Great Ormond Street Hospital for Children NHS Trust

Immunology and Oncology on ITU (including BMT)

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Associated clinical guidelines/protocols:

- Haemophagocytic Lymphohistiocytosis (HLH)
- Admission of BMT recipients to PICU Guideline
- Supportive Care Guidelines for Shared Care: 03 - Infections In The Neutropenic Or Immunosuppressed Patient
- Management of Tumour Lysis Syndrome

Fundamental Knowledge:

List of topics relevant to PIC that will have been covered in membership examinations. They will not be repeated here.

Physiology:

- Innate and acquired immune system: Immune function of phagocytes, B cells, T cells, immunoglobulin & complement
- Host defenses: epithelial/endothelial barriers
- Collagen vascular disease; basic pathophysiology, diagnosis and treatment.
- Inherited immune deficiencies: basic pathiphysiology, diagnosis and treatment.

Information for Year 1 ITU Training (basic):

Year 1 ITU curriculum

Collagen vascular disease as it presents to ITU:

- Vasculitis: pathology, diagnosis, treatment

ITU management of Malignancy associated common problems:

- Tumour Lysis Syndrome
- Febrile neutropenia
- Airway compression in intrathoracic malignancies
- Opportunistic infections

BMT:

- Complications: Graft versus host disease, veno-occlusive disease
- Opportunistic infections

Curriculum Notes for Year 1:

Collagen vascular disease as it presents to ITU:

Vasculitis

Vasculitis is a term that refers to several different conditions, systemic or organ specific, all of which involve inflammation and/or damage to the blood vessels, ranging from moderate to severe. Some conditions, such as Kawasaki disease, involve inflammation and death of tissue in arteries. Other conditions, such as Henoch-Schönlein purpura, may affect both arteries and veins.
The initial treatment of fulminant vasculitis, is immunosuppression with steroids and cyclophosphamide. The vasculitides provide a particular challenge for the critical care team and patients often need major organ support related to these conditions. Effective treatment has revolutionized the prognosis of these conditions however mortality is still approximately 50% for those requiring admission to an intensive care unit.

Kawasaki Disease is an acute, self-limited vasculitis of unknown aetiology. It occurs in children of all races and more commonly occurs in late winter and spring. Boys have it more commonly than girls and ~75% are in children < 5 years old. The aetiology is unknown but data strongly suggests an infectious cause or trigger of the patient's immune system.

> It is defined as: fever of at least 5 days plus 4 or more of the following: polymorphous exantham, bilateral nonexudative conjunctivitis, changes in lips and oral cavity (erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae), cervical lymphadenopathy usually unilateral - more than 1.5 cm (usually unilateral), changes in the extremities (acute: erythema of palms, soles, edema of hands, feet; subacute: periungual peeling of fingers, toes in weeks 2 and 3), rash.

The predominant morbidity results from coronary artery aneurysm or ectasis. This occurs in 15-25% of untreated patients, which can lead to ischemic heart disease, myocardial infarction, and possibly death (via stenosis and or thrombosis of affected vessels).
Differential Diagnosis: Viral infection, Scarlet fever, Toxic shock syndrome, Staphylococcal scaleded skin syndrome, drug hypersensitivity reaction, Stevens- Johnson syndrome, Juvenile rheumatoid arthritis
Reason for ICU admission: poor myocardial function, low cardiac output, myocardial ishemia
Treatment: Aspirin initially 80/100 mg/kg divided in 4 doses, IVIG 2g/kg (both proven beneficial), Pentoxyfylline, Plasmaphoresis, Heart Transplant (rarely).

ITU management of Malignancy associated problem

Trends in childhood cancer mortality were extremely positive during the period from the 1960's to the 1980's. However progress in further reducing mortality has not been as rapid during the last two decades. Survival is nonetheless relatively high, with a 'cure ' rate of 60-70% generally. Screening for is not practicable due to the rarity of the disease, the absence of specific indicators and because the causes remain largely unknown. Genetic predisposition may account for as much as 4%

Tumor Lysis Syndrome is the rapid destruction of malignant cells usually associated with high tumour burden and rapid response to treatment.
Most commonly associated with high-grade lymphomasm (Burkitt Lymphoma), acute leukaemia, but may occur with other tumours. Hyperuricemia, hyperkalemia, Hyperphosphatemia Hypocalcemia, and hypoglycemia can all occur as a result. Acute renal failure and arrhythmias are life-threatening complications. Patients should receive prophylactic hyperhydration to maintain good urine output, allopurinol to increase uric acid solubility and alakalinize urine to pH.7.0-8.0 with bicarb +/- acetazolamide. Haemodialysis may be necessary for some patients. Along with hydration and urinary alkalinization, allopurinol has been the standard agent for the management of hyperuricemia in patients with a high tumour burden who are at risk for tumor lysis syndrome. However, this agent often fails to prevent and treat this complication effectively. Rasburicase, a recombinant urate oxidase, acts at the end of the purine catabolic pathway and, therefore, does not induce accumulation of xanthine or hypoxanthine, which can precipitate in the kidneys and lead to impaired renal function. Rasburicase may represent an effective alternative to allopurinol in rapidly reducing uric acid levels, improving patients' electrolyte status, and reversing renal insufficiency.

