Management of Primary Immunodeficiency

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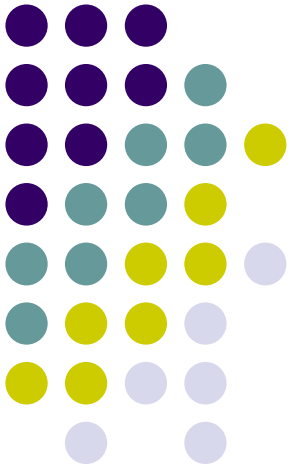
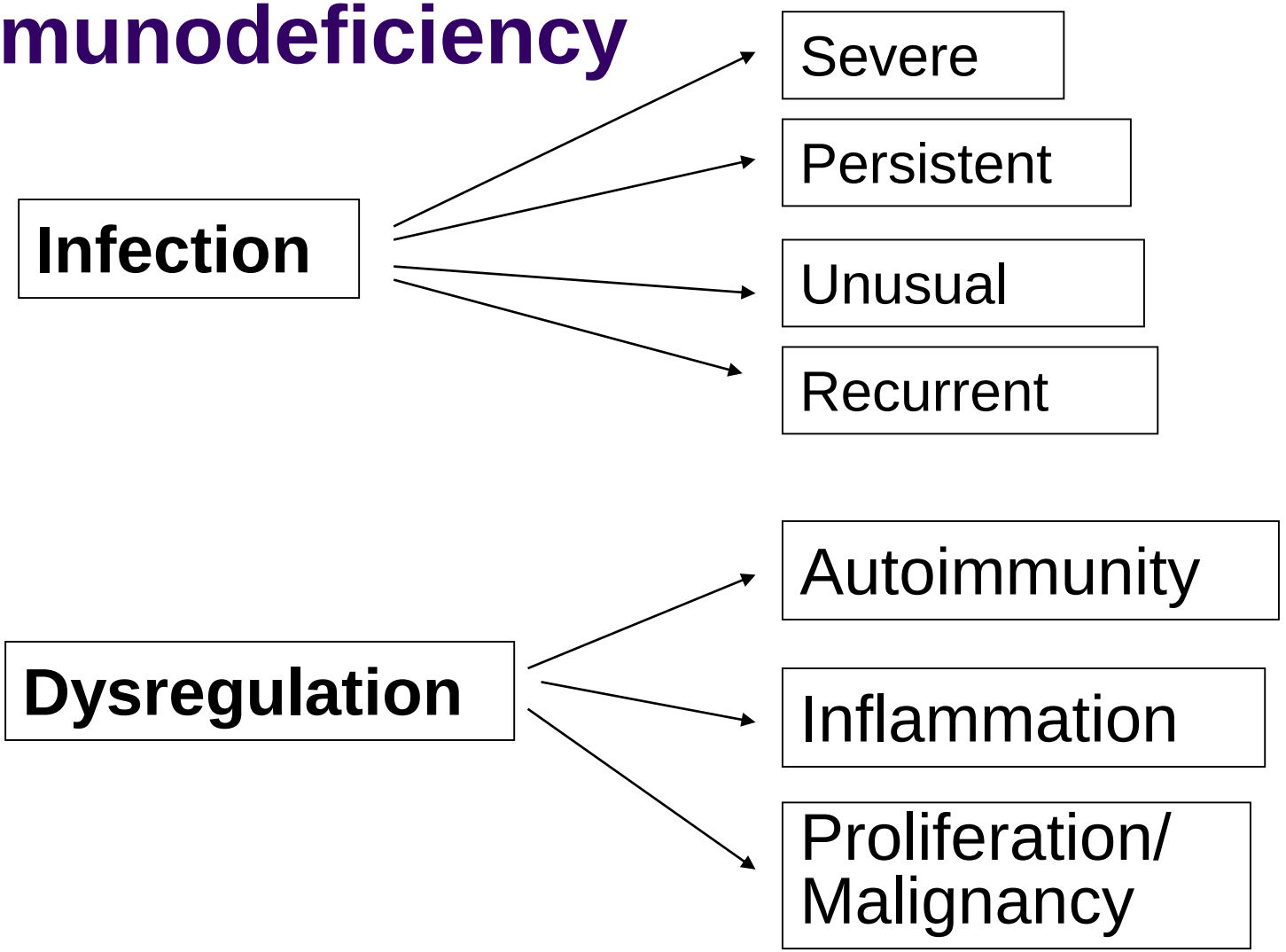


