with Ifosphamide.
 - vii. CNS toxicity can also be seen mainly with Ifosphamide.
 - c. Temozolomide (Temodar): Is an oral alkylating agent.
 - i. Useful in brain tumors
 - ii. Side effects are few including myelosuppression, nausea and vomiting, fatigue, constipation, and transaminase elevations.
 - d. Busulfan: Another oral alkylating agent.
 - i. Wide range of activity
 - ii. Side effects include extreme myelosuppression, and so this drug is useful as a condition agent in bone marrow transplant. It can also cause pneumonitis, hepatic veno-occlusive disease or with BMT dosing, seizures (requires anti-seizure medication when giving BMT doses), and skin hyperpigmentation.
 - e. Melphalan: Designed specifically to be taken up by melanin producing cancers (melanoma).
 - i. Wide range of activity in adults, but used mainly in transplant in children.
 - ii. Side effects include myelosuppression (also useful in BMT), skin rash, pulmonary fibrosis, and secondary leukemia.
3. Natural Products
 - a. Anthracyclines – such as Doxorubicin, Daunorubicin, and Mitoxantrone, these bind to DNA between base pairs, a process called intercalation. The anthracyclines interfere the DNA uncoiling which is necessary for replication. They also impair the action of Topoisomerase II leading to strand breaks, and can also for free radicals damaging DNA.
 - i. Wide range of activity
 - ii. Side effects include myelosuppression, N/V, cardiotoxicity (is cumulative), radiation recall (causes late skin burn at prior site of XRT), and severe mucositis
 - iii. Highly pigmented, and will see pigment in the urine (red for doxo and daunorubicin, blue for mitoxantrone).
 - b. Bleomycin.
 - i. Useful in germ cell tumors and Hodgkins disease.

- ii. Pulmonary fibrosis a common side effect. We monitor pulmonary function tests in these patients.
- c. Actinomycin D –
 - i. Active in Wilm’s tumor, Ewing’s sarcoma, rhabdomyosarcoma
 - ii. Side effects include myelosuppression, N/V, mucositis, diarrhea

4. Plant Products:

- a. Vincristine/Vinblastine – disrupts microtubules preventing mitosis
 - i. Wide range of activity
 - ii. Side effects include peripheral neuropathy – jaw pain, constipation, loss of deep tendon reflexes, hand and foot drop, possibly SIADH, myelosuppression (with Vinblastine only)
- b. Etoposide or VP-16 – inhibits Topoisomerase II and therefore prevents DNA uncoiling and recoiling
 - i. Wide range of activity
 - ii. Side effects include myelosuppression, secondary AML, skin rash – possibly Stevens-Johnson syndrome
- c. Camptothecans- Topotecan and Irinotecan: These drugs induce DNA strand breaks by blocking activity of topoisomerase I.
 - i. Topotecan is active against neuroblastoma and rhabdomyosarcoma. Myelosuppression and diarrhea are side effects.
 - ii. Activity of irinotecan is being tested in rhabdomyosarcoma. Diarrhea is a major side effect of this drug.

5. Other Agents:

- a. Asparaginase – An enzyme derived from bacteria that deprives leukemia cells of asparagine by blocking the formation of asparagine from aspartic acid.
 - i. Useful in ALL and AML
 - ii. Side effects include hypersensitivity reactions, impaired hepatic protein synthesis with possibly subsequent bleeding or thrombosis, CNS toxicity including confusion or coma, and pancreatitis.
- b. Corticosteroids- Prednisone, Dexamethasone. These drugs are directly toxic to lymphoid cells. Binding to glucocorticoid receptors leads to apoptosis of these cells.
 - i. Useful in lymphomas, lymphocytic leukemia, and histiocytosis.
 - ii. Numerous side effects, including hypertension, behavior changes, glucose intolerance,

6. Targetted Therapies. Many new drugs are being tested in patients with cancer that are targeted to affect the cancer cell while sparing normal tissue.

- a. Antibody targeting. This approach uses an antibody that is complexed to a toxin, radioactive particle, or that activates the immune system to kill the tumor cell.
 - i. Rituximab: A highly specific mouse/human chimeric antibody. Useful in B-cell lymphomas, lymphoproliferative disorders, and autoimmune disorders (ITP). Thought to achieve tumor kill by activating antibody-dependent cellular toxicity.
 - ii. Myelotarg: Used for relapsed acute myelogenous leukemia. Is an antibody to the cell surface protein CD33 complexed to calectamycin, an antibiotic that intercalates between DNA strands.

- b. Imatinib Mesylate or STI-571 (Gleevec). This drug is a specific inhibitor of the Abl class of protein tyrosine kinases and inhibits the function of the BCR-ABL fusion protein produced by the t(9;22) or Philadelphia Chromosome that is the cause of chronic myeloid leukemia (CML). Gleevec is now the standard of care for treatment of CML and gastrointestinal stromal tumor (GIST) caused by over-expression of c-kit, a tyrosine kinase related to Abl. Gleevec is also being tested to determine its role in treatment of Philadelphia chromosome positive ALL.

Case Studies:

1. Your patient is receiving Cisplatin and mannitol infusions. You are called because his urine output has diminished. You should:

- A. Given furosemide.
- B. Give a 20ml/kg fluid bolus.
- C. Check I's and O's prior to making decision.

Answer: C. Patient may have over diuresed with mannitol and may need fluids, or the patient may be retaining fluids and need lasix.

2. Your patient who is being treated for acute lymphoblastic leukemia presents to your clinic with a 1 week history of clumsiness, and actually fell down the stairs. On exam, you notice that he has a "slapping gait", and decreased patellar reflexes. You should:

- A. Get a myelogram.
- B. Do an LP.
- C. Check if vincristine was given recently.

Answer: C. Foot drop is a common side-effect of vincristine. Doses are only changed for severe symptoms (ie patient can't walk).

3. Your patient is receiving high dose methotrexate. You are trying to keep urine pH > 7. It has dropped to 6 and has been checked twice. What should you do:

- A. Blow it off.
- B. Give Diamox.
- C. Recheck

Answer: B. Diamox can be given to alkalinize the urine. You could also increase the sodium bicarbonate fluid rate if the patient's I's and O's are blanced. Finally, you could give a bolus of sodium bicarbonate at a dose of 1 mEq/kg/ over 1-2 hours.

4. Your patient is receiving cisplatin and his IV fluids are D5 ½ NS with 10 mEq of KCl/L and 150 mg MgSO4/L. You are paged because your patient is unresponsive. You arrive, and the patient has stable vitals but is not responsive to pain. His limbs are flaccid, and DTR's are decreased. You should:

- A. Change IV fluids.
- B. Check meds given recently. Is patient on morphine?
- C. Send electrolytes and magnesium stat.
- D. Verify magnesium sulfate in the IV fluids is in milligrams and not milliequivalents.

Answer: All of the above. It is not unheard of to have the wrong amount of magnesium in the IV fluids, such as the bag containing 150 milliequivalents rather than milligrams. Additionally, patients on PCA pumps can become overmedicated on morphine, and can present with acute mental status changes.

5. Your patient is hot to trot. He had received high dose methotrexate, and was experiencing delayed excretion. His MTX level yesterday was 0.9. You are on the telephone, and the nurse hands you a note saying that the patient's methotrexate level is now 0.05, and asks, using hand signals, whether she can discharge the patient. You should:

- A. Ask nurse to wait, and check the level on the computer.
- B. Discharge the patient.

Answer: It is not unusual for mistakes to be made based on the incorrect position of a decimal point. In this case, a seasoned nurse at another institution called the laboratory and then wrote down both on the note to the MD and in the chart that the MTX level was 0.05. In actuality, the level was 0.5. The child went home, and returned with severe mucositis, burns on his hands and feet, and pancytopenia that lasted 1 month.

Fever and Neutropenia

1. Fever is defined as a temperature > 38.5 C or 101.5 F. Low-grade fever is defined as a temperature > 38.0 or 100.0 F.
2. Mild neutropenia is defined as an actual neutrophil count (ANC) < 1500 . (In African Americans, ANC < 1000). Moderate neutropenia is defined as ANC 500-1000. Severe neutropenia is ANC < 500 . Severe neutropenia creates a risk of overwhelming bacterial infections, as the neutrophils protect against bacteria invading through the skin and mucous membranes. $ANC = WBC \times (\text{Neutrophil} + \text{band } \%)$. The actual phagocyte count (APC) $= WBC \times (\text{neutrophil} + \text{band} + \text{mono}\%)$
3. Any cancer or aplastic anemia patient with fever, and particularly those who are on high-intensity chemotherapy, should be carefully assessed for the possibility of a serious infection. Patients with true fever ($T > 101.5$; or 2 fevers over 101 more than 1 hour apart during a 24 hour period) and severe neutropenia (ANC < 500 or expected to be at this level within 48 hours) are generally hospitalized and observed on antibiotics until their neutrophils begin to recover and they are infection free. Patients with persistent low grade fever or low-grade fever who are ill and have severe neutropenia are also admitted to rule out/treat infection. Patients who have a central line in place and have fever without neutropenia should have a blood culture done. Antibiotic therapy is optional based upon the clinical situation.
4. Ill patients who are afebrile or hypothermic and yet are severely neutropenic can also have serious infections. Therefore, patients who are ill and are at their neutrophil nadir (around 10 days following high dose chemotherapy) should be assessed and possibly admitted. Corticosteroids, particularly decadron, can block febrile responses. Therefore patients receiving steroid therapy for leukemia or lymphoma, particularly those with active marrow involvement, should be evaluated carefully in this setting.
5. Patients in lower intensity phases of chemotherapy (such as maintenance in ALL) and who are neutropenic for short periods of time that have evidence of recovering counts (a rising APC) can be discharged at the judgment of the treating physician.
6. Stay ahead of febrile neutropenic patients because once you get behind the eight ball you and the patient lose.
7. 10-20% of febrile neutropenic cancer patients have bacteremia at presentation.
8. Examination of the mouth, lungs, and perineum/rectal area should be done at admit and every day.
9. No rectal meds to neutropenic patients.

