Infections in Nephrotic Syndrome

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Introduction

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Infections in Idiopathic Nephrotic Syndrome

Leading cause of mortality in childhood Nephrotic syndrome

The incidence of infections in hospitalized children ranging from 1-2% for invasive bacterial infections in developed countries to 25-35% for overall infections in developing nations.

Etiology

- Bacterial infections
  - Cellulitis and soft tissue infections
  - Peritonitis
  - Non localized bacterial infections -sepsis
  - Pneumonia
  - UTI

- Viral infections
  - Parainfluenza
  - Influenza
  - RSV
  - Adenovirus
  - EBV

- Other infections:
  - Fungal
  - Parasitic
  - Tuberculosis

Causative organisms for bacterial infections

- Streptococcus pneumoniae (most common)
- Alpha hemolytic streptococci
- Streptococcus hemolyticus
- Gram negative bacteria
- E.coli
- Staphylococcus
- H.influenza

Various postulations :

Loss of immunoglobulins in the urine
Edema fluid acts as a culture medium
Protein deficiency, leading to malnutrition
Decreased bactericidal activity of the leucocytes due to altered T-lymphocyte function
Altered complement levels
Immunosuppressive therapy
Urinary loss of a complement factor (Properdin, Factor B) that opsonises the bacteria

Pathophysiology

- Hypogammaglobulinemia
  - IgG1 levels are markedly reduced during early phases of relapse, due to both increased renal clearance of IgG and decreased synthesis in the liver.
  - IgG1-3 are decreased during the later phases of relapse.
  - But IgG2 remain low for about a year after achieving remission. This leads to increased susceptibility of infection.
  - Also, the defective T lymphocyte function prevents conversion of IgM to IgG.

- Loss of Factor B and Properdin factor i.e. factors which modulate complement system, in the urine leads to decreased opsonization of the bacteria (streptococcus pneumonia, hemophilus influenza) and hence increased propensity to infection

Clinical symptoms

1) FEVER : is the alarming sign which points towards infection.

In fact in the presence of immunosuppressants the fever may be masked, delaying the detection. Hence presence of fever must be investigated thoroughly.

2) Abdominal pain/diarrhea/vomiting with fever – point towards spontaneous bacterial peritonitis

3) Cough and fever with chills points towards pneumoniae

4) Fever with swelling and redness of skin in any region points towards cellulitis

5) Fever with burning micturition points towards UTI

- So, there must always be a high degree of suspicion.

Hence signs at examination and investigations become very important in every case of fever and every case of relapse which must be investigated and treated to rule out an underlying infection

Clinical Signs

- General examination : lethargic, dull, point towards some possible infection; Irritablility or drowsiness point towards severe infection.
- Pallor and anasarca are seen in most cases as they come in relapse with infection
- Core periphery temperature difference
- Capillary refill time
- Blood pressure

These three help in identifying a sick child. But anasarca can be misleading sometimes, but help err towards detection than missing.

- Systemic examination:
  - Abdominal examination – tenderness ++, moderate to tense ascites
  - Respiratory examination – presence of crackles and bronchial sounds point towards pneumonia. Wheeze can be present because of fluid accumulation secondary to the relapse state
  - CVS examination – presence of gallop rhythm points towards pulmonary edema, murmurs could point towards infective endocarditis
  - CNS- Excessive irritability or drowsiness could point towards meningitis or infected cerebral venous thrombosis

Clinical investigations

- Complete blood count – Neutrophilic leucocytosis points towards infection, high hemoglobin and PCV could point towards intravascular dehydration indirectly pointing towards a severe clinical state
- C- reactive protein and procalcitonin help in detecting an underlying infection.
- BUN/creatinine – help in assessing the fluid status and hence help in fluid management.
- Electrolytes – help in guiding the fluids and supportive treatment

- Ascitic tap (if indicated) - to diagnose SBP – Z technique should be used to prevent oozing
- Chest X ray – if suspecting any lung infection
- Urine examination – to detect urine infection
- Blood culture must be done for all cases of suspected infection

Spontaneous Bacterial Peritonitis

- Definition : Clinical symptoms (abdominal pain, tenderness, diarrhea, vomiting) with >100 cells/mm3 and >50% neutrophils and/or positive culture.

- Causative organisms : most commonly Strep pneumoniae, followed by E.coli, less commonly hemophilus, strep B and the other gram negative organisms.

Management of Peritonitis

- Diagnosing Peritonitis – Diagnostic ascitic tap to be done immediately at clinical suspicion and sent for culture sensitivity along with cytology.
- Initial broad spectrum antibiotic must be started to cover for S.pnemoniae with 3rd generation cephalosporin – cefotaxime/ ceftriaxone or combination of ampicillin and aminoglycoside
- In case of a patient who has received steroids for >14 days, a stress dose of steroids must be given.