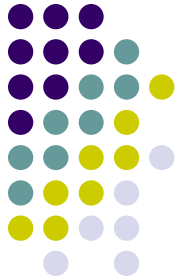
Manifestations of immunodeficiency



Approaches to Management

- Supportive
- Corrective

Supportive management



- Treatment of infection
- Prevention of infection
- Monitoring for and management of complications
- Psycho-social

Corrective therapy

- Stem cell transplantation
- Gene therapy

Who needs which approach?

- If infections or other complications are life-threatening

  and/or

- Life expectancy is significantly reduced

even with the best available supportive treatment

Then corrective therapy should be considered

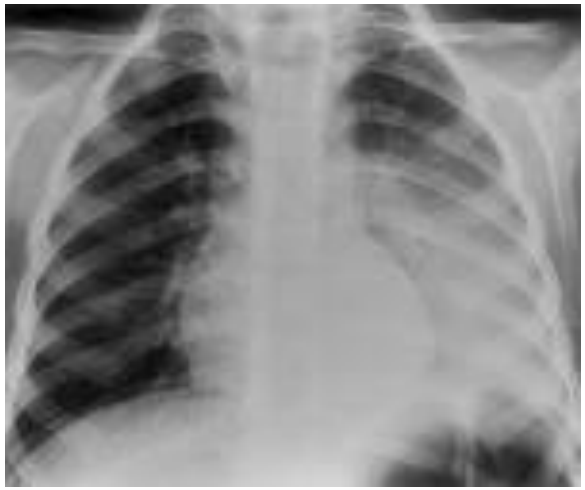
- All patients need supportive treatment
- Those with antibody deficiency require lifelong supportive treatment
- Those with more complex PID are likely to need corrective therapy

Supportive management

Supportive management

- ***Treatment of infection***
  - Prompt
  - Adequate doses
  - Longer courses
- Prevention of infection
- Monitoring for and management of complications
- Psycho-social

