BUGS

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Tuberculosis backstaging Crohn's Disease

Research efforts in Crohn's disease (CD) have been uniquely successful in identifying several susceptibility genes namely the NOD2/CARD15 gene[1,2] on chromosome 16 which has been shown to be associated with ileal disease and earlier onset, the OCTN1/SLC22A4-OCT/SLC22A5 genes[3] on chromosome 5q and the DLG5 gene.[4] These and other associations such as with TLR4 and MDR1 genes [5,6] suggest a strong probability of the involvement of infectious agents as triggers for CD.

Histopathological similarities between animal paratuberculosis caused by Mycobacterium avium subspecies paratuberculosis (MAP), intestinal tuberculosis and CD were reported as early as 1913. Several studies have been conducted in the past in an attempt to isolate MAP from human tissue samples, but results remain inconsistent, mostly due to the challenges in cultivating MAP and the differences in methodology. In 1996, using RT-PCR, Mishina and colleagues found viable MAP in all of eight patients with CD and two ulcerative colitis (UC) patients.[7] In 2000, Naser and colleagues cultured MAP using Mycobacterial Growth Indicator Tube (MGIT) in seven of eight tissue samples from CD patients and none from three controls.[8] In the same year, they identified MAP using the same methodology in breastmilk from two lactating mothers with CD.[9] Lending more support to the MAP hypothesis for CD, Bull et al[10] isolated viable MAP from MGIT culture of biopsy samples in 34/37 (92%) of patients with CD and 9/34 (26%) of controls. Most recently, in 2004, Naser and colleagues[11] investigated the presence of MAP in peripheral blood samples of 28 patients with CD, nine with UC, and fifteen without inflammatory bowel disease (IBD). PCR and culture in buffy coat preparations was used to test for MAP. MAP was identified in 13/28 CD patients (46%), 4/9 with UC (45%) and 3/15 (20%) without IBD. Viable MAP was cultured from 14 (50%) of CD patients, 2 (22%) with UC and none of the individuals without IBD.

Thus, MAP has been judged to be a leading candidate among infectious agents on the basis that the human and animal forms of the disease are similar and that MAP can be cultured from intestinal and lymph nodes, breastmilk and peripheral blood. The presence of MAP in the blood of patients with and without IBD suggests that MAP is common in the environment, with exposure most likely through food and water supply. Evidence from the UK suggests that people are exposed to MAP through retail milk supplies and that this route may be a source of zoonotic disease.

1. Ogura Y. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 2001;411:603-6.
2. Hugot JP. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature 2001;411:599-603.
3. Peltekova VD. Functional variants of OCTN cation transporter genes are associated with Crohn's disease. Nat Genet 2004;36:471-5.
4. Stoll M. Genetic variation in DLG5 is associated with inflammatory bowel disease. Nat Genet 2004;36:476-80.
5. Brant SR. MDR1 Ala893 polymorphism is associated with inflammatory bowel disease. Am J Hum Genet 2003;73:1282-92.
6. Franchimont D. Deficient host-bacteria interactions in inflammatory bowel disease? The toll-like receptor TLR)-4 Asp299gly polymorphism is associated with Crohn's disease and ulcerative colitis. Gut 2004;53:987-92.
7. Mishina D. On the etiology of Crohn disease. Proc Natl Acad Sci USA 1996;93:9816-20.

8. Schwartz D. Use of short-term culture for identification of Mycobacterium avium subsp. paratuberculosis in tissue from Crohn's disease patients. Clin Microbiol Infect 2000;6:303-7.
9. Naser SA. Isolation of Mycobacterium avium subsp paratuberculosis from breast milk of Crohn's disease patients. Am J Gastroenterol 2000;95:1094-5.
10. Bull TJ. Detection and verification of Mycobacterium avium subsp. paratuberculosis in fresh ileocolonic mucosal biopsy specimens from individuals with and without Crohn's disease. J Clin Microbiol 2003;41:2915-23.
11. Naser SA. Culture of Mycobacterium avium subspecies paratuberculosis from the blood of patients with Crohn's disease. Lancet 2004;364:1039-44.