Febrile neutropenia definition is a temperature >38^{o}C measured twice over a one hour period in a patient with neutropenia of < 1.0 X 10^{9}/L. Fever is the commonest symptom of infection in neutropenic children with malignancy and demands a septic work up and urgent empirical antibiotic therapy. A combination of ceftazidime and amikacin are first line antibiotic therapy in these children but review of microbiology and advice is warranted. Neutropenic children with persistent fever despite broad-spectrum antibiotics have a 20% risk of developing an invasive fungal infection thus the empirical use of an antifungal agent may be necessary in neutropenic patients with unexplained fever. In these patients the signs of marrow recovery remain the key criterion in evaluating the safety of discontinuing antimicrobial therapy.

Opportunistic infections Bacteria constitute the predominant pathogen for paediatric cancer patients but invasive mycoses, viruses and parasitic infections are emerging as important pathogens. In a recent review of childhood ALL 3% of children died of treatment related diseases, with bacterial infections as the most common cause of death. Girls and Down syndrome patients had a higher risk of death.

The long-term survival of children with cancer has dramatically improved because of multimodal treatment strategies, thus intensive care medicine has become more relevant for these patients. Treatment of childhood malignancies in dedicated paediatric oncology units using a comprehensive multidisciplinary team approach, protocol-based therapy, and local support is associated with improved outcomes. Several recent retrospective studies have shown a great improvement in survival of oncology patients admitted to the intensive care unit especially those with either systemic or respiratory infection needing ventilation. The most frequent indications for PICU admission were shock and respiratory disease. Analysis of long-term survival gave estimates of 50% survival for all oncology patients admitted to a PICU. In selected immunosuppressed patients with pneumonitis and acute respiratory failure, early initiation of non-invasive ventilation is associated with significant reductions in the rates of endotracheal intubation and serious complications and an improved likelihood of survival to hospital discharge.

Airway compression in intrathoracic malignancies

Clinical presentation of childhood mediastinal masses is often nonspecific or incidental. It is not uncommon for children to present with a mass in the head and neck region. The majority of these lesions are inflammatory in nature, but other etiologies include congenital, benign non-inflammatory, benign neoplastic, and malignant neoplastic lesions. In the paediatric age group, a great many are congenital and malignant neoplastic lesions. Some of the tumors, such as hemangioma, are quite common, while others, like Langerhans cell histiocytosis, are rare. It is important to have a working knowledge of these pathologic processes in order to determine the clinical significance of a given lesion upon presentation. These mases have the propensity of developing acute airway compromise, which is closely associated with superior vena cava obstruction. Such patients should be managed as a complex cardiorespiratory syndrome, by an experienced multidisciplinary team. Respiratory symptoms and signs are the most common mode of presentation. Every case of unexplained respiratory failure must be subject to a systematic approach that considers lung disease, bronchoconstriction, large airway obstruction, and external compression of the airway. Factors associated with the development of acute airway compromise are anterior location of the mediastinal mass, histological diagnosis of lymphoma, symptoms and signs of superior vena cava syndrome, radiological evidence of vessel compression or, pericardial effusion and pleural effusion. Using volatile anaesthetic agents is recommended in the patient with an inherently unstable pharynx and/or trachea, in whom airway patency relies on a spontaneously breathing technique and intact airway reflexes.
Prone position is beneficial in ventilated children with airway compression.

BMT

BMT is currently used for patients with haematological malignancies (leukaemia, lymphoma), solid tumours (sarcomas, neuroblastoma), and nonmalignant conditions (aplastic anemia,

autoimmune disorders, myelodysplastic syndrome, immunodeficiency syndromes, congenital disorders of metabolism). For some of these conditions, BMT is now standard therapy; for others, it is used as a rescue when standard therapy is unsuccessful.