Active infection - examples



Bacterial

Pneumonia in antibody deficiency

Early and aggressive treatment of respiratory infection with antibiotics

Often intravenous

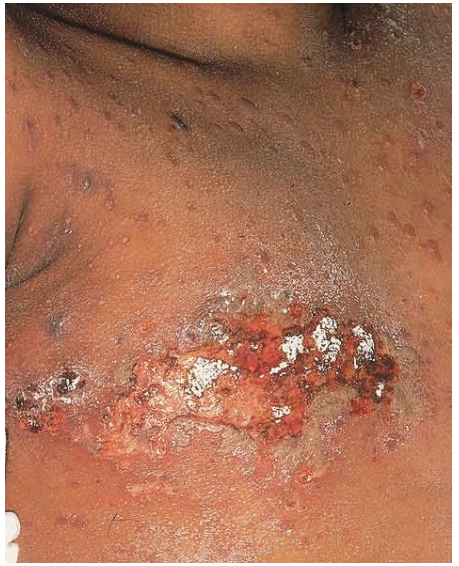
Prolonged courses

Viral

Shingles (herpes zoster) with satellite chicken pox lesions

May need treatment with anti-viral drugs – aciclovir – in patient with PID

Chicken pox can cause life-threatening pneumonitis



Active infection - examples

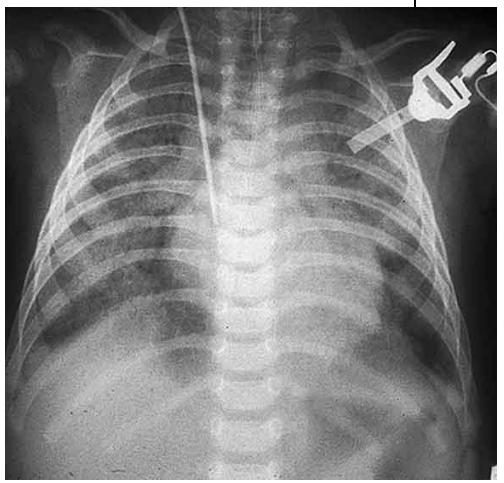
Unusual

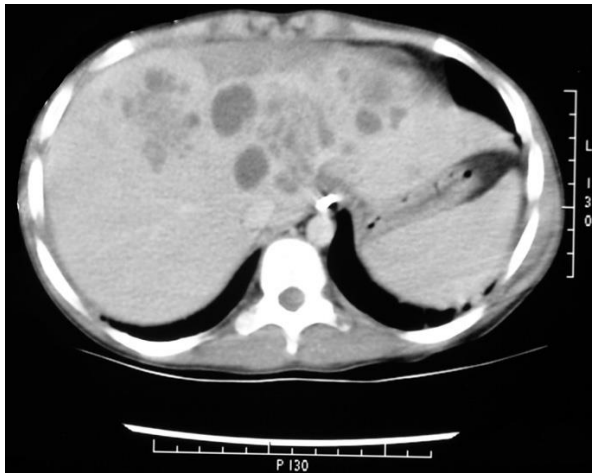
Pneumocystis pneumonia in an infant with severe combined immunodeficiency

Often presenting illness

Needs specific therapy – Cotrimoxazole

Life-threatening





Fungal

Liver abscesses in patient with chronic granulomatous disease

Require prolonged anti-fungal therapy

Very difficult to eradicate

Supportive management

- Treatment of infection
- ***Prevention of infection***
  - Immunoglobulin replacement
  - Antibiotic prophylaxis
- Monitoring for and management of complications
- Psycho-social

Immunoglobulin replacement

- Purified immunoglobulin (antibody)
- Manufactured from pooled human plasma
  - Pool sizes around 10,000
- Complex manufacturing process to minimise risk of infection
- Mainstay of treatment for all patients with primary antibody deficiency, and many others with more complex disorders
- Can be given intravenously or subcutaneously (under the skin)

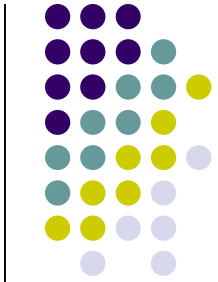
Immunoglobulin replacement

- Intravenous
  - Every 3-4 weeks
  - Usually in hospital
- Subcutaneous
  - Every 1-2 weeks
  - Almost always at home
- Effective in preventing most infections

Home therapy - advantages

- Flexibility
- Less disruption to family life
- Time saving
- ?cost saving

Prevention of infection



- Immunoglobulin replacement
  - Lifelong treatment
  - Purified immunoglobulin (IgG) manufactured from donated human plasma – pools of approx 10,000
  - Intravenous (IV) or subcutaneous (SC)
  - IV: every 3 weeks
    - hospital or home
    - 3-4 hours
  - SC: every week
    - almost always home
    - 1 hour
- Antibiotics
  - Prompt treatment of infection
  - Prophylaxis
- Monitoring for infection and organ damage