10. For patients who have blood cultures growing gram negative organisms, an aminoglycoside should be added until the organism is identified and sensitivities are complete. When a positive culture is identified, empiric therapy can be modified based upon the organism and sensitivity. Gram negative coverage must be continued until there are signs of count recovery, even if a gram + organism is identified. This is because polymicrobial sepsis is common and you may not have identified all organisms.
12. General criteria for stopping empiric antibiotic therapy for fever and neutropenia. If cultures are negative and there are no clinical signs of infection, antibiotic therapy should be continued until the patient is afebrile for at least 24 hours and there are signs of marrow recovery with an increasing WBC (from 0.1 to 0.2 may be enough in some settings). Patients who have positive blood cultures or an identified clinical infection (e.g. pneumonia) should receive a defined course of antibiotic therapy (7-14 days depending on infection and organism) and continue treatment at least until there are convincing signs of marrow recovery.
13. Patients with acute myelocytic leukemia and ALL patients receiving prolonged corticosteroid therapy such as given during induction or reinduction are at high risk for fungal infections. An appropriate antifungal (amphotericin B or voriconazole) should be added to patients if the patient remains febrile 4-5 days into antibiotics. Consider addition of empiric antifungals on day 5-7 in other patients with fever and neutropenia.
14. Neutropenic patients on broad spectrum antibiotics should be on some type of oral candidiasis prophylaxis, usually Fluconazole or Nystatin. Note that fluconazole alters metabolism of many drugs.
15. Most neutropenic cancer patients who become febrile do not have a source or have positive cultures initially. The use of early empiric antibiotics is justified by reduced morbidity and mortality.
16. Risk of infectious complications from neutropenia increase with the length of time the patient is neutropenic. A low risk patient is one whose neutropenia is anticipated to resolve within 1 week of starting antibiotics.
17. Antibiotics must be started STAT within 1 hour of admit. Mono-therapy with Cefepime (or comparable antibiotic) is used for a majority of patients. This is the most important therapeutic intervention, and is chosen because of its broad spectrum & coverage of pseudomonas.
18. Patients who received high dose ARA-C (Cytarabine) with their most recent chemotherapy or have a source suggestive for gram positive infections should be started on Vancomycin and Cefepime. Patients who receive high dose ARA-C have a high incidence of gram positive infections/sepsis, and toxic death from Strep viridians. The presence of an indwelling catheter is not an indication for routine empiric use of vancomycin.
19. Fever that recurs after defervescing can be result of fungal infection. Fungal blood cultures should be sent and consideration of imaging of sinuses and chest to pelvis by CT to look for fungus. Consider also echocardiogram.
20. If patient has a line tunnel infection, persistently positive blood cultures, recurrent cultures with same pathogen, candida, VRE or polymicrobial sepsis, central line should be removed.
21. Bronchoscopy should be considered in patient with pulmonary infiltrates not responding to broad spectrum antibiotics. A serum galactomannin level is a non-invasive way to assay for Aspergillus, although its predictive value has not yet been validated in children. Transbronchial or open lung biopsy may be necessary to diagnose aspergillus or other forms of invasive fungus.

22. Aztreonam is useful in patients needing gram negative coverage who are allergic to cephalosporins.
23. Viral respiratory cultures can be useful in patients with respiratory symptoms. Empiric anti-influenza therapy should be considered during “flu season”.
24. Typhlitis (neutropenic colitis) is an infection of the colon that involves invasion of colonic flora the colonic bowel wall, presenting with abdominal pain, vomiting, diarrhea and styptic shock. Typhlitis is treated with bowel rest and antibiotics typically double coverage (third generation cephalosporin plus aminoglycoside plus metronidazole for anaerobes).

Case #1

16 year boy being treated with AML presents with fever and WBC 200. His most recent chemotherapy was ARA-C 1 week ago, but he isn't sure of dose. The best choice for antibiotic coverage would be:

1. Cefepime
2. Vancomycin
3. Vancomycin and Cefepime

Answer # 3. Better to cover for gram + in patient with history of ARA-C since incidence of Strep viridans sepsis is significant with high dose ARA-C. If it turns out not to be high dose ARA-C you could stop the Vancomycin.

Case #2

An 18 year-old girl has neutropenia secondary to AML. She has been on treatment with Vancomycin & Cefepime and on day #4 she develops recurrent fever. On PE she says the nurse examined her rectal area; the nurse is not around for you to check with but she will be back in AM. You should:

1. Wait till tomorrow to talk to nurse
2. Examine the perirectal area.

Answer #2. Examine the perirectal area yourself. If there are signs of a perirectal infection, you should add a second gram negative drug such as an aminoglycoside and add an anaerobic coverage such as metronidazole.

Case #3

A 5 year old boy is on maintenance treatment for ALL. He is on 6 M.P. daily and MTX weekly. He is admitted for F& N. After two days, he is afebrile. His counts are increasing with an AGC of 750, and his cultures are negative. You would:

1. Keep him to complete at least 3 days of antibiotics.
2. Wait till the AGC is 1000
3. D/C home on no antibiotics.

Answer #3. This is a “low risk patient” and his counts are recovering.

Case #4

An 8 year old boy being treated for lymphoma has chemo was 1 week ago. He presents with fever and ANC 500, you order blood and urine cultures. The patient can't urinate at this time. You tell the nurse to:

1. Give antibiotics after the blood culture drawn and get the urine culture later
2. Wait until patient urinates to give the antibiotics
3. I & O catheter patient

Answer #1. Start antibiotic STAT in fever & neutropenia patient. We avoid I & O catheters unless absolutely necessary.¹⁻⁶

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Immune Thrombocytopenic Purpura.

1. Immune thrombocytopenic purpura (ITP) in children usually presents with the sudden onset of bruising, petechiae, and bleeding in an otherwise healthy child.
2. ITP typically follows two weeks after a viral prodrome.
3. ITP is usually caused by antibodies to platelets that lead to opsonization and destruction of platelets in the spleen.
4. Platelet counts are usually very low (<10,000).
5. Typical ITP occurs in a well child.
6. Atypical symptoms include fever and bone pain, and atypical signs include leukocytosis, leukopenia, anemia, hepatosplenomegaly or lymphadenopathy. The major confounding diagnosis is leukemia. Any patient being worked up for ITP should trigger thoughts of “could this be leukemia?”
7. The peripheral smear usually shows large (young) platelets.
8. The proper treatment for a non-bleeding patient with ITP is controversial, and ranges from non-treatment to steroids (4 mg/kg/day divided bid X 1 week, and then tapered). Some physicians will treat these patients with intravenous immunoglobulin (IVIG) or anti-D therapy (WinRho).
9. Patients with significant bleeding or wet purpura (mucous membrane bleeding) usually receive IV IgG (0.8gm/kg X 1) or WinRho (75 mcg/kg). This treatment is thought to raise the platelet count slightly faster than prednisone. A rise in platelets is not always within a day, and yet second doses are not indicated for a non-bleeding patient.

10. ITP in young children is usually self-limited; 50% have complete resolution in 2 months, 75% in 4 months, and 90% in six months. ITP in teenagers is more likely to become chronic, with >50% of patients have symptoms greater than 6 months. Menorrhagia can be a major problem in young women with ITP.

11. ITP can be a presenting sign of autoimmunity, and is frequently associated with systemic lupus erythematosus. This is particularly true in teenage girls, and these patients should be screened for lupus by testing for antinuclear antibodies (ANA).

12. Chronic ITP is defined by lack of resolution after 6 months.

13. Treatments for chronic ITP include steroids (prednisone, dexamethasone), dapsone, vincristine, 6 mercaptopurine, cytoxan and rituximab.

14. Splenectomy is contemplated in patients with ITP that lasts > 1 year. Many centers will contemplate splenectomy after 6 months of symptoms. Reasons splenectomy may be contemplated earlier are participation in contact sports, life-threatening hemorrhage refractory to other treatments and poor tolerance of other treatments. Reasons splenectomy is postponed beyond 1 year is age < 5 and parental/child concerns about splenectomy. Greater than half the patients with chronic ITP will eventually go into remission over time without splenectomy. Approximately 75% of patients who undergo splenectomy respond.

15. Prior to splenectomy, and spleen scan should be performed to evaluate for secondary splenic tissue.

16. Prior to splenectomy, patients should be immunized against pneumococcus, meningococcus, and Haemophilus influenza. Patients < 5 years should be given the 7 valent conjugated vaccine (Prevnar) which is more immunogenic in young children. Patients who are older than 5 should receive the 24 valent polysaccharide vaccine (Pneumovax). Patients who receive meningococcal vaccine at age < 5 should be boosted 1 year post-splenectomy. Patients who have received all of their HIB vaccines do not need additional vaccination.

17. Refractory ITP is thrombocytopenia that does not respond to traditional agents IVIG and prednisone or splenectomy. Refractory ITP will sometime respond to more global immunosuppression or T-cell specific agents (cyclophosphamide, cyclosporine).¹⁻⁵

Cases:

1. A 14 year old girl presents with menorrhagia and purpura. There is no history of fever or bone pain. Physical exam is normal. CBC shows HGB 13, WBC 6.5, and PLT 6.

This is classic ITP. However, because of this patient's age and sex, she should be worked up for lupus.

2. A 5 year old boy presents with fever, epistaxis, and malaise. He is seen in the ER where exam shows shoddy lymphadenopathy in the neck and groin. CBC shows WBC 3.7, HGB 11, and PLT 77.

This patient has mild pancytopenia, and should undergo a bone marrow aspirate. The working diagnosis is leukemia until proven otherwise. Certain infections (CMV, EBV, HIV, and others), medications (antibiotics, antiseizure, antihistamine, antineoplastic meds), and autoimmune disorders can also cause pancytopenia. Giving steroids to this child would make diagnosing and treating his leukemia more difficult. Prednisone would partially treat leukemia, and the symptoms might improve for a time only to come roaring back. There is concern that pretreatment with steroid breeds resistant leukemia, and would require more therapy to cure.

3. A seven year old girl comes to your office with sudden onset of easy bruising. This child has been followed by you for genitourinary reflux, and has a horse-shoe kidney. She also is small for age. A CBC is performed that shows a WBC of 7, HGB 12, and platelets of 75.

This patient could have Fanconi's anemia. Fanconi's anemia is classically associated with short stature and thumb abnormalities. However, 30% of patients have a completely normal phenotype. In addition, the VACTERL associations are seen in Fanconi anemia, and patients with these (Vertebral, Cardiac, Tracheo-esophageal fistula, Renal, and Limb anomalies) and cytopenias should be worked up for Fanconi Anemia. These patients present at an average age of 7, and usually begin with thrombocytopenia but progress to pancytopenia. This patient actually had a hemivertebra on CXR, and was labeled as ITP for two years before developing pancytopenia, when the correct diagnosis was made.

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Lymphoma Teaching Points

Lymphomas (~1700 cases/yr.) are the third most common subgroup of pediatric cancers in the U.S., comprising about 15% of cancer that occurs before age 20. The incidence of lymphomas increases significantly from 0-20, with lymphomas accounting for about 3% of tumors 0-5 years and 24% 15-19 years. The two major subcategories of lymphoma are Hodgkin's disease (HD; 850-900 cases/yr) and Non-Hodgkin's lymphoma (NHL; 750-800 cases/yr.). NHL is more common in younger children, and HD is more common in adolescents.

Hodgkin's Disease:

Reed Sternberg cells are the malignant cells in Hodgkin's disease (HD). These are atypical, multinucleated giant cells that are pathognomonic of HD. There is a background mixture of benign lymphocytes, inflammatory cells, and stromal cells that make up the rest of the tumor. HD is the only lymphoma where the malignant cells are vastly outnumbered by benign cells in a given tumor.

HD is highly associated with prior Epstein-Barr virus infection.

There are four subtypes of HD:

Lymphocyte Predominant. (10-15% of cases). Fibrosis not generally seen, mainly lymphocytes. Can be mistaken for reactive hyperplasia, and often many cuts from tumor necessary to identify Reed Sternberg cells. Usually localized, seen more often in males and young patients.

Mixed Cellularity. (30% of cases, more common in children.) Numerous Reed- Sternberg cells present, small areas of fine fibrosis also present. Background of inflammatory cells. Usually presents with advanced disease with nodal involvement.

Lymphocyte Depleted. Common in HIV-infected patients and rare in children. Many Reed-Sternberg cells, and malignant reticular cells, and few lymphocytes. Can have diffuse fibrosis and necrosis. Often present with disseminated disease involving bone and bone marrow.

