Paediatric Society CME
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The wide spectrum of causes of fever

Beyond malaria – causes of fever in outpatient Tanzanian children
D'Acremont V, et al N Eng J Med 2014; 370: 809-17

Describe the population of febrile children that were studied?
1005 children between 2 months and 10 years with an axillary temperature of 38 C or higher, without severe malnutrition or emergency signs. The illness had to be less than one week in duration, and the child had not received antibiotics or antimalarial drugs in the previous week. So the data apply to an outpatient and mild-moderately unwell febrile children, they do not directly apply to children with *prolonged* fever, or those with critical illness.

What were the proportions of viral, bacterial and parasitic disease?
Viral: 70.5%
Bacterial: 22%
Parasitic: 10.9%

What were the common causes of respiratory infection?
62% had respiratory infections, only 5% had radiographically confirmed pneumonia
The common causes of respiratory viruses were influenza, rhinovirus, adenovirus, RSV, parainfluenza, metapneumovirus, bocavirus, coronavirus and enterovirus.

What was the commonest cause of systemic infections (systemic fever)?
Human herpesvirus 6 was the commonest cause of systemic fever, parvovirus was the second most common cause.

What proportion of the children had malaria, and what percentage of the children with malaria had another condition?
105 of 1005 (10%) children with fever had malaria, but 51% of these 105 children with malaria also had another infection (acute respiratory infection, gastro, systemic viral syndrome, bacteraemia)

How common was urinary tract infection?
59 (5.9%) had UTI.

How common was Human Herpes Virus 6 infection, and what clinical infection does this virus commonly cause?
This was an interesting finding of the study, that HHV-6 was the commonest virus causing systemic viral infection (79 cases / 1005 = 8%). Most of the HHV-6 infections were in infants. HHV-6 causes *roseola infantum*, featuring a high temperature (often 40 C) lasting 3-5 days, followed by a rash. HHV-6 may also cause hepatitis, febrile convulsions, encephalitis

and myelosuppression. It is acquired in young infancy in most children, with nearly 100% of people exposed to HHV-6 by 3 years of age. HHV-6 accounts for one third of febrile seizures in children younger than 2 years. HHV-6 is present in CSF in about 10% of cases of suspected viral encephalitis, and the CSF and salivary glands are a source of latency after the primary infection. HHV-6 is believed to be a cause of many cases of temporal lobe epilepsy. HHV-6 can reactivate in immunosuppressed patients, including HIV.

Immune system in malnutrition

The immune system in children with malnutrition – A systematic review
Rytter MJH, et al. Public Library of Science (PLOS) ONE 2014; 9: Issue 8: e105017

What are the more common infections likely *resulting from* severe malnutrition?

Gastrointestinal – cryptosporidium, bacterial diarrhoea
Invasive bacterial infections – Gram negative sepsis
Yeast or fungal infections
Several other infections are associated with malnutrition, such as TB and HIV, pneumocystis but these infections may *cause* malnutrition or be associated with immune deficits related to HIV, rather than be immune dysfunction caused by malnutrition per se.

The 3 different types of immunity include barrier function, innate and acquired immunity, what are the components of each of these?

1. Barrier function – physical integrity of epithelium of the skin and gut mucosa, antimicrobial factors in secretions (lysozyme, IgA, gastric acidity), and commensal bacteria

2. Innate immunity – a non-specific response to infectious agents from granulocytes, monocytes, macrophages, complement, acute phase proteins

3. Acquired immunity – a specific response from thymus (location of maturation and proliferation of T-cells), cellular T-cell immunity, humoral B-cell immunity, immunoglobulin, creating long-lasting immunological memory. The acquired immune system also regulates tolerance to self and commensal bacteria in the gut.

What are the effects of severe malnutrition on barrier immunity?
Atrophy of skin, e.g. kwashiorkor
Gut mucosal thinning and atrophy, decrease in villous height, lymphocytic infiltration, pro-inflammatory cytokines, and sparse endoplasmic reticulum (where protein synthesis takes place).
Increased intestinal lactulose permeability, bacterial translocation, and higher blood levels of lipopolysaccharide.
Higher secretory IgA
Decreased gastric acid secretion
Different flora than well-nourished children

- Mouth yeasts
- Stomach and duodenum overgrowth with bacteria (usually sterile)

- More pathogenic bacteria in colon – more Gram negative bacteria, compared to well-nourished children where Gram positive commensals predominate.