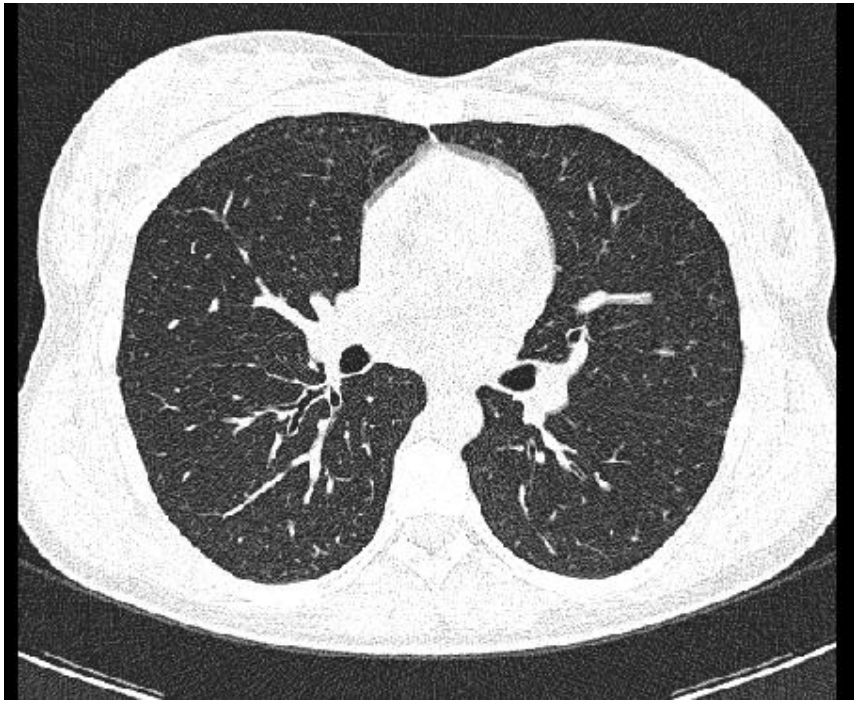
Supportive management

- Treatment of infection
- Prevention of infection
- ***Monitoring for and management of complications***
- Psycho-social

Possible complications

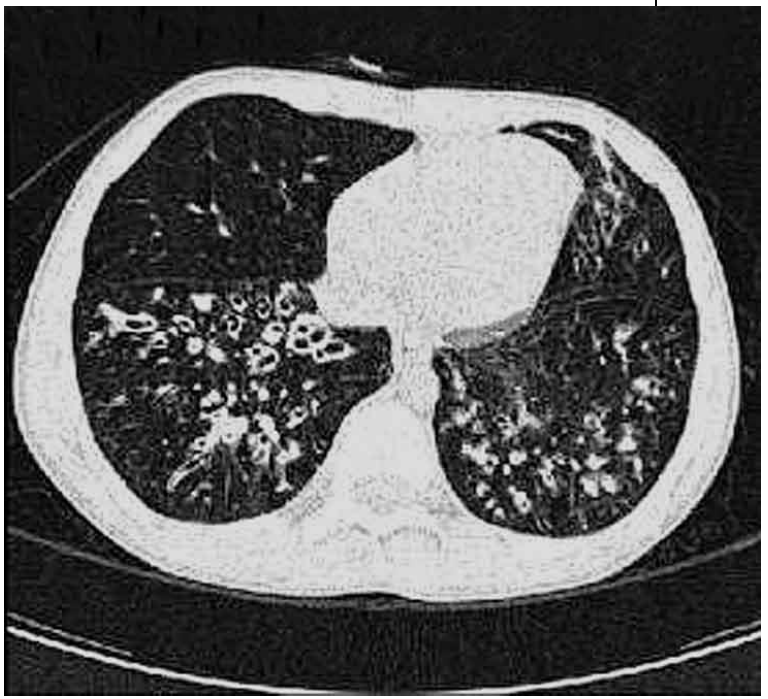
- Organ damage resulting from infection – esp lungs
- Autoimmunity
- Inflammatory complications – can affect any organ
- Lymphoproliferative disease – enlarged lymph nodes, liver, spleen
- Malignancy – esp lymphoma and gastric carcinoma

Bronchiectasis



Normal chest CT scan

Chest CT scan should be performed at diagnosis and at intervals depending on clinical progress