Nodular Sclerosing. (Represents 40% of younger patients, 70% of adolescents.) Orderly collagenous bands divide tumor into nodules. Usually involves nodes in the lower neck and mediastinum.

Systemic symptoms including fatigue, anorexia and slight weight loss are common in HD. Itching and pain upon alcohol consumption are also associated with HD. A minority of patients has more extensive weight loss, fatigue, and fever defined as “B” symptoms: (1) unexplained weight loss >10% within the prior 6 months; (2) unexplained fever >38C on a daily basis for 2 weeks; (3) “drenching” night sweats (like wetting the bed). The presence of any of these 3 qualifies as B symptoms, and are associated with a poor prognosis.

Patients present most commonly with painless supraclavicular or cervical lymphadenopathy. Supraclavicular adenopathy is always pathologic; however, it must be distinguished from low cervical adenopathy. Supraclavicular nodes grow up over the clavicle from below. Some children have axillary or inguinal adenopathy. Subdiaphragmatic only disease occurs in <5% of pediatric HD patients.

Affected lymph nodes are usually described as firm and rubbery. They may be tender, but do not usually have the classic signs of infection (heat, redness, pain). Nodes may grow very slowly and are often described as being present for months.

Two-thirds of patients have mediastinal involvement. This may be asymptomatic, or may cause non-productive cough, wheezing or symptoms of tracheal compression. A chest X-ray is key if one is concerned about the possibility of HD. Tracheal compression can lead to sudden death during anesthesia, and sedatives and heavy anesthesia should be avoided in patients with significant airway compression. Any patient with a mediastinal mass should be carefully evaluated by an experienced anesthesiologist prior to sedation.

Differential diagnosis includes lymphadenitis, mononucleosis, other inflammatory causes of lymphadenopathy, NHL (usually grows much faster than HD), other cancers such as nasopharyngeal carcinoma (nodes are rock hard and fixed). It can sometimes be difficult to distinguish a large thymus in a young child from a mediastinal mass.

Excisional biopsy is the method of diagnosis. Fine-needle aspirates lead to sampling error, and may falsely reassure the practitioner.

HD spreads along contiguous lymph node chains until late in the disease. Patients are staged I (single lymph node or region), II (two or more nodal regions on same side of diaphragm), III (disease above and below the diaphragm), IV (disseminated disease outside of lymph nodes).

Treatment of HD includes chemotherapy alone for localized disease, and chemotherapy plus involved field radiation for advanced stage disease. Optimal treatment depends on the stage of the disease, the size of the nodal aggregates, and whether or not patient has B symptoms. Patients with lymphocyte predominant disease are treated differently than those with other subtypes.

Nodal masses may not disappear completely, especially with NS HD. Because of this, patients often have residual masses of scar tissue. Nuclear medicine studies can be used to determine if a residual mass still has active disease. Until recently, Gallium scans were used. Positron emission tomography (PET) scans are now becoming the scan of choice for following HD.

Prognosis: HD carries an overall prognosis of 85-90% event free survival. High risk features include bulky mediastinal disease, extranodal extension of disease, B-symptoms, and advanced stage disease (stage III or IV).

Long-term side effects of treatment include risk of infertility, hypothyroidism, secondary breast cancer from radiation therapy, and pulmonary fibrosis from bleomycin.

Non-Hodgkin's Lymphoma (NHL):

Malignancy can arise in any subset of lymphoid cells, and lymphomas are treated based on their subtype and cell of origin.

B and T-cell lymphomas often arise from mutations that occur when T-cell receptor or immunoglobulin genes undergo rearrangement.

B-Cell lymphomas.

Burkitt's lymphoma, Burkitt's-like lymphoma, and large B-cell lymphoma can be considered together as they are closely related and respond similarly to treatment. They represent a continuum of tumors that arise from common mutations.

Burkitt's Lymphoma

Burkitt's lymphomas are mature B-cell lymphomas that express surface immunoglobulin. In equatorial African Burkitt's lymphoma, the tumor typically arises in the jaw in lymphatic tissue that is present in the area of erupting teeth. African BL is highly associated with EBV (95% of cases), whereas non-African Burkitt's generally is not.

In the US and Europe, BL is termed "sporadic". These lymphomas typically arise in the abdomen in mesenteric lymph nodes, though they can arise in any lymphatic tissue. 15% are associated with EBV infection. Intussusception due to a bowel wall primary tumor is not unusual. BL should be high in the differential diagnosis of any child older than 3-4 years of age with intussusception (a common Board question).

These differences may be related to the age at which patients are infected with EBV and other socioeconomic factors. The immunosuppressive effect of malaria may also play a role in the pathogenesis of BL in Africa.

BL is associated with HIV infection and immunosuppression in general, particularly T-cell immunosuppression.

BL is associated with nonrandom reciprocal translocations between chromosome 8 and 14. These juxtapose the *c-myc* gene to the region of the immunoglobulin heavy chain, which places *c-myc* (normally not very active) under the regulation of the immunoglobulin locus (very active in lymphocytes). *c-myc* is involved in cell proliferation, and translocation leads to a proliferative state.

Histologically, BL has a "starry sky" pattern due to light staining macrophages within the bulk of the darkly staining tumor cells.

BL is a very aggressive malignancy, with the shortest doubling time of all pediatric malignancy. As a result, tumors grow rapidly and patients often have evidence of tumor lysis from tumor turnover at the time of diagnosis. They can present with or rapidly develop renal failure following treatment. One must be very careful giving corticosteroids to a patient with active Burkitt's lymphoma.

Major advances have been made in the treatment of advanced stage BL. When these tumors were treated like other pediatric NHL, patients fared very poorly. Development of extremely aggressive and short multi-agent chemotherapy regimens dramatically improved outcome for patients with BL and event-free survival exceeds 90% for localized disease and between 70-90% for disseminated disease. Relapses typically occur within the first year of cessation of therapy, and patients are highly unlikely to recur after that time. Prevention and management of

tumor lysis are critical at the outset of treatment. Intrathecal therapy to prevent recurrence in the central nervous system is required. Unlike HD, radiation therapy is not part of up-front treatment of non-Hodgkins B-cell lymphomas. BL typically express CD20 on the surface and the anti-CD20 monoclonal antibody Rituximab is now being tested in these patients.

Large B-cell Lymphoma (LBLC)

More common in adults than in children.

A variety of mutations can lead to this morphologic subtype of B-cell lymphoma. 5-10% have t(8;14). Other translocations involved the bcl-6 gene due to a t(14;18), and these are more common in adults.

Mediastinal tumors can arise from the malignant counterpart of the B-cells normally present in the thymus.

Burkitt's-like Lymphoma (BLL).

Histologically, these tumors are similar to BL, but have more variability in size and shape of the cells. BL and BLL are not distinct entities, and many BLL contain the t(8;14) that is associated with BL. These tumors are treated identically to BL and have a similar prognosis.

T-cell Lymphomas:

Lymphoblastic lymphoma:

Patients typically present with a mediastinal mass, which often is more rapidly growing than Hodgkin's disease. Patients may present with pleural effusions, pericardial effusions, and superior vena-cava syndrome.

Tracheal compression can lead to sudden death during anesthesia, and sedatives and heavy anesthesia should be avoided in patients with significant airway compression.

Patients with mediastinal masses should undergo a bone marrow aspirate. Many patients with a rapidly growing mediastinal mass due to NHL will also have bone marrow involvement. If there is > 25% marrow involvement, it is considered to be T-cell ALL. The bone marrow aspirate/biopsy may prevent the need for an intrathoracic biopsy. Similarly, cervical or axillary nodes are preferentially biopsied, even if smaller than the intrathoracic nodes, often using light anesthesia with the patient sitting upright.

Lymphoblastic lymphomas are usually of the T-cell phenotype. However, a small percentage arise from B-cells. These tumors usually present with very limited disease, in contrast to T-cell lymphoblastic lymphoma, including tumors of the bone, skin, or isolated lymph nodes.

Treatment of T-cell lymphoblastic lymphoma is similar to treatment of T-cell acute lymphocytic leukemia, and begins with more intense treatment followed by approximately 2 years of maintenance therapy. Treatment includes intrathecal chemotherapy. Radiation therapy is not typically used in these patients unless they have CNS disease.

Prognosis: Lymphoblastic lymphomas have a long-term event free survival in the 80-90% range.

Anaplastic large cell lymphoma.

Anaplastic large cell lymphoma is unlike the other NHL's of childhood in that it can present with a more indolent course. Like patients with HD, these patients frequently have fever and weight loss.

Unlike other NHL's, these tumors most often arise in lymph nodes. They can also involve the skin and bone. A classic finding is lymph node involvement and skin, especially the skin of the lateral thorax. GI tract is rarely involved.

80% of children with ALCL have a 2;5 translocation. This juxtaposes the tyrosine kinase ALK with the nucleophosmin causing inappropriate expression of an activated ALK protein.

Histologically, tumors contain large cells of varying shapes, with horse-shoe nuclei. Some cells may resemble Reed-Sternberg cells. Tumors almost always express CD30 (Ki-1) and ALK.

In adults, ALCLs can transform from more indolent lymphomas such as Hodgkin's disease or cutaneous T-cell lymphomas.

Current treatment approaches combine initial high dose chemotherapy with a more prolonged maintenance phase, similar to but shorter than therapy for acute lymphocytic leukemia.

Post-Transplant Lymphoproliferative Disease (PTLD):

NHL can occur in patients who are immunosuppressed following solid organ transplant. These lymphomas are usually of B-cell origin and frequently are activated by EBV. PTLN is a spectrum of disease that ranges from polyclonal to monoclonal tumors indistinguishable from Burkitt's lymphoma. Treatment of PTLN includes decreasing or discontinuing immunosuppression (if feasible), and chemotherapy. Most PTLN are CD20 positive and Rituximab is often included in therapy. PTLN can often be cured by less intensive chemotherapy than typically used for other NHL.[1-5]

Questions:

1. A patient presents with a history of "constipation" and is anuric. Patient's abdomen is very distended and hard. CT shows an enormous mass that appears to be arising from the bowel. What is the likely diagnosis?

Answer: This patient most likely has "sporadic" Burkitt's lymphoma. This is the way most patients with BL present in the US. The anuria is due to tumor lysis, which frequently complicates BL at diagnosis. Successful treatment depends on successfully managing tumor lysis syndrome, particularly the hyperkalemia that is associated with renal failure.

2. A patient presents with a history of chronic cough that has been present for 5 months. Over this time frame the patient has had persistent low-grade fevers and a 12% weight loss. The patient has had drenching night sweats. The patient has firm lymphadenopathy at the base of the neck, and CXR shows a mediastinal mass. What does this patient most-likely have?

Answer. This patient most likely has Hodgkin's disease, although could also have lymphoblastic lymphoma. The B-symptoms include drenching night sweats, >10% weight loss, and fever are associated with a more aggressive course,

3. A patient presents with a history of facial swelling and shortness of breath. CXR performed in outlying ER shows a massive mediastinal mass. What does this patient most-likely have?

Answer. This patient most likely has lymphoblastic lymphoma, although they could also have T-cell leukemia or less likely, Hodgkin's disease. This case illustrates the more rapid onset of lymphoblastic lymphoma, although these tumors can be indolent. A critical piece to initial management is the anesthesia, which can be difficult to impossible in a patient with tracheal compression.