Steroids for Tuberculosis Meningitis

Tuberculosis meningitis is the severest form of infection with Mycobacterium tuberculosis, causing death or severe disability in more than half of those affected in spite of antituberculosis chemotherapy. The role of adjunctive treatment with corticosteroids was evaluated for the first time on a large scale in a recent Vietnamese study.[1,2] Thwaites et al[1] performed a randomized, double-blind, placebo-controlled trial in patients over 14 years of age who had tuberculosis meningitis, with or without HIV infection. Adults previously untreated for tuberculosis received three months of isoniazid, rifampin, pyrazinamide and intramuscular streptomycin, followed by six months of isoniazid, rifampin and pyrazinamide. Ethambutol was substituted for streptomycin in patients with HIV infection, and was added to the regimen for three months for patients who had been previously treated for tuberculosis. Stratification was based on severity of disease as follows: Patients with Grade 1 disease (better status; no focal neurologic signs) received two weeks of intravenous dexamethasone therapy (0.3mg/kg/day for week 1 and 0.2mg/kg/day for week 2) and then four weeks of oral therapy (0.1mg/kg/day for week 3, and then a total of 3mg / day, decreasing by 1mg per week). Patients with Grade II (focal neurologic signs) and Grade III (severest symptoms) received intravenous treatment for four weeks (0.4mg/kg/day for week 1 decreasing by 0.1mg per week to 0.1mg/kg/day for week 4) and then oral treatment for four weeks, starting at a total of 4mg/ day and decreasing by 1mg each week.

Treatment with dexamethasone was associated with a reduced risk of death, but not severe disability. The treatment effect was consistent across subgroups that were defined by disease severity grade and HIV status. Significantly fewer adverse effects were noted in the dexamethasone group as compared to placebo. The authors summarize that: '…this study provides clinical evidence that early treatment with dexamethasone and antituberculosis drugs improves survival among patients over 14 years of age with tuberculosis meningitis, regardless of disease severity.'

1. Thwaites GE. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med 2004;351:1741-51.
2. Donald PR, Schoeman JF. Tuberculous meningitis, ed. N Engl J Med 2004;351:1719-20.

Bacterial Meningitis re-reviewed

A nationwide prospective evaluation study was conducted in the Netherlands to study clinical features and prognostic factors of bacterial meningitis.[1,2] The epidemiology of bacterial meningitis is changing around the globe and this can be attributed to the Haemophilus influenzae type b vaccination, and the introduction of conjugate vaccines against Streptococcus pneumoniae. From 696 episodes of community-acquired bacterial meningitis, the most common pathogens were Streptococcus pneumoniae (51% of episodes) and Neisseria meningitides (37%). Only 44% of the patients reported the classic triad of fever, neck stiffness, and a change in mental status. About 95% reported at least two of the four symptoms of headache, fever, neck stiffness and altered mental status. The overall mortality rate was 21% and mortality was found to be higher among those with pneumococcal meningitis than among those with meningococcal meningitis (30% vs 7%). Risk factors for an unfavourable outcome were advanced age, presence of otitis or sinusitis, absence of rash, a low score on Glasgow Coma Scale on admission, tachycardia, a positive blood culture, an elevated erythrocyte sedimentation rate, thrombocytopenia, and a low cerebrospinal fluid white cell count.

1. van de Beek D. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med 2004;351:1849-59.
2. Swartz MN. Bacterial meningitis--a view of the past 90 years, ed. N Engl J Med 2004;351:1826-8.

Ceftriaxone Rocks!

Ceftriaxone (Rocephin), a third generation cephalosporin, is a drug of choice for severe infections, such as typhoid and meningitis, in children. The drug is eliminated via the kidneys and in bile. It has been known to bind calcium and precipitate biliary pseudolithiasis[1] and nine cases of nephrolithiasis have also been described. A Turkish group[2] prospectively investigated development of renal stones in 51 children (age range 1 month to 14 years). Nephrolithiasis (2-3mm) was detected by abdominal ultrasound in four cases after 5-7 days of treatment however, none of the children were symptomatic. The stones disappeared after about three weeks except in one case (present until seven months). Serum and urine biochemistries including calcium, oxalate, citrate and uric acid remained within normal limits. The study suggests that younger children (less than one year) may be at higher risk of developing renal calculi after ceftriaxone therapy and that screening with abdominal ultrasound may prevent complications.

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1. Bonnet JP. Early biliary pseudolithiasis during ceftriaxone therapy for acute pyelonephritis in children: a prospective study in 34 children. Eur J Pediatr Surg 2000;10:368-71.
2. Avci Z. Nephrolithiasis associated with ceftriaxone therapy: a prospective study in 51 children. Arch Dis Child 2004;89:1069-72.