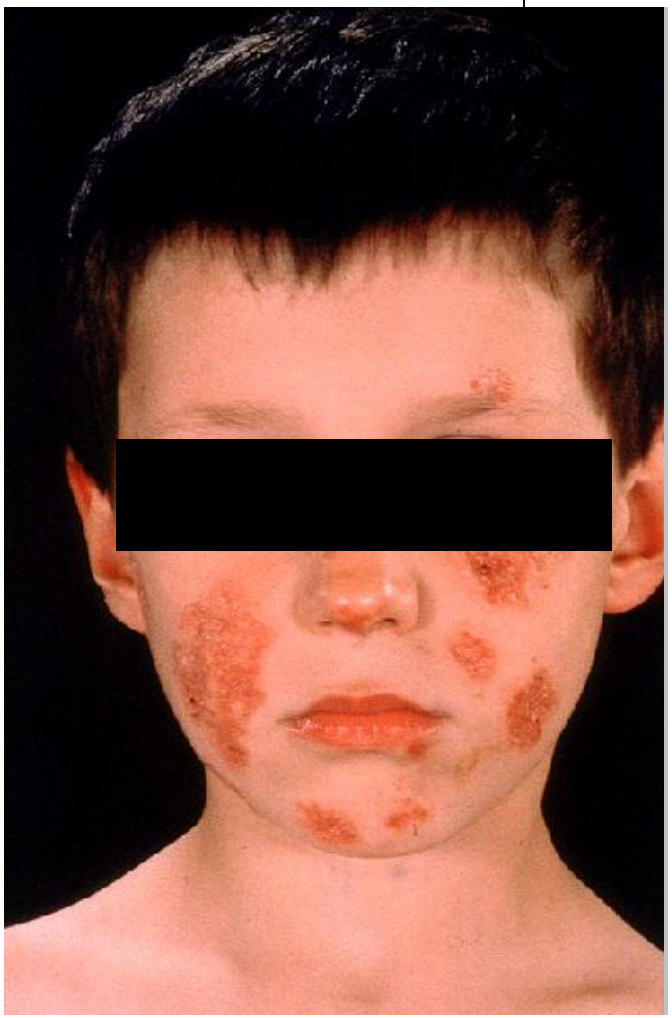


Bronchiectasis

Irreversibly damaged airways – widened, scarred, reservoir for infection

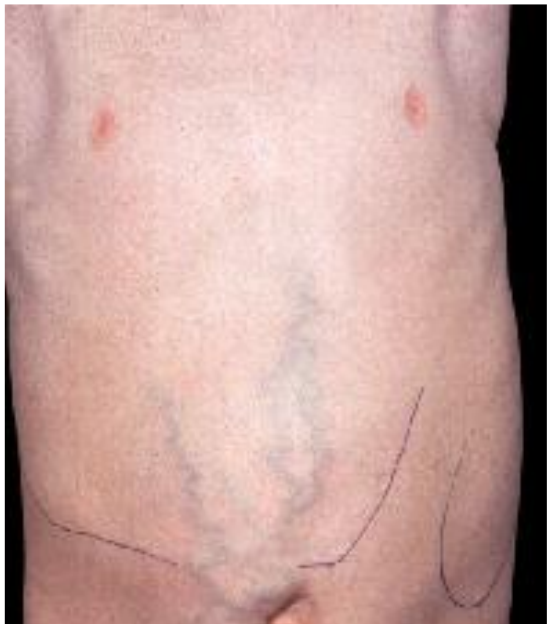
Inflammatory complications

- Granulomatous lesions
- Can affect any organ
  - Skin
  - Liver
  - Spleen
  - Lungs
  - CNS
  - Gut
- May be presenting feature of immune deficiency
- Treatment with immunosuppressive drugs – eg steroids

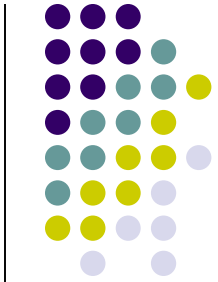


Liver disease

- **Sclerosing cholangitis – may be linked with cryptosporidium infection**
- **Autoimmune**