4. A patient presents with axillary lymphadenopathy and papular skin lesions that appear and disappear. The patient has had low grade fevers. The lymphoma that this patient most-likely has is:

Answer. Anaplastic large cell lymphoma. One way that these patients will present is with lymphadenopathy associated with papular skin rash that can be indolent and can wax and wain.

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MYELOID LEUKEMIA TEACHING POINTS

Epidemiology

1. Leukemia accounts for ~31% of all childhood cancer occurring before age 15 years and about 25% of that which occurs before 20 years of age
2. About 3250 cases of leukemia/yr in US before age 20
3. Acute myelogenous leukemia (AML) comprises about 20%, chronic myelogenous leukemia (CML) comprises about 3% of childhood leukemia cases. Other rare myeloid leukemias account for 1-2% of cases.
4. AML incidence peaks in first 2 years of life, declines to a nadir at 9 years and increases slowly thereafter during the adolescent years.
5. CML is rare in early childhood, then begins to increase in incidence in mid adolescence
6. Juvenile myelomonocytic leukemia (JMML), previously termed juvenile chronic myelogenous leukemia (JCML), is a rare disorder that occurs almost exclusively before 2 years of age.
7. Incidence of AML has been stable over past 20 years in US, with the exception of perhaps an increase in cases diagnosed before one year of age.
8. Little is known about the causes of myeloid leukemias, but there appears to be little role of classic genetic predisposition, lifestyle factors such as diet or environmental exposures such as electric power lines
9. Children with Down syndrome have a markedly increased risk of AML (10-20 fold increase), particularly acute megakaryocytic leukemia (M7 AML; see below) that occurs in the first 2 years of life. AML in DS is more responsive than that which occurs in children without DS and is generally treated less intensively.
10. Children with DS also can develop transient abnormal myelopoiesis in the first month of life that looks like M7 AML, but usually resolves spontaneously.

AML

Presenting Symptoms

1. Major symptoms are those caused by bone marrow failure due to replacement of normal marrow elements with leukemia cells: pallor and fatigue (anemia); bruising, petechiae and bleeding (thrombocytopenia); and infection (neutropenia).
2. Coagulopathy is more common in AML than in ALL, and is particularly common in those with acute promyelocytic leukemia (APML or M3 AML; see below)

3. Extramedullary disease can also occur in AML, sometimes manifesting itself as tumor masses termed granulocytic sarcomas or chloromas. These are especially common in monocytic subtypes of AML (M4 and M5; see below)
4. Bone pain (general irritability in younger children) is common due to expansion of the marrow cavity
5. Fever is relatively common and is usually not due to infection and often resolves within days of beginning therapy
6. About 5% of patients have CNS involvement at diagnosis, which is most often asymptomatic. However, can have symptoms due to CSF pleocytosis (headache, neck stiffness, irritability, vomiting) and/or signs of increased intracranial pressure. Cranial nerve palsies are occasionally observed.
7. Patients with AML who have very elevated white blood cell counts (>100-200,000) may exhibit signs due to hyperleukocytosis that can include hypoxemia due to pulmonary “sludging” and stroke-like CNS symptoms.

Diagnosis and initial evaluation

1. Differential diagnosis includes non-malignant (JRA, mononucleosis or other viral infection, ITP, pertussis/parapertussis, aplastic anemia) and malignant (lymphoma, small round blue cell tumors such as neuroblastoma, Ewing’s sarcoma, etc.) disorders
2. Initial evaluation should include a careful history and PE that specifically addresses areas outlined above.
3. Laboratory evaluation should include tests needed to establish the diagnosis and define the extent of involvement: CBC with review of peripheral smear, bone marrow aspirate +/- biopsy (morphology, immunophenotype, cytogenetics, molecular genetics), LP, Chest Xray to exclude mediastinal mass (must do prior to any general anesthesia!).
4. In addition, need to define other problems that may be present including screens for metabolic abnormalities: lytes, BUN, Cr, Ca, Mg, Phos, uric acid.
5. If febrile, culture and treat empirically with broad spectrum IV antibiotics

Detailed characterization of leukemia

1. Bone marrow morphology: AML blasts are typically larger than those seen in ALL and have cytoplasmic granules. Cytochemical stains show +myeloperoxidase; monocytic forms can express non-specific esterase (NSE). Auer rods (needle like azurophilic granules) are diagnostic of AML
2. Leukemias must be characterized by flow cytometry to define the pattern of surface and cytoplasmic antigen expression. AML cells typically express myeloid associated antigens (CD13, CD14, CD33). Some cases may also express lymphoid antigens, especially T-cell antigens such as CD7.
3. AML cases are subclassified by the FAB (French-American-British) classification system into subtypes M0-M7. M0 is minimally differentiated, M1 and M2 displayed increased granulocytic differentiation. M3 is APML and exhibits arrest at the promyelocyte stage of differentiation. M4 and M5 display more monocytic features, M6 is erythroid leukemia and M7 is acute megakaryocytic leukemia.
4. Cytogenetics are performed to identify common non-random abnormalities that may have prognostic significance. Some of these abnormalities can also be identified by specific molecular screening tests.

Genetics of AML

1. At least 75-80% of AMLs have identified cytogenetic abnormalities. These reflect underlying genetic changes involved in disease pathogenesis. They are somatic mutations, not germline defects so they are not present in normal cells and disappear when remission is achieved.
2. Non-random chromosome translocations (exchanges of genetic material between chromosomes) are common in AML and define specific subtypes of disease. These commonly create fusion genes and proteins. Major subcategories include the abnormalities that affect the core binding protein family: t(8;21) and AML1-ETO and inv(16) and CBF α -SMMHC.
3. APML is a clinically distinct subtype of AML characterized by the t(15;17) that produces PML-RAR α fusion. It is treated differently from other subtypes of AML (see below)
4. Chromosome deletions also occur in AML; the most common are cases with monosomy 7 or deletions of all or part of chromosome 5. These subtypes are often associated with a myelodysplastic (MDS) phase and are often refractory to chemotherapy.

Prognostic Factors

1. Adverse: high WBC (>100,000; less important in children), antecedent MDS or secondary AML induced by chemotherapy treatment, monosomy 7, complex cytogenetic abnormalities
2. Favorable: t(8;21), inv(16), t(15;17)

Treatment

1. As recently as the early 1970s, childhood AML was largely incurable. Since then cure rates have steadily improved such that 40-50% of children with AML are cured today
2. Therapy for AML is much more intensive, but shorter (lasting 6-9 months) than ALL therapy, involving repeated cycles of aggressive chemotherapy that generally lead to marrow aplasia and substantial risks of infection. Treatment is largely inpatient and infectious complications are a major issue. Toxic death rates for AML therapy are still 5-10%.
3. Most US groups consider matched sibling stem cell transplant to be the therapy of choice for AML.
4. Major active agents include the anthracyclines (Daunomycin, Doxorubicin, Mitoxantrone) and Ara C, given either at conventional or high (HiDAC) doses.
5. APLM1 is caused by the 15;17 translocation that produces a retinoic acid receptor alpha fusion protein, PML-RAR[] blocks myeloid differentiation. [] acologic doses of retinoic acid overcome this differentiation block and allow cells to differentiate terminally and die. Retinoic acid is now a standard component of all APLM1 treatment regimens, and has revolutionized treatment of this subtype of AML.
6. Other new "targeted" therapies under study include myelotarg, in which the potent but highly toxic chemotherapy agent calicheamycin is conjugated to an anti-CD33 monoclonal antibody. This is internalized into CD33+ cells and the chemotherapy agent is released intracellularly.
7. If relapse occurs, chance of salvage depends on various factors. One of strongest is the time of relapse following initial diagnosis (the sooner one relapses, the lower the chance of salvage). Relapse regimens almost always include stem cell transplantation.

CML

Presenting Symptoms

1. Patients usually have non-specific complaints and are not toxic. They may have fatigue from anemia, bone pain or abdominal symptoms due to massive splenomegaly
2. Laboratory evaluation typically shows a markedly elevated WBC (usually 100,000+) and platelet count (usually 500,000+, often >1,000,000) with all mature elements and few blasts
3. Exam is usually notable for splenomegaly, often massive
4. Some patients exhibit symptoms due to hyperleukocytosis (see above)

Diagnosis and initial evaluation

1. Clinical picture and blood counts are often pathognomonic
2. Disease is tri-phasic with indolent chronic phase (CP) characterized by marked expansion of myeloid cells. Average length of chronic phase is 3 years, but can go over 20 years.
3. Patients inexorably transform (15-20%/yr) into a "blast crises" that is indistinguishable from AML (75-80%) or ALL (20-25%) and is often refractory to chemotherapy
4. A transition state, termed the accelerated phase, is seen in some patients.
5. Initial evaluation must make diagnosis and define stage of disease (vast majority present in CP)

Genetics of CML

1. CML is caused by t(9;22) or Philadelphia chromosome, which creates BCR-ABL fusion protein. All patients must have cytogenetic studies, preferably of bone marrow, to identify the Philadelphia chromosome.
2. Patients in CP have no other cytogenetic abnormalities and presence of other clonal cytogenetic abnormalities is generally considered indicative of accelerated phase
3. BCR-ABL mRNA can be detected by RT-PCR, and the fusion gene can be identified via fluorescence in situ hybridization (FISH)

Treatment

1. CML is not cured by standard ALL or AML regimens and these generally do not eradicate the Philadelphia chromosome.
2. Disease can be readily controlled by Hydroxyurea, an oral chemotherapy agent with minimal side effects, but HU does not change the natural history of the disease
3. Stem cell transplantation is curative. Cure rates in children are 80-90% for those with an HLA-identical sibling donor and 50-70% for those with a suitable matched unrelated donor.
4. Treatment of CML has been revolutionized by the recent development of Imatinib mesylate (Gleevec), a potent oral inhibitor of the tyrosine kinase activity of BCR-ABL protein.
5. Gleevec induces rapid hematologic remissions in >95% of patients with CML in CP and most have complete or partial disappearance of Philadelphia chromosome and enter "cytogenetic remission". This never occurs with HU.
6. Most (>90%) patients who attain cytogenetic CR are still in CR 2 years later, but long term efficacy of Gleevec is unknown at that time. Resistance can develop and is often due to acquired mutations in BCR-ABL that prevent binding by Gleevec, or to amplification of BCR-ABL.
7. Role of SCT in the Gleevec era is controversial.