Infection and GVHD remain the major source of morbidity and mortality in patients who have a BMT. Certain risk factors place patients undergoing BMT at increased risk for infections. Host factors, type of transplant (allogeneic versus autologous), immunosuppressive regimen, and graft reactions are the major categories of risk factors to consider. The baseline medical status of the recipient of a BMT can lead to an increased predilection to infection. Underlying medical state, previous immune status, prior colonization, prior latent infections, and medications all determine the recipients' baseline medical status. Patients with malignant conditions probably have a higher risk of infection than patients with non-malignant conditions, such as autoimmune disorders, because of the immunosuppression associated with the malignancy. Fungal infection risk is particularly increased after 5-7 days of continuous neutropenia, and most centres begin empiric therapy for fungi after this period if associated fever has occurred while on antibiotics. Previously, fungal infection treatment had been with either conventional or liposomal amphotericin B. Newer agents have improved the treatment available for invasive fungal infections (Voriconazole). Reactivation of **HSV** infection can occur any time following transplantation. HSV infection also does occur, Acyclovir is the treatment of choice, when patients do not respond to acyclovir, foscarnet can be tried. **CMV** was the leading cause of morbidity and mortality in patients after BMT however the advent of surveillance with early use of ganciclovir has profoundly decreased severe CMV disease. CMV-specific immunoglobulin has been used in addition to ganciclovir in some patients whilst Foscarnet is second line treatment and cidofovir has also been shown to be effective as a third line treatment. Varicella infections can occur in the late post transplantation period, prevention should be attempted following exposure with the administration of varicella zoster immunoglobulin and IV acyclovir. The addition of RSV immune globulin therapy to traditional ribavirin therapy has shown promise in preventing the progression of RSV upper respiratory infection to lower respiratory disease and also in the treatment of RSV pneumonia **Adenovirus** is increasingly being recognised as a significant pathogen in children following bone marrow transplantation. The virus is endemic in the general paediatric population, and frequently causes severe disease in immunocompromised patients, especially children. Infections can affect a variety of organs with gastrointestinal and urinary tract diseases being the most common. When disseminated infection occurs, reported mortality rates are as high as 60%. New molecular diagnostic techniques have meant that adenoviral infections can now be detected early, often before symptoms have developed. We now screen for adenovirus infection to allow early initiation of treatment –ribavirin or cidofovir. It is hoped that this approach, will reduce the deaths from this common virus in high-risk children. Prophylaxis against **PCP** should begin with engraftment and continue until 6 months after the transplantation. The use of haematopoietic colony-stimulating factors, such as GCSF, has been shown to reduce the period of neutropenia; however, the incidence of bacteraemia and outcome has not been influenced. Granulocyte transfusion does not appear to be beneficial, even in the presence of profound neutropenia.

Post transplant viral surveillance occurs at GOSH in all patients after BMT using viral PCR tools to detect and estimate viral loads. PCR is available for adenovirus, CMV and EBV. These levels are done on Tuesdays and Thusdays. The decision to start antiviral treatment will depend on viral load and the clinical picture.

Graft-versus-host disease (GVHD) is a condition in which the stem cell graft attacks the donor tissue. Prevention of this condition is best accomplished by HLA matching of donor and recipient. However even when patient and donor are genotypically matched the occurrence rate of GVHD is still 30-70%. T cell depletion of donor stem cells prior to transplant by various methods can reduce the risk of GVHD but this is also associated with a higher rate of graft failure and increased risk of post transplant lymphoproliferative disorder. By definition, GVHD is classified as acute if it occurs before day 100 post-transplant and chronic if it persists or develops beyond day 100. Acute GVHD is typified by – fever, rash, diarrhoea and liver dysfunction. The rash is erythematous and maculopapular often seen on the soles and or palms, though it may become more widespread. Acute GVHD is given a clinical score Grades

I to IV (the higher grades are associated with higher morbidity and mortality). Treatment for acute GVHD includes glucocorticoids such as methylprednisolone or prednisone in combination with cyclosporine. Satisfactory responses to this steroid treatment are observed in 50% to 75% of patients. New drugs and new strategies are available now or are in clinical trials that can supplement standard treatment, including: monoclonal antibodies, alemtuzumab (Campath), antithymocyte globulin and FK506.
Chronic GVHD develops between Day 100 and 2years post transplant. Chronic GVHD can occur de novo or the acute picture can develop into the chronic form. Chronic GVHD is clinically like an autoimmune disorder such as scleroderma (skin changes, gastrointestinal problems, liver dysfunction, dry eyes, pulmonary fibrosis).

Venoocclusive disease (VOD)
This is predominantly a clinical diagnosis without a clearly defined gold standard. The prevalence and incidence of VOD following BMT differ markedly among centres. Early estimates of incidence were 10-20%, but recent data suggest that as many as 50% or more of patients undergoing BMT develop VOD; liver dysfunction contributes to death in ap-proximately 25% of such patients. VOD commonly develops within 20 days following transplant.
Diagnosis (presence of two of the following three clinical criteria)
a. Tender hepatomegaly, right upper quadrant pain of liver origin
b. Sudden weight gain due to fluid retention including ascites (increase greater than 2% of baseline, although some use a 5% increase as the threshold),
c. Hyperbilirubinemia (Bilirubin > 34.2 micromol/l)
having excluded the following as causes:
a. GVHD (this usually manifests later post transplant and is associated with a cholestatic picture)
b. Sepsis
c. Congestive heart failure
d. Hepatitis (typically cytomegalovirus)
e. Fungal liver disease
Note: Many of the above can occur concomitantly with VOD.

Only a small subset of VOD cases is diagnosed histologically. Endothelial injury, leading to deposition of coagulation factors within the terminal hepatic venules, is believed to be the key event in the pathogenesis of VOD. Heparin has been given to patients to reduce the risk of VOD but there is little evidence of its clinical benefits. In fact no agent for the treatment or prevention of VOD has been properly evaluated in a randomised, prospective trial. Defibrotide is used to treat VOD at GOSH; this is a single stranded polyoxyribonucleotide that has effect on the vascular endothelial cells. Defibrotide appears safe and its benefits are currently under investigation. Other agents used include recombinant tissue plasminogen activator; use may be complicated by bleeding as patients are often also thrombocytopenic.

