Paediatric Society CME
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TUBERCULOSIS

Treatment of tuberculosis
Horsburgh CR Jr, et al. New England Journal of Medicine 2015; 373:2149-2160

- **In the first 2 months treatment of TB, why is there a biphasic kill curve, and what are the implications of this for therapy?**
  The biphasic kill curve indicates there are at least two subpopulation of bacteria that differ in their intrinsic drug susceptibility: one population that is rapidly killed, and the other that responds more slowly. The bacteria that are not rapidly killed may be slowly replicating or non-replicating (so that antibiotics which act on rapidly dividing cells will have minimal effect – for example Rifampicin acts on RNA polymerase), or may be in some other metabolic state (e.g. oxygen abundance) that makes them less susceptible to killing with some drugs. The other factor is persistent disease, with some bacteria sequestered in thick-walled granulomas, abscesses and cavities. Some anti-TB drugs (such as rifampicin and pyrazinamide) penetrate caseous foci well, whereas some new drugs (such as moxifloxacin) do not.

- **What other explanations are there for poor clinical responses?**
  Inadequate antimycobacterial drug levels. For example, isoniazid, rifampicin and pyrazinamide absorption is decreased when the drug is taken with food. Some people have variations in genetically-determined metabolic pathways in the liver, such as "fast acetylators" who are likely to have low isoniazid levels, and "slow acetylators" who are at a greater risk of liver toxicity because INH levels will be high. The other factor is acquired drug resistance, which is mostly thought to be due to random genetic mutations. Some antibiotics can induce bacterial mutations, and exposure to sub-therapeutic levels of antimycobacterial agents has been associated with emergence of resistance. Adherence is the other factor.

- **What is the current standard treatment regimen for drug-sensitive TB, and why is ethambutol added?**
  Induction phase is 2 months of rifampicin, isoniazid, and pyrazinamide. Ethambutol is added as protection against unrecognised resistance to one of the 3 core drugs. Where the source of transmission or isolate is known to be fully drug susceptible (very rare in children) ethambutol is not needed.

- **What are the common drug toxicities?**
  Drug toxicity occurs in 15% of patients in TB treatment. The most common are hepatotoxic effects (3-13% of patients), gastrointestinal disorders, allergic reactions and arthralgias. Hearing loss, nephrotoxicity and prolonged QT-interval are common with some of the MDR TB drugs.

- **What is the recommended regimen for MDR tuberculosis?**
  WHO recommends that the initial regimen includes *4 drugs to which the patient is susceptible*, *plus* pyrazinamide. The need to use more drugs for MDR reflects the poorer antimycobacterial activity of these drugs compared with INH, rifampicin and pyrazinamide. The drugs used for MDR are also more toxic than first line drugs. These include injectable agents (kanamycin, capreomycin), Aminosalicylic acid, fluoroquinolones (levofloxacin, moxifloxacin), and ethionamide. Some newer agents such as bedaquiline are not yet widely available. The duration of treatment is 20 months, and at least 8 months has to be given with an intravenously administered drug (such as kanamycin, capreomycin or amikacin).

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Chikungunya Fever

Chikungunya virus and the global spread of a mosquito-borne disease
Weaver SC and Lecuit M. New England Journal of Medicine 2015; 373:1231-1239

- **Where in the world did Chikungunya virus originate and what promotes its global spread?**
  Chikungunya virus was first found in Tanzania in the 1950s, but is believed to have first emerged beyond Africa to Asia in the 19th century. Chikungunya has a non-human primate host, and mosquito vectors. The virus first circulated in beyond Africa in sailing ships carrying people, Aedes aegypti mosquitos, and water for mosquito propagation. It has spread more rapidly in the 20th and 21st centuries because of air travel, and urbanisation with dense populations and water sources in houses and back-yards, and because of the emergence of another vector Aedes Albopictus. A. aegypti and A. albopictus live in overlapping and different environments so there is opportunity for different types of outbreaks of the 2 virus lineages.

- **What are the clinical features of Chikungunya fever?**
  Short incubation period (3 days), followed by abrupt onset of high fever (>39 C), intense tiredness, severe arthralgia, myalgia, headaches, and rash (20-80% have a maculopapular rash). Joint pain is symmetric and localised in arms and legs, large joints being most affected, sometimes also small joints and vertebral column. Most (85%) of infected patients develop disease symptoms (i.e. unlike other viruses there are not many asymptomatically infected people). Acute infection last 1 week. Severe Chikungunya can be associated with encephalopathy, encephalitis, myocarditis, hepatitis, and multi-organ failure.

- **Which children are most commonly affected?**
  Neonates are at risk for severe infection if born to mothers with viraemia, transmitted through maternal blood. Encephalopathy is common in these neonates, and can lead to long term neurological sequelae. Chikungunya can infect the meninges, ependymal cells and choroid plexus (the tissues within the CNS ventricular system that make CSF). Young children tend to have severe disease.

- **What are the long-term sequelae of Chikungunya fever?**
  Persisting or relapsing arthralgia occurs in up to 50% of patients. Whether this is associated with persisting infection or more likely the inflammatory response. Only treatment is non-steroidal anti-inflammatory drugs, sometimes immunosuppressive drugs such as methotrexate is used.

- **Are there any blood tests that can help diagnose Chikungunya?**
  In an area where there is known Chikungunya virus outbreak the clinical features of high fever and polyarthralgia are almost diagnostic. There is a PCR test, a “reverse transcriptase PCR”, which can also be multiplex (which means it can test for other arboviruses viruses as well, such as dengue or Ross river virus. A four-fold rise in Chikungunya IgG between acute and convalescent serum is also diagnostic in a patient with clinical features of the virus infection. Lympopenia, thromboctytopenia, increased AST and ALT, hypocalcaemia (none of these are diagnostic). In chronic arthritis Chikungunya virus IgM and IgG stay increased.

- **How can Chikungunya fever be prevented?**
  Like dengue, prevention is mostly through vector control: reduce human contact with A. aegypti and A. albopictus. Both mosquitos bite in the day-time (and only adult females bite and transmit Chikungunya and dengue). Avoid standing water and rubbish dumps where mosquitoes lay eggs and larvae form. Wearing protective clothing, repellents, insecticide-impregnated curtains and

bed-nets. Insecticide resistance is emerging and making impregnated material potentially less effective in future. Vaccine under development, may be easier than with dengue as Chikungunya has limited antigenic diversity.