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Palliative Care Learning Points

1. Demographics of Childhood Deaths

Age 0-1 30,000 annual deaths
Congenital abnormalities, prematurity, perinatal events, SIDS
Age 1-14 14,000 annual deaths
Trauma, cancer, congenital conditions
Age 15-21 16,000 annual deaths
Trauma, cancer, heart disease

2. Differences from Adults

- ~ Relative rarity
- ~ Epidemiology/etiology
- ~ Interpersonal dynamics
- ~ Developmental/communication issues
- ~ Legal/non-autonomy issues
- ~ Symptom measurement tools
- ~ Symptom management tools
- ~ School/community issues
- ~ Acuteness/suddenness
- ~ Bereavement issues

3. Goals of Palliative Care

- ~ Optimal living in the face of life challenge/limitation
- ~ Child- and family-focused service
- ~ Care at home, limiting hospitalization

- ~ Balance between sustaining life/attempts at cure and relieving suffering
- ~ Consistency of care by the same interdisciplinary team
- ~ Holistic education of professional and lay caregivers
- ~ Enhancing comfort of professional and lay caregivers

4. *Tasks of Palliative Care Team*

- ~ Establishing a child and family care plan
- ~ Minimizing symptoms
- ~ Assisting in child's and family's grief work
- ~ Facilitating conflict resolution
- ~ Optimizing the child's quality of life
- ~ Supporting the parents, siblings and friends
- ~ Educating the child, family and caregivers
- ~ Minimizing hospital time as far as possible
- ~ Bereavement counseling
- ~ Facilitating closure for professional caregivers

5. *Reimbursement Issues*

- ~ Reimbursement mechanisms very limited
- ~ Time-intensive counseling, education, advocacy, family support, communication: either limited or no reimbursement
- ~ Federal and state initiatives (eg, Florida's Partners in Care) are under development

6. *Ways to Support a Seriously Ill Child*

- ~ Take time to listen empathetically to child and family individually and together
- ~ Acknowledge the child's understanding and decision-making ability
- ~ Let the child control the conversation and set the pace
- ~ Give detailed explanations when asked about the illness, prognosis, dying process, etc
- ~ Be truthful; use simple concrete language
- ~ Acknowledge ones own feelings
- ~ Use art, music, stories, play
- ~ Verify a child's understanding
- ~ Be ready for strong emotion strongly expressed

7. *Language*

- ~ The concept of hospice care may be rejected, and especially "terminally ill" label
- ~ "Palliative", "supportive", "advanced", or even "home care" may be preferred

8. *Approaching the Concept of Palliative Care*

- ~ Acceptance of a final illness and failure of life-sustaining measures is especially hard in pediatrics
- ~ Therefore this is likely to involve a gradual process with repeated conversations
- ~ The palliative care team is best introduced early, often at diagnosis, to children and families facing the probability of incurability
- ~ The transition from the intensive care team to the palliative care team should be as gradual and smooth as possible
- ~ The traditional "less than 6 months prognosis" is not relevant to pediatric palliative care
- ~ The extent of palliative care team involvement can vary widely and is dictated entirely by the child's and family's needs and wishes
- ~ The child's involvement, as developmentally appropriate, in planning and decision-making is essential
- ~ The palliative care option should never be seen as "doing nothing" or "giving up hope"
- ~ It is quite possible for a child and family to be discharged from palliative care services if the outcome proves unexpectedly favorable

9. *Ethical and Legal Issues*

- ~ “Parties shall assure to the child who is capable of forming his or her own views the right to express those views freely in all matters affecting the child, the views of the child being given due weight in accordance with the age and maturity of the child.”
- ~ Legalities, practicalities and realities will often seem in conflict
- ~ Development of the child’s sense of autonomy varies broadly, especially in the teenage years
- ~ The child’s decision-making capacity can be assessed by offering developmentally appropriate explanations and choices, then asking the child to restate the information in their own words; chronically ill children often have understanding and decision-making abilities well beyond that of age-matched peers
- ~ Factual information, good communication, and caregiver availability to the child and family are key
- ~ Relief of suffering and provision of physical, psychological and spiritual comfort are of overriding importance
- ~ NIH mandates that children aged 7 or older must provide assent to participate in experimental treatments
- ~ In obtaining informed consent/assent physicians must be completely prepared to accept refusal to participate and must avoid at all times all forms of coercion
- ~ Baby Doe: Federal regulations require continuing life-sustaining measures to infants less than 1 year, regardless of the projected quality of life, unless the infant is permanently comatose or imminently dying. However, if the condition is irreversible, *life-sustaining treatment is not required*, and palliative care is an appropriate alternative.

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Pediatric Hematology/Oncology Transfusion Policy Guidelines

Irradiated Blood Products

All pediatric cancer patients will receive irradiated blood products in order to prevent transfusion related graft-versus-host disease.

Filtered Blood Products

All pediatric cancer and sickle cell patients will receive filtered blood products. Filtration is an effective way to eliminate the risk of CMV infection in patients with cancer, and prevents alloimmunization.

CMV Negative Blood Products

CMV negative blood products will be reserved for cancer patients who are documented to be CMV seronegative and are scheduled to undergo a bone marrow transplant. At the time of transplant, these patients are more immunocompromised, and the low level of CMV that may remain in a filtered product can still pose a risk.

Washed Products

Washed blood products will be reserved for patients who have had life threatening allergic reactions in spite of pretreatment with diphenhydramine (1.25 mg/kg) and hydrocortisone (2mg/kg). Washing blood products significantly decreases their lifespan in the circulation and effectiveness.

Erythrocyte Transfusions

Transfusion of packed red blood cells will occur in patients with symptomatic anemia (hemoglobin < 8 with tachycardia).

Asymptomatic patients with chronic anemia should have a lower threshold for transfusion.

Transfusions of PRBC's will be considered in patients with hemoglobin > 8 who are likely to fall lower and require transfusion in the next 1-2 weeks (eg a patient who has recently received high dose chemotherapy who will be discharged from the hospital).

An extended cross-match will be performed on patients who will undergo multiple transfusions over a life-time. These include patients with sickle cell disease, thalassemia, Diamond-Blackfan Anemia, and aplastic anemia.

Dosage: A transfusion of 10cc/kg will increase the hemoglobin 2.5-3.0 g/dl. In patients > 20 kg, the transfusion volume should be rounded to the nearest number of PRBC units (volume of a prbc unit is 240-360 cc's) .

Transfusion time: In uncomplicated patients PRBC transfusions should be infused over 2-3 hours. Faster rates of transfusion may be considered in some settings by experienced physicians.

In patients with slowly developing anemia and Hgb < 5 g/dl, PRBC's should be administered slowly (2ml/kg/hour) until desired Hgb level is achieved. The use of diuretics and exchange transfusion should be considered in patients with signs of heart failure.

Platelet Transfusions

Platelet will be transfused for patients with thrombocytopenia (platelets < 10,000/microliter) or platelet dysfunction and bleeding.

Prophylactic platelet transfusions:

1. Platelets < 10,000/microliter
2. Platelets < 20,000/microliter , and bone marrow infiltration, severe mucositis. DIC, anticoagulant therapy, platelets likely to fall below 10,000 prior to next evaluation, or higher likelihood of bleeding due to local tumor invasion.
3. Platelets <50,000/microliter and DIC, extreme hyperleukocytosis, prior to lumbar puncture, CVL insertion, or major surgical procedure.

Apheresis platelet units will be reserved for those patients likely to receive multiple transfusions in a lifetime, such as patients with aplastic anemia or patients likely to undergo bone marrow transplant, to decrease donor exposure and the risk of alloimmunization.

Starting platelet dose will approximate 1 unit per 10 kg, which is expected to raise the platelet count by 50,000 platelets/microliter. Higher doses can be considered in septic patients, or patients with DIC, or splenomegaly.

Platelet refractoriness will be defined as inadequate rise in platelet counts as measured within 1 hour of platelet transfusion.

Approaches to platelet refractoriness:

1. Make sure platelets are ABO compatible.
2. Ask for fresh units.
3. Test for HLA antibodies and platelet specific allo-antibodies.
4. Consider IVIG (0.5 gm/kg) and Amicar in patients with significant bleeding.

Granulocyte Transfusions:

Granulocyte transfusions will be reserved for neutropenic patients (ANC<500) with life threatening bacterial or fungal infections who are unlikely to recover their neutrophils within a week, or patients with severe neutrophil dysfunction.

Patients should be tested for presence of HLA allo-antibodies prior to first transfusion, and then biweekly throughout course. Patients are frequently alloimmunized, and this can lead to poor increments and severe reactions. In patients who develop alloantibodies, compatible donors should be used.

Dose of neutrophils will be 1×10^9 neutrophils/kg in children with a maximum dose of 3×10^{10} neutrophils in larger patients.

Transfusion time will be 2-3 hours.

Fresh Frozen Plasma:

Indications:

1. Life-threatening bleeding in patient who has received warfarin.
2. Severe liver disease
3. DIC
4. Massive Transfusion
5. Isolated congenital factor deficiency that does not have a safer, more appropriate product.

Dosage: 10cc's/kg of ABO compatible product. Doses as high as 20 cc's/kg can be given to patients with congenital factor deficiency.

Monitoring:

Coagulation studies (PT/PTT) should be performed after plasma infusions, and monitored at least every 12 hours in patients with ongoing transfusions.

Cryoprecipitate:

Indications:

1. Severe liver disease
2. DIC
3. Afibrinogenemia or significant hypofibrinogenemia with other associated indications
4. Von Willebrand's -2nd line therapy
5. Factor XIII deficiency

Dose:

Adult(70kg): 10 bags

Child: 1-2 bag/10kg body weight should increase fibrinogen by 60-100 mg/dL

Neonate: 1 bag will increase fibrinogen by >100mg/dL.

vWD: Adult: 10-12 bags q 12 hours

Child 1 bag/6kg q 12 hours

FXIII def: 1 bag/10kg every 7-14 days

Cryoprecipitate should be transfused within 6 hours of thawing, over 2-3 hours.

Anemia

1. Anemia is defined by age- and gender-dependent norms for the hemoglobin/hematocrit level (see table).

Table: Normal RBC Values by Age & Gender

Age	Hgb (g%)	HCT (%)	MCV (fL)	MCHC	Reticulocytes
30 weeks	15.0	45	120	32	5-10
Term	16.5	50	110	33	3-6
1-3 days	18.5	55	110	33	1.5-4.5
1 month	14	45	100	32	0.1-1.5
6m-2yrs	12.0	35	80	33	0.5-1.0
6-12 yrs	13.5	40	85	34	0.5-1.0
12-18 yrs	15m/14f	45m/40f	90	34	1-3