What are the effects of severe malnutrition on innate immunity?

Higher granulocytes, chemotaxis of neutrophils reduced, microbicidal activity of granulocytes reduced.
Lower natural-killer cells, lower dendritic cells.
Increased acute phase reactants (CRP).
Decreased acute phase suppressants (albumin, transferrin, alpha-fetoprotein).
Low levels of C3.

What are the effects of severe malnutrition on acquired immunity?

Thymus atrophy "nutritional thymectomy" (thymus tissue is diminished by cortisol and adrenaline, which are elevated in the stress response of malnutrition, and protected by growth hormone, leptin and prolactin, which are low in malnutrition).
Lower levels of T-lymphocytes in blood.
Lower levels of CD4+ lymphocytes in blood.
Diminished delayed type hypersensitivity response (Mantoux test).
Low number of B-lymphocytes in blood (flow cytometry studies).
Elevated levels of IgA, related to dermatosis og kwashiorkor.
Reduced seroconversion to vaccines.
Lower levels of anti-inflammatory cytokines and higher level of pro-inflammatory cytokines, especially in the GI tract.
A predominant Th2 immune response (humoral) with some immunoglobulins (IgA, IgE, IgD, IgM) increased in some studies.
Impaired Th1 response (cellular) with thymic atrophy, reduced T-cells, reduced CD-4+ lymphocytes, diminished DTHR (Mantoux).

Aminoglycoside antibiotics

What do I need to know about aminoglycosides?
Germovsek E, et sl. Archives Diseases in Childhood Education Practice Edition 2017; 102:89-93

What infections can be treated by aminoglycosides?
Gram negative aerobic bacteria and staphylococci (Gram positive)
Severe urinary tract infections (such as acute pyelonephritis), severe neonatal sepsis, neonatal meningitis, and endocarditis.
The most commonly used aminoglycoside is gentamicin. Tobramycin is often more effective against pseudomonas. Amikacin is effective against some Gram negative bacilli which are resistant to gentamicin. Amikacin and kanamycin are effective against some forms of multi-drug resistant tuberculosis.

How do aminoglycosides penetrate into a bacteria cell membrane?
Aminoglycosides are hydrophilic drugs, so they cannot easily penetrate the hydrophobic bacterial cell membrane, so they can only enter the cell using an electron transport system, which is only available in aerobic bacteria. Daily dosing leads to high peak concentrations and lead to more rapid and higher bacterial kill, whereas toxicity is not increased because aminoglycoside uptake in the kidney and ear are saturable.

How do aminoglycosides interrupt protein synthesis?
Binding irreversibly to the 16S ribosomal RNA receptor on the 30S subunit of the bacterial ribosome. Therefore the bacteria cannot produce proteins or replicate.

How are aminoglycosides distributed and excreted?
Because aminoglycosides are hydrophilic, they distribute throughout total body water. Neonates with a higher proportion of body water, have a higher volume of distribution. Aminoglycosides are excreted unchanged by the kidneys, and because of immature renal function in neonates and infants the elimination half-life is prolonged (adult renal function level is reached at one year). 36 hour dosing is appropriate in neonates in the first week of life, after that 24 hour dosing is appropriate.
For children with burns (because of fluid loss) and endocarditis, more frequent gentamicin dosing is often needed.

What is the toxicity of aminoglycosides, and what exacerbates them?
Ototoxicity may be irreversible (up to 25% of children on a prolonged course of amikacin for MDR-TB become permanently deaf).
Nephrotoxicity should be monitored during aminoglycoside administration by measuring creatinine and urea, and avoidance of other nephrotoxic agents. Nephrotoxicity may be reversible.
Aminoglycosides also (rarely) impair neuromuscular function and in myasthenia gravis