Paediatric patients admitted to the ICU after BMT generally have a poor prognosis. However intensive care continues to play an important role in the care of these patients therefore it is important to try to delineate those that may do well. Decisions regarding treatment options and limitation of care in this group of patients should be based on ongoing outcome research in this field. Jacobe et al at Gosh reviewed the outcome of bone marrow transplant recipients admitted to intensive care and reported a 22.5% survival. There was no difference between the survivors and non-survivors in terms of underlying diagnoses, age at BMT, or time to ICU admission after BMT. Type of BMT, conditioning regimen, and presence of significant graft vs. host disease was not found to influence outcome. Of importance patients who died in the ICU had a significantly longer length of stay compared with the survivors. Of ten BMT patients with respiratory failure associated with pulmonary infection, there were no survivors among those who remained ventilated at 48 hrs. The majority of patients who died in the ICU did so after either withdrawal or limitation of treatment.

In summary ICU admission can be beneficial to selected children post-BMT but it may be less useful in proven viral pneumonitis. Where mechanical ventilation is required, the duration of this support should be limited unless there is rapid improvement.

Other sources of information:

References.

1. Jacobe SJ, Hassan A, Veys P, Mok Q. Outcome of children requiring admission to an intensive care unit after bone marrow transplantation. Crit Care Med. 2003 May;31(5):1299-305.
2. Huaringa AJ, Leyva FJ, Giralt SA, Blanco J, Signes-Costa J, Velarde H, Champlin RE.Outcome of bone marrow transplantation patients requiring mechanical ventilation. Crit Care Med. 2000 Apr;28(4):1014-7.
3. Keengwe IN, Stansfield F, Eden OB, Nelhans ND, Dearlove OR, Sharples Paediatric oncology and intensive care treatments: changing trends.A. Arch Dis Child. 1999 Jun;80(6):553-5.
4. Hallahan AR, Shaw PJ, Rowell G, O'Connell A, Schell D, Gillis J. Improved outcomes of children with malignancy admitted to a pediatric intensive care unit. Crit Care Med. 2000 Nov;28(11):3718-21.
5. Christensen MS, Heyman M, Mottonen M, Zeller B, Jonmundsson G, Hasle H. Treatment-related deaths in childhood acute lymphoblastic leukaemia in the Nordic countries: 1992-2001.Br J Haematol. 2005 Oct;131(1):50-8.
6. Martin PL.To stop or not to stop: how much support should be provided to mechanically ventilated pediatric bone marrow and stem cell transplant patients? Respir Care Clin N Am. 2006 Sep;12(3):403-19.
7. Kache S, Weiss IK, Moore TB. Changing outcomes for children requiring intensive care following hematopoietic stem cell transplantation. Pediatr Transplant. 2006 May;10(3):299-303.
8. Fiser RT, West NK, Bush AJ, Sillos EM, Schmidt JE, Tamburro RF. Outcome of severe sepsis in pediatric oncology patients. Pediatr Crit Care Med. 2005 Sep;6(5):531-6.
9. Renyi I, Bardi E, Udvardi E, Kovacs G, Bartyik K, Kajtar P, Masat P, Nagy K, Galantai I, Kiss C. Prevention and Treatment of Hyperuricemia with Rasburicase in Children with Leukemia and Non-Hodgkin's Lymphoma. Pathol Oncol Res. 2007;13(1):57-62.
10. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, Shulman ST, Bolger AF, Ferrieri P, Baltimore RS, Wilson WR, Baddour LM, Levison ME, Pallasch TJ, Falace DA, Taubert KA; Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease; Council on Cardiovascular Disease in the Young; American Heart Association; American Academy of Pediatrics. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation. 2004 Oct 26;110(17):2747-71.
11. Grigull L, Pulver N, Goudeva L, Sykora KW, Linderkamp C, Beilken A, Seidemann K, Schmid H, Welte K, Heuft HG. G-CSF mobilised granulocyte transfusions in 32 paediatric patients with neutropenic sepsis. Support Care Cancer. 2006 Sep;14(9):910-6.