Test for Orthopaedics

Joint replacement surgeries are increasingly performed in modern day orthopaedics. The most common causes of prosthetic joint failure are aseptic loosening and infection. Differentiating these two entities is important because their management differs. A study from Mayo Clinic[1] reports a simple, rapid and accurate test for differentiating prosthetic joint infection (PJI) from aseptic failure (AF) based on synovial fluid leucocyte count and neutrophil percentage. The study investigated 133 patients for joint failure post-total knee arthroplasties. Based on intraoperative findings, histopathological tissue examination and synovial fluid culture, patients were classified in the PJI or AF groups (34 and 99 respectively). The total leukocyte count was significantly higher in the PJI group (median 18.9x103/↑l) compared to the AF group (median 0.3x103/↑l). Similarly, the neutrophil percentage was also higher (medians 92% vs 7% respectively). The authors propose 1.7x103/↑l for total leukocyte count and 65% neutrophils as cutoff values for optimal sensitivity (94% and 97% respectively) and specificity (88% and 98% respectively) to differentiate AF from PJI. Previous studies had recommended higher cutoffs and therefore had lower sensitivities for diagnosing PJI. However, this study was limited to knee joints only and other joints may have different leukocyte count cutoffs. Causative microorganisms in the PJI group included Staphalococcus aureus, Propionobacterium acnes, Corynebacterium juikeium, Pseudomonas aeroginosa and Enterococcus spp. Synovial cultures yielded the organism in 77% of PJI and grew contaminants in some cases of AF.

1. Trampuz A. Synovial fluid leukocyte count and differential for the diagnosis of prosthetic knee infection. Am J Med 2004;117:556-62.

Vaccine for Cervical Cancer

Persistent infection with human papilloma virus (HPV), especially HPV-16 and HPV-18 serotypes, causes a large proportion of cervical malignancies. North American and Brazilian investigators evaluated the efficacy of a vaccine for both HPV16 and 18 manufactured by GlaxoSmithKline against new and persistent HPV infection, abnormal cytology, and cervical intraepithelial neoplasia (CIN).[1] Over 1100 women (age range, 15-25) with no prior history of HPV infection or abnormal cervical cytology were randomized to receive three doses of HPV vaccine or placebo during a 6-month period. The women were followed for evidence of HPV infection and cervical lesions with periodic Pap smears and self-collected cervicovaginal swabs for upto 27 months.

Vaccinated women were significantly less likely to develop new onset HPV infection compared to the placebo group (0.6% vs. 6.5%), persistent infection (0% vs. 2%), or abnormal cervical cytology (0.4% vs. 4.9%). A small number of patients mostly in the placebo group developed CIN. The vaccine was found to be safe and had only minor injection related side effects. Average antibody titers against the two strains of HPV were much higher than those that occur during natural infection. Given the success of the trial this vaccine has the potential to prevent cervical cancer.

1. Harper DM. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomized controlled trial. Lancet 2004;364:1757-65.

Ironmongering

Iron is a necessity for survival and its metabolism and free concentration are tightly regulated by serum proteins such as ferritin and transferrin. During infection bacteria acquire iron from the host by synthesizing compounds called siderophores that scavenge iron and transport it back into the pathogen by specific receptors. To prevent pathogens from acquiring iron, the innate immune response has now been shown to include hepatocyte secretion of a protein called lipocalin-2 which binds the bacterial siderophores preventing them from shuttling iron into the invading bacteria. Flo et al.[1] report that the secretion of this protein is induced by Toll-like receptors (TLR) which are turned on by bacterial components. Lipocalin-2 knockout mice developed higher levels of bacteremia and infestation of the liver and spleen than wild type mice with a sublethal dose of E. coli. Following bacterial challenge the serum lipocalin-2 levels rose 30-fold in wild type mice within 24 hours. Lipocalin-2 was shown to bind only to a particular class of siderophores and thus can play a protective role in infection with certain types of bacteria (eg E. coli, Salmonella, Corenebacterium diptheriae and Vibrio spp) but not against others such as Staphalococcus aureus which uses another type of siderophore for scavenging iron. This discovery lays the foundation for a new mechanism for innate immune system and has substantial implications for clinical management of infections.

1. Flo TH. Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron. Nature 2004;432:917-21.

Mathematical Modeling for Hepatitis C

About 200 million people worldwide are infected with Hepatitis C virus (HCV). Interferon and ribavirin combination therapy cures about 50% of patients. Ribavirin alone has not been found to be effective in decreasing HCV viral load, but in combination with interferon significantly improves long-term response rates. Mathematical modeling by Dixit et al[1] shows that HCV clearance exhibits a biphasic decay with a fast first phase (1-2 days) and a slow second phase (till end of treatment). They report that ribavirin influences the second, and not the first phase, of viral load decline. Thus, interferon effectiveness determined from the first phase may under-predict the long-term outcome of combination therapy. Patients with slower second phase declines may become responders with combination therapy. In poor interferon responders ribavirin addition should improve end-of-treatment response and sustained virological response. With weekly dosing of interferon, ribavirin addition can prevent viral load resurgence as interferon effectiveness drops over the course of the week. The model fits observed patterns of HCV RNA decline in patients undergoing therapy and rules out a major immunomodulatory effect of ribavirin.

1. Dixit NM. Modelling how ribavirin improves interferon response rates in hepatitis C virus infection. Nature 2004;432:922-4.