Management of Cellulitis

- Common organisms : Staphylococci, Group A streptococci, H. influenzae

- Oral Amoxclav or IV Cloxacillin and ceftriaxone for 7-10 days

Management of Pneumoniae

- Common organisms : S. pneumonia, Haemophilus influenzae, Staphylococcus aureus

Treatment

- Oral: amoxicillin, co-amoxiclav, erythromycin
- Parental: IV ampicillin + IV aminoglycoside; or IV cefotaxime/ ceftriaxone (7–10 days)

Varicella infection

- The unique characteristics are that in immunosuppressed there is more significant morbidity and mortality.
- Also, these patient have atypical lesions or absence of any skin lesions
- Thus, it can become a very severe illness, if left untreated.

Management of Varicella

- Exposure to varicella:
  - In case of immunocompromised individuals especially the susceptible (the unimmunized or those with no history of varicella) a single dose of varicella zoster immunoglobulin must be given. (within 96 hours of exposure)
  - If not available, a single dose of IV Ig (400mg/kg) must be given.

- Confirmed infection:
  - Acyclovir (oral/iv) must be administered for 10 days.
    - Oral dose: 80mg/kg/day in 4 divided doses
    - Parenteral: 1500mg/m2/day in three doses

Adrenal insufficiency

- “High dose steroids” is defined as >2weeks of 2mg/kg/d of prednisolone or equivalents in the year.
- When on high dose steroids, our body’s hypothalamic pituitary axis gets suppressed.
- Hence a small dose of supplementary steroids play a role in helping the body perform its fighting functions and preventing it from collapsing.

When is Stress dose of steroids needed

- Uncomplicated viral illness and upper respiratory tract infections with sore throat, rhinorrhoea, otitis media and/or low-grade fever **may not** require treatment with a stress-dose steroid regimen if the child otherwise appears well.
- Conversely, illness accompanied by fever of ≥38 °C should be accompanied by stress dose of steroids
- Patients undergoing surgery or anaesthesia will also require stress dose of steroids if they have received high dose steroids in the preceding year
- Stress Dose: parenteral hydrocortisone at a dose of 2-4 mg/kg/day, followed by oral prednisolone at 0.3-1 mg/kg/day as a single dose. This should be tapered rapidly after the period of stress.

Outcome of infections

- Unlike children with normal immunity,
  - There is delayed and poor immune response in nephrotic syndrome.
  - If left untreated can quickly lead to sepsis and become a cause for mortality
  - Though not every infection needs hospitalization but prompt treatment with the antibiotics and reducing the steroid dose to stress dosage most of the times helps in preventing a catastrophe.

Prevention of Infection

Vaccination

- Pneumococcal
- Influenza
- Varicella zoster

Pneumococcal Vaccination

- Recommendation :
  - ≤2 years - 2 -4 doses conjugate vaccine (PCV-13)
  - 2-5 years – 1 dose of conjugate vaccine + 1 dose polysaccharide (PPSV-23), 8 weeks later
  - >5 years – 1 dose of polysaccharide vaccine (PPSV-23).

  All must receive a repeat dose after 5 years.

- Timing of administration-
  - Ideal – When not on immunosuppressive medications.
  - But studies show that even in presence of immunosuppressives antibody response is sufficient

- Issues with the pneumococcal vaccination :
  - Not all serotypes are covered with the vaccine, hence episodes of peritonitis and sepsis can occur despite vaccination
  - Even after vaccination the antibody decay is known to occur more rapidly in nephrotic patients than normal patients. Hence despite vaccination infection episodes may occur.

Influenza Vaccination

- Influenza A infection has more severe complications in immunosuppressed
- Recommendation: Annual seasonal vaccine – either intramuscular inactivated or intranasal live attenuated.
    - 2 doses to be given for the 1st time and then single dose annually

During high dose steroid therapy, the patient must not receive intranasal vaccine.

Varicella Vaccination

Recommendation:

- 2 doses of varicella vaccination
- Post exposure prophylaxis with varicella immunoglobulin
- IV acyclovir in case of disease

But vaccination **must not** be given in case patient is on:

- Daily steroid treatment
- High dose steroid treatment in the last 3 months
- Cytotoxic medication in the last 3 months
- Cyclosporin or tacrolimus in the last 1 month

Post exposure prophylaxis for varicella

In case of non immune nephrotic (i.e. no vaccinations in the past, no h/o prior infection, no serological evidence of antibodies despite the vaccination) :

- Varicella Zoster immunoglobulin VZIG

Or

- Purified human varicella zoster immune globulin VariZIG,

To be given intramuscularly or intravenous in case of contraindications to i.m.

Preferably given <4 days but may be given upto 10 days