Information for Year 2 ITU Training (advanced):

Year 2 ITU curriculum

Collagen vascular disease as it presents to ITU:

- Vasculitis: pathology, diagnosis, treatment
- SLE
- JA – life threatening complications
- Dermatomyositis

BMT:

- Indications
- Typical clinical course, significance of donor matching.
- Complications: Graft versus host disease, veno-occlusive disease
- Opportunistic infections
- ITU outcome prediction

ITU management of Malignancy associated problems:

- Tephlitis and bowel perforation
- Other life threatening complications: GI bleeding, opportunistic infections

Others:

- Haemophagocytic lymphohistiocytosis: diagnosis, prognosis, treatment.
- TAM in neonatal Downs Syndrome
- Lymphoproliferative diseaser in transplant (BMT & solid organ) patients

Curriculum Notes for Year 2:

Systemic lupus erythematosus (SLE)

Is a chronic autoimmune disease caused by a copious overproduction of auto antibodies leading to immune complex formation, and binding or deposition of the complexes into tissues This causes damage to any organ in the body but especially the kidney, blood, skin, joints and the central nervous system. There is widespread immune disregulation. Its incidence varies by location and ethnicity, it occurs more often in females, prior to puberty more in male. The disease may occur at birth but is generally less common in children < 8 years old. Because SLE can affect any organ, SLE can be in the differential diagnosis of almost any clinical presentation. Specifically patients often complain of prolonged fever, malaise, fatigue, joint pain, weight loss, loss of appetite and rash. Lupus affects each individual differently and the effects of the illness range from mild to severe. Lupus can potentially be fatal.
Reasons for admission to ICU : lung injury, respiratory failure, sepsis (increased susceptibility to infection due to immunosuppressive treatment), overwhelming systemic inflammation (cytokine storms), cardiogenic causes, neurological causes and gastrointestinal failure (pancreatitis, hepatitis, Arnold-Chiari syndrome, vasculitis mesenteric bed). The diagnosis of SLE is dependent on clinical and lab criteria.

Diagnosis: 4 of 11 criteria are present

1. Butterfly rash

2. Photosensitivity (skin reaction to sunlight)
3. Discoid-Lupus (scaly, raised, coin-shaped rash)
4. Mucosal ulcers in mouth or nose
5. Arthritis
6. Pleuritis
7. Kidney involvement
8. CNS involvement (headache, seizures)
9. Haemolytic anaemia, leucopenia, thrombocytopenia
10. Anti-native DNA antibodies, Anti-Sm antiodies, antiphospholipid antibodies
11. Antinuclear antibodies in > 90% patients; low C3 and C4 levels.

Therapy:

1. Steroids such as methylprednisolone.
2. Non steroidal inflammatory drugs (NSAIDs).
3. Hydroxychloroquine.
4. Azathioprine and Cyclophosphamide can be used if steroids are not effective (cyclophosphamide improves survival in presence renal disease).
5. Plasmaphoresis – limited evidence of benefit in SLE when not associated with TTP.
6. Rituximab – used to effect B cell depletion in patients with refractory SLE. Early reports show some benefit.

SLE can be associated with a prothrombotic state either from association with TTP or APL (antiphopholipid syndrome – antibodies to phospholipids and related proteins). When TTP is present shistocytes are seen on the blood film and gross haematuria is often present. Steroids and immunosuppression may be beneficial for both SLE and TTP, but it is important to diagnose TTP as plasma exchange greatly improves survival in this condition. In APL anticoagulation may be considered.

JA

JA is the most common form of arthritis in children. Typically juvenile rheumatoid arthritis appears between the ages of 6 months and 16 years. The first signs are often joint pain lasts for more than 6 weeks or swelling and reddened or warm joints. Many rheumatologists find that the greater the number of joints affected, the more severe the disease and the less likely that the symptoms will eventually go into total remission. The 3 major types of JA are:

1. **Pauciarticular:** Involvement of 4 or fewer joints during first 6 months, usually involves large joints and may be asymmetrical.
2. **Polyarticular :** Involvement of 5 or more joints during first 6 months;absence of systemic symptoms; Rheumatoid factor positive: (<5% of all JA), affecting small joints, more in female, onset after 10 years of age; Rheumatoid factor negative: (15-20% of all JA).
3. **Systemic** : Involvement of one joint ; a systemic inflammatory reaction which can predominate and be overwhelming associated with high spiking fevers, a rash (evanescent salmon coloured rash usually on the trunk and may occur before the arthritis), hepatosplenomegaly, thrombocytosis, leucocytosis. Cardiovascular involvement can include pericarditis (+/- arthritis), cardiac tamponade (+arthritis), myocarditis, endocarditis, congestive heart failure and valvular insufficiency.This SIRS like reaction may require intensive care support.

Arthritis involving the cricoarytenoid region causing airway compromise or cervical spine causing subluxation and ligamentous laxity may present particular problems on ICU. Steriods are usually the first line of treatment. Immunosuppressants, such as azathioprine and methotrexate, may help those for whom prednisone is ineffective.

Dermatomyositis

Dermatomyositis is one of a group of acquired muscle diseases called inflammatory myopathies. Dermatomyositis is characterized by a rash (typically patchy, bluish-purple discolorations on the face, neck, shoulders, upper chest, elbows, knees, knuckles, and back) accompanying, or more often, preceding muscle weakness (usually affecting the muscles that

are closest to the trunk of the body). Muscle weakness usually happens over a period of days. Some DM patients have muscle pain and difficulty swallowing, or dysphagia. Life threatening complications may occur in DM in the gastrointestinal (bleeding, gut infarction, perforation, aspiration), respiratory (spontaneous pneumothoraces, pulmonary hypertension, interstitial lung disease) and cardiac systems (arrhythmias, myocarditis, severe hypertension). Steroids are usually the first line of treatment. Immunosuppressants such as azathioprine, methotrexate and Cyclosporin A may help those for whom prednisone is ineffective. Further treatment with intravenous immunoglobulin has been shown to be effective and safe.