2. Clinically significant anemia is defined by the presence of relevant symptoms, namely, fatigue, irritability, breathlessness on exertion, anorexia, and slowed developmental milestones. Pica may be present.
3. There are three ways to become anemic: reduced production of red blood cells, destruction of red blood cells, and loss of whole blood.
4. The work-up for anemia must include a detailed history and physical exam. A full dietary history should be obtained, plus details of medication use, ethnicity, growth and development, and pertinent family history (anemia, splenectomy, cholecystectomy). Review of systems must include constitutional symptoms such as weight loss, fevers, and night sweats, potential sites of blood loss (recurrent epistaxes, hematuria, melena), prenatal or perinatal complications.
5. Physical examination may reveal pallor, poor nutrition, signs of systemic illness, glossitis, icterus, tachycardia with flow murmur, tachypnea, and hepatosplenomegaly.
6. Laboratory evaluation should include a CBC with RBC indices, reticulocyte count and blood smear examination, urinalysis, stool exam for occult blood, and a direct Coombs test.
7. Classification by Red Cell Size: A descriptive although etiologically non-specific way to classify anemias is by RBC size: microcytic, normocytic, and macrocytic.
8. Microcytic Anemia: If the patient has a microcytic anemia, iron studies should be obtained (reticulocyte Hgb, serum Fe, TIBC, and ferritin). A screening test for both Fe deficiency and lead poisoning (a now uncommon cause of microcytic anemia) is a free erythrocyte protoporphyrin level.
9. Normocytic Anemia: Renal function studies should be obtained if the anemia is normocytic and appears chronic. Other normocytic anemias include that of chronic disease, bone marrow failure syndromes and leukemia.
 - 9a. Hemolytic Anemia is an etiologically broad group of usually normocytic anemias (but see Thalassemia syndromes below). If the anemia appears hemolytic (normocytic with raised reticulocyte count +/- positive Coombs) liver function studies should be obtained, plus a haptoglobin test (may give falsely low values under 6 months), and red cell osmotic fragility and enzyme measurements considered (to rule out G6PD, pyruvate kinase, and other rarer enzyme deficiencies). Immune hemolysis is typically associated with microspherocytes on the blood smear, formed when macrophages "bite" the antibody-bound red cells, removing part of the membrane to produce schistocytes (cell fragments) and subsequently spherocytes. Non-immune hemolysis (e.g., DIC, HUS, hypersplenism) is typically micro-angiopathic, with cell fragments on the blood smear and often associated thrombocytopenia. Hgb electrophoresis may be indicated if neonatal screening is not available or was not obtained, to rule out Sickle Cell or Thalassemia syndromes. The latter may be associated with microcytic anemia and a history of Bart's Hgb on newborn screening (α -Thalassemia trait) or increased Fetal Hgb and Hgb A₂ (β -Thalassemia trait). The Mentzer index (MCV divided by the RBC) is useful to distinguish iron deficiency from Thalassemia trait (above 13.5 suggests Fe deficiency, below 11.5 suggests Thalassemia trait).
10. Bone marrow Failure or Infiltration: These are another subgroup of normocytic anemias (normocytic anemia with low reticulocyte count and low white cell and platelet counts). A bone marrow aspiration and biopsy should be obtained if aplastic or hypoplastic anemia or leukemia is suspected.

11. Macrocytic Anemia: Aplastic anemias may be associated with macrocytic anemia, the MCV often exceeding 100, and must be distinguished from folate and B12 deficiencies, which characteristically produce a macrocytic anemia (although usually with hypersegmented neutrophils), and sometimes leucopenia and thrombocytopenia.
12. Treatment of iron deficiency: It takes at least 3 months to replenish depleted iron stores, but there should be a reticulocytosis within a week of instituting therapy, indicating early response. Premature infants should receive 3mg/kg/24hrs of elemental iron in 2 divided doses, and older children 6 mg/kg/24 hrs. Iron preparations are variably absorbed, and should be given with meals to avoid gastric irritation. Give vitamin C to increase absorption and avoid antacids and black tea, which lessen absorption. Attention to the diet is essential, particularly reduction in excessive milk and use of iron-rich foods.
13. Treatment of other conditions depends primarily on treatment of the underlying cause. Folate deficiency is treated with folic acid 5mg-15mg/day for 7-14 days, with correction of the diet and/or the underlying cause. B12 deficiency requires lifelong treatment, usually with 100mcg/day for several days by i/m injection, followed by 50-100 mcg i/m monthly.

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Bleeding Disorders Learning Points

1. General Points:

- a. This section is concerned with non-thrombocytopenic causes of bleeding.
- b. It also excludes non-hematological conditions that cause bleeding manifestations due to vasculitis (eg, Henoch-Schonlein Purpura).
- c. The three commonest inherited causes of excessive and/or spontaneous bleeding are (in order of frequency) Von Willebrand's Disease (vWD, sometimes called Hemophilia C), Factor VIII Deficiency (Hemophilia A), and Factor IX Deficiency (Christmas Disease or Hemophilia B).
- d. vWD is usually autosomally inherited; factor VIII and IX deficiencies have X-linked inheritance.
- e. vWD usually presents with mucosal bleeding, particularly epistaxis, dental and post-surgical bleeding, and menorrhagia. Factor VIII and IX deficiencies present with hemarthroses and intramuscular bleeding, but may also be associated with internal bleeding (eg, subdural hematomas in the newborn). Clinical manifestations usually begin when the child starts to walk and fall frequently. Purpura and petechiae are not usually manifestations of these disorders.
- f. Diagnosis depends on suspecting one of these conditions (not infrequently at birth or circumcision), taking a thorough history, particularly a family history, and performing the appropriate laboratory work-up.
- g. Secondary causes of excessive bleeding not primarily or solely due to platelet deficiency or dysfunction include liver failure (due to non-synthesis mainly of factors II, VII, IX, and X, that are made in the liver), septic shock and DIC, excessive consumption of coagulation factors, particularly due to catastrophic blood loss, excessive tissue trauma and burns.

2. Von Willebrand's Disease

- a. Von Willebrand's Disease is an autosomal dominant disorder, marked by platelet non-adhesion to damaged endothelium secondary to decreased vWD antigen, which (a) facilitates platelet adhesion and (b) is the carrier protein for Factor VIII (Factor VIII coagulant: VIII:C). Both the factor VIII antigen and coagulant are low in vWD, usually between 20% and 50%, while in classical hemophilia A only the coagulant is low usually less than 1% to 10%.
- b. By history, these patients will often have a positive family history (on either parental line) of nose bleeds, excessive bleeding after surgery or menorrhagia.
- c. Primary laboratory screening assay includes a platelet function assay (PFA), which has replaced the now defunct bleeding time, and which reproduces the in vivo interaction between the vascular endothelium, platelet adhesion, and vWF interaction. If this value is normal most hematologists do not recommend further laboratory evaluation.
- d. If the PFA is abnormal, definitive laboratory testing is performed. This should include a PTT (usually prolonged), factor VIII antigen and coagulant (activity), vWF multimers (normal in Type I vWD but abnormal in Type II and III vWD), and ristocetin cofactor (low in Type I and Type II, and undetectable in Type III).
- e. Treatment for Type I vWD is usually with desmopressin or DDAVP, which causes increased release of endogenous Factor VIII from endothelial cells. It can be given IV or more often by nasal spray, in a dose of 1-150 mcg spray in 1 nostril (under 50kg) or in both nostrils (over 50kg). This is given q12hrs for a maximum of 3 days (because of its antidiuretic effect). Aminocaproic acid (Amicar) is often used as supplementary therapy after dental or other surgery because of its antifibrinolytic property. The dose is 100mg/kg (max 30g/24 hrs) IV or oral (swish and spit after dental surgery), with a loading dose if possible beforehand, then every 4 hours for 5+ days. For more major bleeding, or for vWD Types II and III, semi-purified factor VIII concentrates must be used, that contain the entire factor VIII/vWF complex, must be used. The more recent genetically engineered factor VIII concentrates do not contain vWF.

3. Hemophilia

- a. X-linked disorders marked by spontaneous bleeding usually muscle or joint bleeds.
- b. Severe disease (less than 1% Factor VIII (Hemophilia A) or Factor IX (Hemophilia B) – is seen in the majority of patients.
- c. Moderate disease indicates a factor level between 1% and 5%.
- d. Mild disease indicates a factor level greater than 5%.
- e. Although mildly and moderately affected patients rarely bleed spontaneously, all patients tend to bleed excessively after trauma.
- f. Genetically engineered recombinant factor replacement is the treatment of choice. There is no proven advantage to one over another.
- g. 1 unit/kg of factor VIII raises the plasma level by 2% for 12 hours (half life = 8-12 hrs); 50 units/kg raises the level to 100%. Continuing doses of 25 units/kg every 8-12 hours will usually maintain 100% factor levels.
- h. Because of its longer half-life (16-24 hrs), 1 unit/kg of factor IX raises the plasma level by 1% for 24 hours or 100 units/kg will raise levels to 100%. Continuing doses of 50 units/kg every 12 hours will maintain 100% factor levels.
- i. At age of 3-4, or earlier if there are frequent early bleeding episodes, patients start on prophylactic therapy. This consists of 50% replacement (25 units/kg Factor 8 or 50 units/kg Factor 9) 3 times per week. An infusaport is usually inserted in younger patients. Patients from about aged 10 can usually learn to give their own IV infusions.
- j. Following muscle or joint bleeds, the factor level should be corrected to 50%, while for CNS bleeds, other internal or life-threatening bleeding, or major surgery, levels should be maintained at 100% for several days.
- k. For elective surgery, standard orders are available, that usually include the use of a continuous infusion (CI) of factor, which is cost-effective in maintaining an adequate level with less overall factor replacement.

This includes guidelines for laboratory monitoring of factor levels and sliding scales for extra bolus doses according to levels obtained.

- l. Regular follow-up by a trained pediatric hematologist is essential. Patients should be screened for understanding of their condition, compliance with the prescribed regimen, recurrent joint bleeding (“target joints”), dental care, LFT’s and hepatitis if they have received non-recombinant factor, and factor VIII antibodies. Dose adjustments should be made to allow for growth. An orthopedic surgeon and dentist trained in hemophilia care should see all patients regularly.
- m. The table lists the laboratory findings in these three and other rarer coagulation disorders.

Table: Laboratory Findings in Coagulation Disorders

Disorder	Platelet Fxn Assay	PTT	PT	TT	Ancillary Tests
Hemophilia A	N	A	N	N	vWF normal or increased, Factor VIIIc usually under 5%
Hemophilia B	N	A	N	N	Factor IX usually under 5%.
von Willebrand’s disease	A	A	N	N	vWF and F VIIIc usually 20%-50%, ristocetin-induced platelet aggregation and ristocetin cofactor activity usually low.
Afibrinogenemia	A	A	A	A	Fibrinogen low; platelet function may be abnormal
Dysfibrinogenemia	N	A	A	A	Reptilase time prolonged, FDP levels increased.
Hypoprothrombinemia	N	A	A	N	Two-stage assay abnormal.
Factor V deficiency	N	A	A	N	Factor V level low
Factor VII deficiency	N	N	A	N	Factor VII level low; Russell’s viper venom time normal.
Factor X deficiency	N	A	A	N	Factor X level low; Russell’s viper venom time abnormal.
Factor XI deficiency	N	A	N	N	Factor XI level low
Factor XII deficiency	N	A	N	N	Factor XII level low
Factor XIII deficiency	N	N	N	N	Clot solubility tests abnormal.