Management of inflammatory complications



- Immunosuppressive drugs – increase susceptibility to infection – delicate balance
- Other new therapies – eg monoclonal antibodies
- Stem cell transplantation – for severe end of spectrum

Supportive management

- Treatment of infection
- Prevention of infection
- Monitoring for and management of complications
- ***Psycho-social***

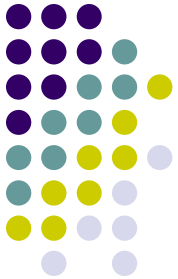
Psychosocial support

- Aim is for normal quality of life
- But impact of lifelong disorder cannot be under-estimated
- Psychological support important in many cases
- Impact on whole family

Corrective therapy

- Stem cell transplantation
- Gene therapy

Corrective therapy – which disorders?



- Severe combined immunodeficiencies ‘SCID’
- Other complex immunodeficiencies affecting T cell function
- Phagocytic disorders

Severe combined immunodeficiency (SCID)

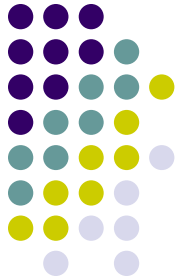
- ‘Bubble’ babies
- Profound deficiency of cell-mediated and humoral immunity
- Unlikely to survive more than a few years without corrective therapy
- Outlook good with early recognition and treatment
- Rare – approximately 1:100,000 live births

SCID: Management

- Initial supportive measures
  - Protection from infection
    - Protective isolation
    - Antibiotic/antifungal/antiviral prophylaxis
    - Immunoglobulin replacement
  - Aggressive treatment of infection
  - Nutrition

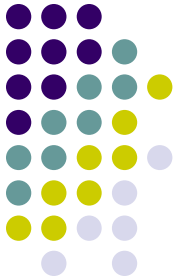
- Definitive
  - Stem cell transplantation
  - Gene therapy

Stem cell transplantation



- Standard Rx for SCID since early 1980's
- Increasing numbers of transplants for other PIDs since mid-1990's
  - Accumulating world-wide experience indicated poor long term outlook in many disorders previously considered less severe
  - Expanding donor panels
  - Improved tissue typing
  - Progress in BMT technology
- Currently 50-60 BMT's for PID per year in 2 UK centres