BMT

BMTs are classified as either autologous or allogeneic, based on the source of the hematopoietic stem cells. In allogeneic transplantations, the stem cells are harvested from a donor patient who is other than the recipient of the BMT. Donors for these transplants may be blood related or unrelated; however, human leukocyte antigen (HLA)–matched sibling transplantations are associated with a lower risk of graft versus host disease (GVHD), and the recipients tend to have faster recovery of their immune system post transplantation. The donor graft may be depleted of T lymphocytes, which are the main effectors of GVHD; however, with these new techniques, higher rates of graft rejection, cytomegalovirus (CMV) infection, invasive fungal infection, and Epstein-Barr virus (EBV)–associated posttransplantation lymphoproliferative disease have been noted. Autologous transplantations involve stem cells that are harvested from the recipient patient. Syngeneic transplants refer to stem cells from an HLA-matched identical twin. Autologous transplantations are performed in patients with bone marrow that is healthy and has no disease. Patients with autologous transplantations tend to have more rapid recovery of their immune system than patients with allogeneic transplantations GVHD does not occur in patients undergoing autologous or syngeneic transplantation. The development of new drugs to treat GVHD combined with early detection and advances in understanding the underlying mechanisms of the disease, have resulted in significant reductions in the morbidity and mortality of this potential complication of transplantation. Multiorgan system involvement exists, with breakdown of barrier defences. Immune deficiency caused by defective humoral and Cell Mediated Immunity and functional asplenia is also associated with GVHD.
Prognostic scoring systems based on physiological parameters have been established in order to predict the outcome of ICU patients. It has been demonstrated that the predictive value of these scores is limited in patients following BMT. Several recent studies have modified the PRISM score to try to help predict survival of those patients post BMT admitted to ICU the oncological PRISM ('O-PRISM') score. Further evaluation of the predictive value of this score needs to be done.

Lymphoproliferative disease (LPD) in transplant (BMT & solid organ) patients

Post transplant lymphoproliferative disease (PTLD) is an unusual entity that has many of the features of immune system malignancy. It is characterized by uncontrolled proliferation of B cells in a context of post transplant immunosuppression. In some situations, reducing the immunosuppression can reverse this proliferation. PTLD has emerged as a significant complication of transplantation. PTLD is difficult to predict and has high morbidity and mortality rates because of the difficulty in prevention and potential for graft loss. The prevalence of PTLD is different for each transplanted organ. The highest rates are reported for the intestine (up to 20%), thoracic organs (heart 2-10%, lung 4-8%), and liver (2-8%). Prevalence in kidney transplants is usually lower (1%), but some centres have reported prevalence as high as 10%. Prevalence in bone marrow transplantation is low (1-2%), except in patients in whom T-cell–depleted marrow is used, for whom rates as high as 24% are reported. Prevalence is highest in the paediatric age group, the relative risk (RR) being 2.81 as compared to adult recipients. Some reports have suggested that prevalence is even higher in patients younger than 5 years. Age may not be an independent risk factor but may depend on the likelihood of the recipient being seronegative for Epstein-Barr virus (EBV) at the time of transplant. Epstein-Barr virus (EBV) viraemia and lymphoproliferative disease (LPD) appear

to be significantly more common in children following reduced-intensity conditioning stem cell transplantation, particularly with selective depletion of recipient T cells relative to B cells following the use of antithymocyte globulin (ATG). A recent report by Cohen et al at GOSH showed that an absolute lymphocyte count of <0.3 x 10(9)/l at the time of onset of viraemia was strongly predictive of development of LPD and that the incidence of viraemia was significantly higher in patients receiving antithymocyte globulin than Campath. Several other studies indicate that the measurement of EBV viral load with semiquantitative PCR is useful in detecting EBV-LPD in high-risk patients before the onset of clinical symptoms. Clinical features of PTLD can be multiple, varied, and complex. In many patients, the early symptoms are nonspecific, including fever, malaise, weight loss and sudden-onset lymphoid mass swelling. Ultrasound, CT scanning, or MRI can be used depending on the area of interest to help make the diagnosis. Bone marrow biopsies are necessary to help define marrow involvement, which may rarely be the only affected tissue. Histopathologic diagnosis of biopsy tissue remains the criterion standard for making the diagnosis of PTLD. PTLD may coexist with acute rejection, and the diagnoses may be difficult to separate. No uniform consensus exists regarding optimal treatment options for PTLD. Most centres recommend a staged treatment regimen based on the degree of clonality and aggressiveness. Reduction of immunosuppression is the first intervention recommended and should be performed in all patients. Corticosteroids are usually continued without dosage modification. Anti-CD20 monoclonal antibody (Rituximab) has recently been used, with promising results, to neutralize the CD20-expressing B cells. Several small-uncontrolled series have documented good success rates (complete or partial remission) in the 60-70% range in polymorphic or polyclonal cases. In some situations, the PTLD lesions may not express CD20; thus, rituximab may not be useful in such cases. Frequent quantitative monitoring of EBV reactivation and preemptive therapy by rituximab seems to improve outcome in patients at high risk of EBV-LPD.