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Pain Control

1. General Principles

- ~ Effective pain control is a moral imperative
- ~ Response to reports of pain must be quick and effective
- ~ Social and emotional issues often lower pain tolerance threshold
- ~ Playing or sleeping may be diversions not indicative of lack of pain
- ~ Use scheduled around-the-clock medications with frequent reassessment
- ~ Use WHO pain escalation (mild, moderate, severe) ladder
- ~ Reassess frequently after any analgesic intervention
- ~ Learn about non-pharmacological as well as pharmacological treatments
- ~ Uncontrolled protracted pain may have long term consequences

2. Assessment Tools

- ~ Assessment must be tailored to the child's age
- ~ Gold standard is self-report
- ~ Physiological measures useful especially in young children
- ~ Behavioral responses are unreliable because they will attenuate with chronic pain
- ~ Infants: CRIES scale useful
Crying, Requires more O₂, Increased VS, Expression, Sleeplessness
- ~ Self-report scales useful over 3 years
eg, Bieri Faces Scale, Oucher Scale in 3-7-year-olds
- ~ Numeric and visual analogue scales effective over about 5 years

3. Correcting Misconceptions

- ~ Serious side effects from opiates are not more frequent in children than adults
- ~ Adequate pharmacological pain relief does not predispose to addiction
- ~ Worsening disease is a much more frequent cause of increased analgesic requirements than tolerance
- ~ Opiates and co-analgesics can control at least 95% of severe pain; invasive procedures are rarely needed

4. Managing Procedure-Related Pain

- ~ Build trust; take time
- ~ Address physical + emotional aspects with pharmacological + non-pharmacological treatments
- ~ Find out about what helped child and what didn't in the past
- ~ Enlist help of parents
- ~ Opioids + sedative hypnotics + local anesthetics + non-pharmacological therapies are often excellent alternatives to general anesthesia
- ~ Conscious sedation requires adequate trained personnel and monitoring equipment
- ~ Local anesthetics often work faster on lighter-skinned than dark-skinned people; use buffered lidocaine, a 27-gauge needle, and slow incremental injection

5. Routes of Delivery of Analgesics

- ~ PO route preferred (cheaper, safer, wide variety, easy to titrate, easily given at home)
- ~ Parenteral route (IV or SC *not* IM) is best for acute severe pain, rapid titration, non-tolerance of PO
- ~ Transdermal route achieves steady state in 12-16 hours, is excellent for long term severe pain control, but may be less effective in febrile sweating restless children (unpredictable absorption)
- ~ Transmucosal lozenges, lollipops, concentrated liquids are helpful for rapid pain relief particularly in children who cannot swallow or have poor IV access

6. Pharmacological Agents

- ~ Acetaminophen (15mg/kg/dose/4-6hrs to max of 75mg/kg/24 hrs) is useful when used regularly for *mild* pain;
- ~ NSAIDs are excellent as primary or adjuvant analgesics in patients with normal platelets and renal function and intact GI mucosae (eg, ibuprofen 10mg/kg/dose/6hrs); COX-2 inhibitors are useful alternatives
- ~ Codeine (1mg/kg/dose/4hrs) is useful for moderately severe pain but only 20% converted to active opioid so side effects (nausea, constipation, CNS) are frequent; consider moving quickly to more effective opiates
- ~ Opioids are used for moderate to severe pain; goal is maximum comfort with maximum function, avoiding frequent breakthroughs and “chasing after” pain, which fuels anxiety and mistrust
- ~ Schedule should be regular round-the-clock, q4hrs for immediate-release opioids, using the same drug for breakthroughs, which should be q1hr for PO and q15mins for parenteral, titrating baseline scheduled doses according to amount of breakthrough doses required
- ~ Recommended opioids are morphine, oxycodone (Percocet), hydromorphone (Dilaudid) and fentanyl
- ~ Long-acting opioids (MS Contin, Oramorph SR, oxycodone, hydrocodone) recommended for long term pain, given q8-12hrs
- ~ Methadone should only be used by clinicians with considerable experience because of its slow onset of action, wide variability in effect, and often very long half-life (up to 80hrs)

Table 1 shows equivalent and starting doses of different opioids:

Table 1

Drug	Equipotent Doses		Starting Dose		PO/IV Ratio	Half-Life
	PO	IV/SC	PO	IV/SC		
Morphine	30mg	10mg	0.3mg/kg	0.1mg/kg	3:1	3 hours
Codeine	180mg	120mg	1mg/kg	0.5mg SC	2:1	3 hours
Oxycodone	20mg	N/A	0.2mg/kg	N/A	N/A	3 hours
Hydromorphone	7.5mg	1.5mg	0.05mg/kg	0.025mg/kg	5:1	3 hours
Fentanyl	N/A	N/A	25mcg		N/A	24 hours

7. Breakthrough Pain

- ~ Due to inadequate analgesia, worsening disease, movement, stress
- ~ Treat with immediate-release opioid, same as baseline drug, and titrate
- ~ Use 10% of total 24-hr requirement or 100% of hourly dose if patient on a continuous infusion
- ~ Extra doses often needed at night; use 2x normal dose at bedtime
- ~ Naloxone (Narcan) is sometimes used to reverse the side effects of opiates (pruritus, constipation, urinary retention), without lessening its analgesic effect.

Table 2 shows guidelines for the use of patient-controlled analgesia.

Table 2

Drug	Basal	Bolus	Lockout	#/hr
	mcg/kg/hr	mcg/hr	mins	
Morphine	10-30	10-30	6-10	4-6
Dilaudid	3-5	3-5	6-10	4-6
Fentanyl	0.5-1.0	0.5-1.0	2-3	2-3

8. Abuse of Analgesics

- ~ Physiological and psychological dependency may occur in patients who are requiring opioids over a long period.
- ~ The incidence is low; for example, less than 5% of patients with sickle cell disease requiring frequent treatment of pain crises become possibly or probably addicted. It should never be seen as a problem in patients with incurable diseases undergoing end-of-life care.
- ~ Management requires the help of psychologists, psychiatrists and social workers trained in addiction medicine, although the primary requisite is self-recognition by the patient and willingness to comply with treatment.
- ~ Immediate recommendations for other staff are (a) to be precisely aware of what drugs the patient has available in the hospital and by prescription at home, (b) to know who the prescribing physician is (particular care must be taken to avoid duplication), and (c) to make use of a “contract” that sets limit on patient use of the relevant analgesics.

9. Non-pharmacological Management of Pain

- ~ Physical, cognitive and behavioral measures can lessen physical and psychological distress
- ~ Guided imagery and hypnosis can relieve breakthrough pain
- ~ Distraction and relaxation may reduce pharmacological requirements
- ~ Massage, acupuncture, acupressure, reiki and therapeutic touch are all effective sometimes
- ~ Music and humor are also valuable adjuvant that may lessen pharmacologic requirements
- ~ These interventions are all free of serious side effects

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Sickle Cell Disease Learning Points

1. Occurs in 1 in 500 African Americans.
2. The gene is also prevalent in Africans, Arabs, Egyptians, Turks, Greeks, Italians, Iranians, and Asiatic Indians.
3. Newborn screen reveals
 - a. Hgb FS (no A) if homozygous SS disease.
 - b. Hgb FSC (no A) if S-C disease
 - c. Hgb FSA if Sickle β^+ -Thal (double heterozygote)
 - d. Hgb FS (no A) If Sickle β^0 -Thal
4. Once a newborn baby is suspected of having Sickle Cell Disease, he or she is referred to a center for quantitative confirmatory hemoglobin electrophoresis and counseling.
5. For severity of disease: $SS \geq \text{Sickle } \beta^0\text{-Thal} > \text{Sickle } \beta^+\text{-Thal} \geq SC$

6. Typical laboratory values for an SS patient:

- a. Hgb 7.5 (range 5.5 - 9.5)
- b. Hct 22 (17 - 29)
- c. Retic 12% (5 - 25%)
- d. WBC 12,000 (10,000 - 20,000)

7. Emergencies in Sickle cell patients:

- a. Vaso-occlusive crisis: localized ischemia/infarction. About a third of the patients have 4-5 episodes a year necessitating 2-3 admissions, lasting typically 5 - 7 days. Treated with **hydration** (one and a half x maintenance IV plus PO). Note: All SS patients are hyposthenuric, i.e. they cannot concentrate their urine secondary to intra-renal medullary sickling so they are high-risk of dehydration. A dilute urine (low specific gravity) does not mean a sickle cell patient is well hydrated!! Treated with **medication** - i.e. narcotics. If old enough use a PCA pump. The right way to start a PCA pump is to IV bolus narcotic until comfortable and then start your basal rate and PCA boluses. Titrate to relief. As a rule sickle cell patients are highly reliable in assessing their own narcotic needs. Treated with **oxygenation** only if patients are hypoxic - do not use O₂ for uncomplicated pain crisis in that this can precipitate an aplastic crisis. Caution: VOC can present similar to other particularly surgical problems such as an acute abdomen, osteomyelitis, septic joint, biliary obstruction, etc. For patients with more than three episodes of severe pain a year, hydroxyurea was shown to decrease the number of crises by half, reduce hospitalization, and decrease the amount of blood transfused and incidence of acute chest syndrome.
- b. Aplastic crisis (transient cessation of erythropoiesis): like all patients with a chronic hemolytic anemia who have high reticulocytes count any marrow suppression can lead to symptomatic anemia. Between 70 and 100 percent of episodes are due to infection by human parvovirus B19. Reticulocytopenia begins about 5 days post-exposure and continues for 7 to 10 days. Check CBC and reticulocytes in family members and contacts with Sickle Cell Disease. Check reticulocyte counts often in patients with fever/infection. Treated with simple pRBC transfusions. Infection confers life-long immunity. No cases of recurrent parvovirus B19 infection have been reported in children with sickle Cell Disease. Because infection during the mid-trimester of pregnancy may result in hydrops fetalis and stillbirth, isolation precaution for pregnant staff is necessary.
- c. Infection: 80% of patients younger than 3 years of age, who die, die of Streptococcus Pneumoniae sepsis. A landmark randomized, placebo-controlled study of Sickle Cell patients 4 months old and younger (done about 20 years ago) demonstrated that administration of penicillin twice a day prevented 80% of the life-threatening infectious episodes. The current practice is therefore to give prophylactic penicillin until 5 years of age. In addition these patients are getting pneumovax (PPV23) at two years of age and repeated at 5 and 10 years of age. When available prevnar (PPV7) should be given at 2, 4, 6 and 12 months of age. Yearly influenza vaccination is also recommended in all Sickle Cell patients to prevent severe morbidity.
- d. Acute Chest Syndrome: Incidence 21 events/100 patient-years. Mortality 4-9%. Most common complication of surgery and anesthesia.

Definition:

- a. New pulmonary infiltrate on chest x-ray
- b. Fever
- c. Respiratory signs and symptoms (tachypnea, wheezing or cough).

Risk factors: Winter, high sickle hemoglobin and WBC, aseptic necrosis or fracture, cigarette smoke, prior history of ACS.

Causes: Bone marrow embolism, fat embolism, infection (Chlamydia, Mycoplasma, RSV, Staphylococcus aureus and Streptococcus pneumoniae).

Treatment:

- a. Supplemental Oxygen
 - b. Transfusions (in an emergency, also exchange transfusion to decrease the % S Hgb to < 30%).
 - c. Antibiotics (cephalosporin and macrolide)
 - d. Incentive spirometry
 - e. Bronchodilators (even if there is no wheezing)
 - f. Limited hydration (no more than 1.5 times maintenance)
 - g. After recovery: Follow PFT, consider hydroxyurea, and in recurrent ACS consider bone marrow transplantation.
 - h. Be careful to avoid over-sedation with narcotics.
-
- e. CNS changes: Another true medical emergency requiring emergent exchange transfusion. Sickle patients are at risk for stroke so any neurologic change should prompt rapid therapy (exchange transfusion) and neuro-imaging studies. Approximately 50% of children with sickle cell disease and a first stroke who do not receive chronic transfusions will develop another stroke within 3 years. Giving blood transfusion on a regular basis (so called, hyper-transfusion regimen) will reduce the incidence of a recurrent stroke to only 10%. Current national recommendations are that transfusion should be continued for at least 5 years.
 - f. Splenic sequestration (sudden pooling of a large amount of blood into the spleen leading to acute splenomegaly, profound anemia and hypotension): typically occurs in patients < 3 years old, (but can occur at any age in patients with Hb S-C disease or sickle beta-thalassemia) can present with signs and symptoms of severe hypovolemic shock. Hgb values can be as low as 1-2 gm/dl. Requires emergent transfusion therapy with whole blood or pRBCs and FFP. The goal of transfusion is to prevent shock, not to restore hemoglobin to normal or to the steady state. After transfusion the spleen shrinks and hemoglobin increases more than predicted due to release of trapped RBC from the spleen.
 - g. Priapism: Painful erection from intra-penile sickling. The incidence is about 35%. Mean age of onset 15 years. There are no controlled studies which determine the effectiveness of treatment in arresting acute problems and in preventing subsequent sexual dysfunction. Treat with pain meds, hydration, and transfusion. Consider exchange transfusion if not better within 24 hours and surgical therapy if exchange fails. Priapism tends to recur. About 21% of patients with a history of priapism will develop erectile dysfunction.