Types of transplant



- Matched sibling
- Matched family
- Unrelated
- Haploidentical - parental

- Bone marrow
- Umbilical cord blood
- Peripheral blood stem cells

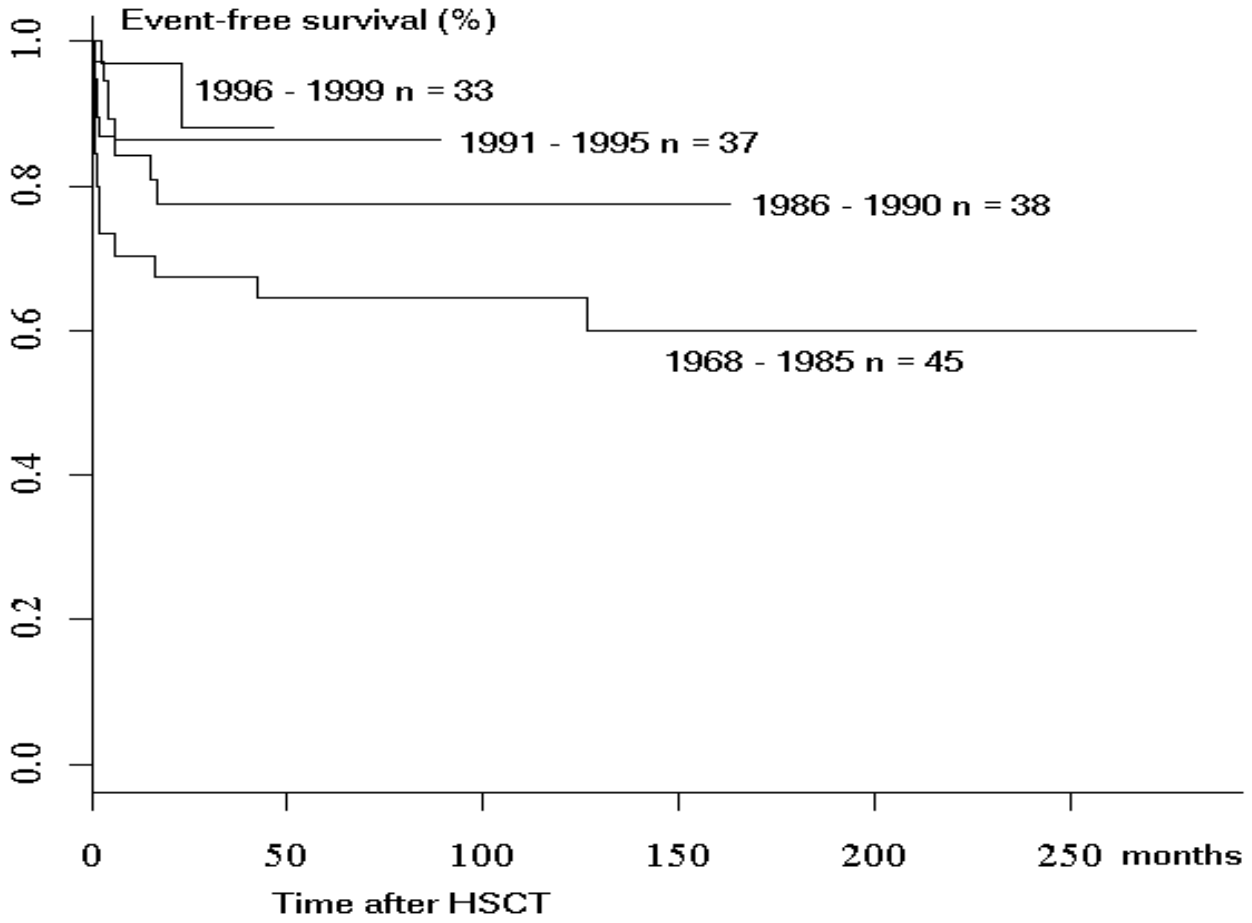
SCT – what is involved?

- Chemotherapy in most cases
- Prolonged period of extreme susceptibility to infection and bleeding
- Infusion of cells is similar to blood transfusion – not an ‘operation’
- Prolonged period of isolation in hospital
- Risks
  - Infection
  - Bleeding
  - Graft versus Host Disease
  - Rejection
  - Veno-occlusive disease
- Not undertaken lightly!

SCT outcomes

- SCID w/o complications, sibling donor BMT
  - 90%+ success rate
  - Longest survivors 20+ years
  - Immune competence maintained
- Undefined immunodeficiency, established complications – eg liver disease, unrelated donor BMT
  - May be as low as 50% success

Cumulative survival after BMT for SCID



SCT – possible outcomes

- Successful
  - Full immune reconstitution
  - Normal growth and development
- Partial success
  - Partial immune reconstitution – long term Immunoglobulin in some cases
  - Correction of underlying T cell defect
  - Prevention of dysregulatory complications
- Unsuccessful
  - Death
  - Chronic GvHD
  - Rejection