Transient abnormal myelopoiesis

This is a unique myelodysplastic syndrome which occurs primarily in infants with Down's syndrome or other abnormalities of chromosome 21.Transient abnormal myelopoiesis (TAM), or Down's syndrome transient leukaemia (DS-TL, as it is also known, occurs in approximately 10% in neonates with Down's syndrome (DS) and in phenotypically normal neonates with trisomy 21 mosaicism. The disorder seems to show a male gender bias, with male: female ratio 1.6:2.1. This transient leukemia (TL) has been shown to be a clonal proliferation of blast cells exhibiting megakaryocytic features. The pathogenesis involves mutation of GATA1 (on chromosome X) which normally encodes a transcription factor integral to normal development of erythroid, megakaryocyte and basophilic/mast cell lines. The pathogenetic role of trisomy 21 is unclear.
Usually it presents as an incidental finding on a full blood count when circulating blasts are noted although thrombocytopenia can also be associated. In most infants this disorder is reported to regress spontaneously by the age of 2-3 months. The cause for spontaneous regression of TAM is not clear.
In 20% TAM cases however there is a more severe clinical picture with multi-organ failure, hyperviscosity, cardiopulmonary failure, splenomegaly (+/- spleen necrosis), myelofibrosis and liver failure. TAM in a sick neonate necessitating ICU admission does not resolve spontaneously and has a high mortality (of all infants with TAM 11-17% will not survive the initial presentation).Rising bilirubin and transaminases plus a failure to normalise the blood count are all indicators of a poor prognosis. Early aggressive treatment, including a combination of exchange transfusion and low dose cytosine arabinoside (the blasts of TAM are sensitive to this), may be crucial for their survival.
Approximately 20 – 30 % of infants who survive TAM may go on to develop a subsequent haematologic disorder, most often acute nonlymphocytic leukaemia (though mosaics do not). This occurs usually within the first 3 years of life at a median age of 20 months. The acute leukaemia is of the M7 phenotype (acute megakaryoblastic leukaemia).

Haemophagocytic lymphohistiocytosis (HLH):

Haemophagocytosis = the pathologic finding of activated macrophages engulfing red blood cells, leucocytes, platelets and their precursor cells.

HLH can either occur sporadically (secondary HLH) or can be inherited as the autosomal recessive condition known as familial HLH (FLH). For either type HLH usually occurs in infants and children but occasionally sporadic HLH can be seen in adults. There appears to be some seasonal variation with most cases occurring in the summer.

Both FLH and sporadic HLH can be triggered by infections and are clinically indistinguishable. The conditions which may trigger sporadic HLH include:

- Infections: viral, bacterial, fungal, parasitic
- Collagen vascular diseases
- Malignancies (particularly T cell lymphomas)

The diagnosis of HLH requires that five out of eight criteria be fulfilled.

1) Fever (undulent and protracted but may decline spontaneously)
2) Cytopenia (two of three lineages most commonly thrombocytopenia and anemia)
3) Splenomegaly (pronounced and progressive)
4) Hypertriglyceridemia and/or hypofibrinogemia,
5) Hemophagocytosis(bone marrow, spleen, lymph nodes commonly and occasionally in the liver, CNS or skin).
6) Low or absent NK-cell activity
7) Hyperferritinemia
8) High plasma levels of soluble CD25 (soluble IL-2 receptor).

Table. Clinical signs and laboratory abnormalities associated with hemophagocytic lymphohistiocytosis

Clinical sign	**% of patients affected**
Fever*	60-100
Splenomegaly*	35-100
Hepatomegaly	39-97
Lymphadenopathy	17-52
Rash	3-65
Neurologic signs	7-47
Laboratory abnormality	**%**
Anemia*	89-100
Thrombocytopenia*	82-100
Neutropenia*	58-87
Hypertriglyceridemia*	59-100
Hypofibrinogenemia*	19-85
Hyperbilirubinemia	74

*Proposed diagnostic criterion for HLH

Reference*: Fisman DN. Hemophagocytic Syndromes and Infection. CDC 2000 Vol 6, No. 6*

Laboratory investigation:

- High levels of ferritin and fibrin degradation products infer high risk mortality.
- Hypertriglyceridemia is a common finding in systemic disease with fever.
- Elevated serum transaminase (>900 U/L) or hyperbilirubinemia (>300 micromol/L)
- Elevated lactate dehydrogenase, hyponatremia and low protein/albumin are other common findings, which are associated with the general inflammatory condition.
- Coagulation abnormalities are common during active disease, in particular hypofibrinogenemia and DIC.