8. Transfusion.

a. Alloimmunization: Up to 36% of patients with sickle cell disease will develop either immediate or (more often) delayed transfusion reactions. These may be related to racial and ethnic differences of minor blood group antigen profile. It may also be related to transfused leukocytes and recipient immunogenetics. To address this problem all newly diagnosed patients with Sickle Cell Disease will have a complete red blood cell phenotype. (Preferably before they have been transfused). The transfused blood should be leukocyte filtered and matched for blood groups C, c, Kell (K), and Kidd (JkA, JkB).

b. Iron overload. Chronic transfusion can lead to iron overload and hemosiderosis, especially of the heart and liver. Chelation with Desferal is usually started after a cumulative 120ml per kg of transfused blood and a serum ferritin level of 2000 - 2500 mg/ml. Since ferritin is an acute phase reactant and may not be a true reflection of iron stores, the national recommendation is now to perform a liver biopsy for quantitative iron content.

Chelation is begun when iron content in the liver is 7 mg/g dry weight or more. Desferal is given at home by pump subcutaneously over 8-12 hours, 5 days a week. For patients who are non-compliant, Desferal can be given in the hospital as a continuous infusion over 48 hours.

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Thrombophilia or Hypercoagulable States

1. Definition: tendency to have thrombosis as a result of an inherited or acquired molecular defect.
2. Hypercoagulability disorders can be correctly diagnosed in about 85% of cases. Clinical thrombosis often arises from more than one “hit”, e.g., trauma including surgery or oral contraceptives in a previously asymptomatic patient with an inherited disorder. Some individual defects are more thrombogenic than others, as are multiple abnormalities.
3. Risk factors: Autoimmune disease, cancer, cardiac disease, cardiac valve replacement, catheters, chemotherapy, dehydration, drugs (e.g., phenothiazines, phenytoin), hyperlipidemia, infection especially sepsis, Kawasaki’s disease, liver disease, oral contraceptives, pregnancy, renal disease, sickle cell disease, surgery, thalassemia and trauma.
4. Individual Inherited Syndromes: Most significant inherited disorders are deficiencies of antithrombin, protein C and S, activated protein C resistance/factor V Leiden mutation, antiphospholipid syndrome (lupus anticoagulant and anticardiolipin antibody), homocystinemia, plasminogen abnormalities, prothrombin G20210A mutation and sticky platelet syndrome.
5. Mnemonic - CALMSHAPES: protein C deficiency, Antiphospholipid syndrome, factor V Leiden, Malignancy, protein S deficiency, Homocystinemia, Antithrombin 3 deficiency, Prothrombin G20210A mutation, Elevated factor VIII, Sticky platelet syndrome.
6. Investigation: Clinical features that suggest hypercoagulability include thromboembolism early in life, positive family history, thrombosis at unusual sites (e.g. upper extremity), spontaneous or recurrent episodes
7. Confirmatory tests for children with thromboembolic events.

<i>Location</i>	<i>Gold standard</i>	<i>Current practice</i>
DVT in upper system	Venography	Venography and USG of internal jugulars
DVT in lower system	Venography	USG then proceed to venography if needed
Pulmonary embolism	V/Q scan	V/Q scan; value of spiral CT not certain

Tip of CVL	Echocardiogram	Echocardiogram; USG
Arterial thrombosis	Angiography	Doppler may suffice, may need angiography
Ischemic stroke	Angiography	MRI, MRA
Sinovenous thrombosis	MRI, MRA	MRI, MRA

8. Laboratory Studies: Complete laboratory work-up is generally unreliable during acute thrombosis or while on anticoagulants. Basic work-up for thrombotic disorders should include the following: PT, PTT, Factor V Leiden assay, protein C and S levels, cardiolipin antibodies, lupus anticoagulant, ANA titer, antithrombin III assay, prothrombin G20210A mutation, fibrinogen, plasminogen activator inhibitor-1 assay, platelet aggregation and homocysteine level. Appropriate studies to rule out acquired risk factors listed above should also be considered.
9. Screening of healthy children of adults diagnosed with thromboembolic risk factors: the thrombotic risk of healthy children with a single thrombophilic defect is extremely low, therefore screening in these children under 15 years is unjustified as being non-cost-effective.
10. Treatment: Low-molecular weight heparin (LMWH) 1 mg/kg SQ q12 hours has become the most often used therapy, both acute and long term. Advantages are predictable pharmacology, more certain compliance, lack of interference from drugs or diet, lower risk of heparin-induced thrombocytopenia (HIT), and probably lower risk of osteoporosis. Single-dose (q24hrs) is quite often used in adult hematology practice. Initial monitoring with anti-Xa levels with desired results between 0.5 and 1.0 is recommended.
11. Oral anticoagulants (e.g., warfarin), can also be used, which reduce plasma levels of vitamin-K-dependent factors (II, VI, IX, X, PC, PS). Start with 2 – 5 mg PO qd and adjust based on the INR, with a target level of 2.5. Alterations in dosage may be needed with concurrent use of antibiotics, steroids, anticonvulsants, and TPN, especially in infancy, when oral anticoagulants are best avoided. Long term use is associated with osteoporosis. Because of their less predictable pharmacokinetics, laboratory monitoring must be carried out more frequently than when using LMWH.

Transfusion Therapy

Please see our attached transfusion guidelines below.

In addition, please note the following.

1. Blood transfusions can be risky, and should be prescribed in a thoughtful way. Transmission of HIV, Hepatitis B and C, and West Nile virus are only a few of the pathogens that can be transmitted via blood transfusions.
2. Cancer patients should receive only irradiated and filtered (leukocyte depleted) blood products. Irradiation inactivates donor-derived lymphocytes and prevents transfusion associated graft-versus-host disease. Leukocyte depletion prevents cytomegalovirus infection and also decreases transfusion associated reactions (febrile reactions). It is usually unnecessary to order CMV negative blood products in our cancer patients because they are leukodepleted.
3. We reserve CMV negative blood products for patients who are known to be going to bone marrow transplant. This is because they are even more profoundly immunosuppressed at the time of transplant, and the theoretical risk of transmitting CMV from a leukodepleted CMV positive blood product.
4. Sickle cell patients and other hematology patients not receiving myeloablative chemotherapy or lacking functional T-cells can receive non-irradiated blood.
5. Sickle cell patients and any other hematology patients who are likely to receive lots of blood products (aplastic anemia) should received filtered blood in order to decrease alloimmunization and febrile reactions. The antigens on the leukocytes are very immunogenetic.

6. The indication for washed products is repeated (ie more than one) severe allergic reactions following transfusion. Washing products significantly decreases their post-transfusion life span and utility.
7. Blood should be typed only when a patient might need blood but the need is not yet clear. Blood should be typed and cross-matched only when there is a clear need or an emergency.
8. Blood is typed to determine the major blood group antigens (ABO). Cross-match is performed to determine whether patient has significant antibodies to minor erythrocyte antigens that might cause a transfusion reaction.
9. Sickle cell and thalassemia patients and other pediatric patients who are likely to receive many transfusions should have extended red blood cell phenotyping in order to fully characterize their minor blood group antigen. The blood bank will strive to give them units that more closely match their extended phenotype to avoid the development of erythrocyte antibodies.
10. The indication for plasma transfusion is limited to severe liver disease, disseminated intravascular coagulation, and isolated congenital factor deficiencies for which there is not a safer or more appropriate product. A person with Hemophilia A should receive recombinant factor VIII, if available.
11. Transfusion reactions.
 - A. Acute hemolytic. Due most often to ABO incompatibility. Signs and symptoms include fever, chills, back pain and chest pain, and shortness of breath. Patients can develop shock, causing renal failure, and disseminated intravascular coagulation. If this is suspected, transfusion should be stopped immediately, as these reactions can be fatal. A direct coombs test will demonstrate antibody on the patient's red blood cell surface. This reaction is the reason for strict guidelines regarding identification of patient and blood products.
 - B. Transfusion related lung injury (TRALI). Presents as acute respiratory distress 1-6 hours following transfusion of plasma or plasma containing blood component (platelets). Patients will have fever, respiratory distress, bilateral pulmonary infiltrates on CXR suggesting edema, and severe hypoxemia. TRALI may be due to antileukocyte antibodies causing agglutination within the lungs, or alternatively due to biologically active lipids that are present in the transfused product.
 - C. Allergic reactions. Plasma proteins within the transfused products can cause allergic reactions. Patients with a history of allergic reaction should receive premedication with antihistamine (diphenhydramine), and if this does not take care of the problem, hydrocortisone (1mg/kg), 30 minutes prior to the transfusion. Washing products (replacing the plasma with saline) will prevent allergic reactions, but will decrease the effectiveness of the transfusion. Leukoreduction does nothing for allergic reactions. Recurrent severe allergic reactions to blood products are associated with IgA deficiency.
 - D. Febrile reactions. Febrile reactions are believed to be due to leukocytes, or alternatively, due to bioactive cytokines within the product. Fever can indicate an ABO incompatible product and bacterial contamination, and these possibilities should at least be considered. These reactions most often occur during platelet transfusions. The incidence of these reactions can be decreased by prestorage leukodepletion, which is not currently performed on most units transfused at this hospital.
 - E. Hyperkalemia. Can be seen in patients receiving massive transfusions or transfusions from erythrocytes that have been stored for a long time. Erythrocytes that are less than 5 days old should be used in patients receiving exchange transfusion or getting a massive transfusion.
 - F. Sepsis. Because platelets are stored at room temperature, this is a particular problem with platelet transfusions.¹⁻⁵

Cases:

1. A nurse calls you because a neutropenic patient who came in for a short-stay transfusion has now spiked a fever. The patient is rigoring but is otherwise asymptomatic. The blood bag and the patient's arm band match. On physical exam, you look for an alternative source, and do not find one.

This patient is probably having a non-hemolytic febrile transfusion reaction, but should be monitored for sepsis (blood cultures, in patient monitoring).

2. The blood bank is confused. You are night float, and the day time resident has ordered irradiated blood for a patient with sickle cell anemia. What should you do?

Unless this patient is also a cancer patient, getting a bone marrow transplant, or has some underlying T-cell immunodeficiency, they do not need irradiated blood. Irradiation is to prevent transfusion related graft-versus-host-disease.

3. The nurses call you to ask for premedication orders for a brand new patient with leukemia who is about to get platelets.

While it may seem like we premedicate everybody for transfusions, premedication should be reserved for those patients who have had prior febrile or allergic reactions. If in doubt, you or the patient's nurse can ask the parents whether they have had problems with transfusions in the past.

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