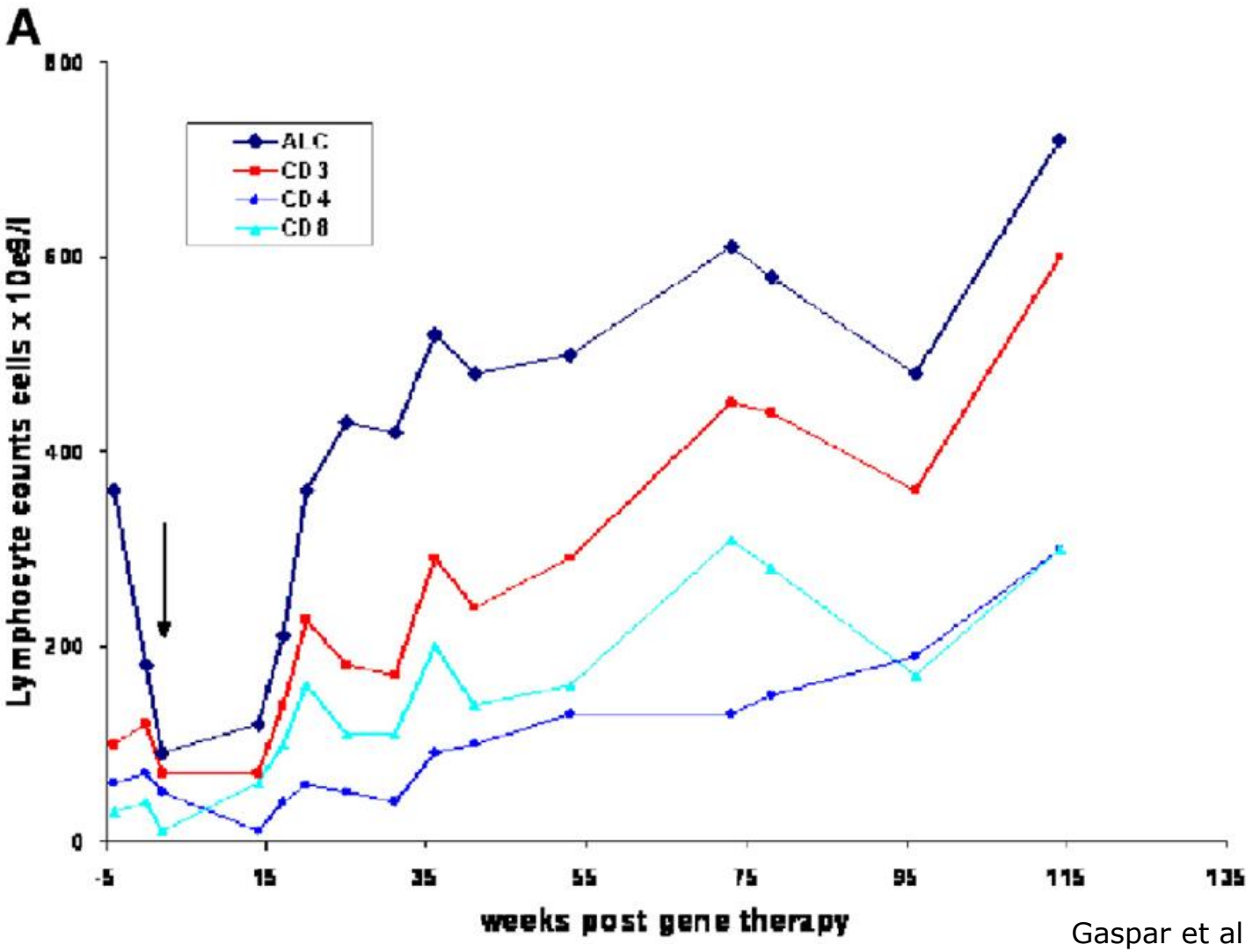
Gene Therapy

- PIDs ideal candidates for gene therapy – ability to remove bone marrow and manipulate in lab
- Clinical trials for
  - X-linked SCID
  - ADA deficiency
  - X-linked chronic granulomatous disease
  - Wiskott Aldrich syndrome
- X-SCID
  - Approx 25 patients in France and UK
  - Early results highly successful – longest follow-up 6+ years
  - 5 cases of leukaemia – linked with gene insertion site

Gene therapy – what is involved?

- Chemotherapy in some (not in SCID)
- Bone marrow harvest
- Manipulation of bone marrow in laboratory
  - Insertion of gene using viral vectors
- Transfusion of gene-transfected cells
- Risks
  - Short-term risks lower than BMT esp with less chemotherapy
  - Minimal risk of GvHD
  - Long-term: Leukaemia
- Each case considered individually national advisory committee

Reconstitution of T-cells in SCID



Gaspar et al Mol Ther 2006