Immune-system derangement with hypercytokinemia is typical and is probably mediating the symptoms. A striking finding in FHL patients is the low or absent natural killer (NK) cell activity as well as T-cell cytotoxicity.

Differential diagnoses: HLH can mimic any form of severe sepsis and they can co-exist so robust infection screening should be performed, but particular infections should be sought:

- TB, EBV, CMV, Adenovirus, Parvovirus B19, HIV, HHPV6 and throat and rectal swabs taken for viral culture.
- Fungal antigen testing
- Look for any evidence of T cell lymphomas (as these have a strong association with HLH) searching for cell markers and T cell receptor gene rearrangement tests.
- Any history of travel or animal contact should prompt a search for leishmaniasis, brucellosis, rickettsioses, leptospirosis

The diagnosis of FHL (familial HLH) is justified by a positive familial history, and parental consanguinity is suggestive. The incidence of primary HLH in children was estimated to be 0.12 per 100,000 children born per year, i.e. one per 50,000 live births.
FHL typically presents in infancy and early childhood and is almost invariably fatal with a median survival without therapy of two months. Importantly, the inheritance is recessive, and the family almost never knows the disease when their first child is affected. Three mutations have been described:

- Mutations in the perforin gene (PRF1 which maps to 10q21-q22) have been described but the role of perforin in the pathogenesis of HLH is unclear. Perforin is expressed in cytotoxic lymphocytes (NK, CD8, CD56 cells) and it inserts into the membrane of a target cell and creates a pore, allowing the entry of granzyme B and inducing cell death. Mutations in PRF1 interfere with pore formation. This mutation is found most commonly in the West in 30-50% patients particularly black African and Hispanic patients.
- MUNC13-14 gene maps to 17q25 and is found in 30% HLH patients worldwide. Mutations in this region interfere with normal secretion of cytolytic granules leading to widespread accumulation of lymphocytes and mature macrophages, sometimes with haemophagocytosis. NK function may be normal or abnormal. There is no specific assay for MUNC13-14 protein.
- Syntaxin II (STX11) gene mutations are found in a small number of patients of Turkish-Kurdish origin. No specific assays are available yet.

Treatment

For FLH the treatment is haematopoietic stem cell transplantation following chemotherapy and immunotherapy to induce remission.HLH-2004 chemo-immunotherapy includes etoposide (toxic to macrophages), dexamethasone, cyclosporine A and in selected patients, intrathecal therapy with methotrexate and corticosteroids. The Histiocyte Society in 1994 developed a common treatment protocol (HLH-94), which was updated in 2004 (HLH-2004). Sporadic HLH may resolve spontaneously with treatment of the underlying precipitant but this is not always the case; some patients will require treatment with chemotherapy and even consideration for BMT if there is no remission 8 to 10 weeks into the disease course. EBV associated HLH is almost universally fatal and will require such aggressive treatment.

Prognosis: For patients requiring ICU treatment the outlook is poor with less than 50% surviving to discharge. If readmission to ICU at any other point in the illness is required there have been no survivors on GOSH ICU.

Other sources of information:

Websites.

- www.printo.it/pediatric-rheumatology
- pediatric rheumatology European society www.pres.org.uk
- British Society for Paediatric and Adolescent Rheumatology **www.bspar.org.uk**
- www.cincinnatichildrens.org – FHL and molecular genetics.

References.

1. Cohen J, Gandhi M, Naik P, Cubitt D, Rao K, Thaker U, Davies EG, Gaspar HB, Amrolia PJ, Veys P. Increased incidence of EBV-related disease following paediatric stem cell transplantation with reduced-intensity conditioning. Br J Haematol. 2005 Apr;129(2):229-39
2. Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi-Benissan G, Dupon M, Reiffers J, Cardinaud JP. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med. 2001 Feb 15;344(7):481-7.
3. Hoskote A, Chessells J, Pierce C. Transient abnormal myelopoiesis (TAM) causing multiple organ failure. Intensive Care Med. 2002 Jun;28(6):758-62. 2002.
4. Ouachee-Chardin M, Elie C, de Saint Basile G, Le Deist F, Mahlaoui N, Picard C, Neven B, Casanova JL, Tardieu M, Cavazzana-Calvo M, Blanche S, Fischer A. Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis: a single-center report of 48 patients. Pediatrics. 2006 Apr;117(4):e743-50.
5. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007 Feb;48(2):124-31.
6. Brink DS. Transient leukemia (transient myeloproliferative disorder, transient abnormal myelopoiesis) of Down syndrome. Adv Anat Pathol. 2006 Sep;13(5):256-62.
7. Massey GV, Zipursky A, Chang M. A prospective study of the natural history of TAM in neonates with Down syndrome: Children's Oncology Group Study. Blood 2006 Jun 15, 107(12):4606-13.
8. Homans AC, Verissimo AM, Vlach V. TAM of infancy associated with trisomy 21. Am J Pediatr Hematol Oncol 1993. Nov:15(4):392-9.