Antibiotics

Mohammad Saeed (Department of Biological and Biomedical , The Aga Khan University, Karachi)

Statins prevent sepsis

In a prospective observational cohort study of 361 patients in Israel, Almog et al. aptly demonstrated that statin therapy of greater than one month duration was highly protective against severe sepsis and ICU admission.1 Sepsis is a grave health problem of massive proportion, and one of the leading causes of death worldwide. Statins have been shown to decrease all-cause mortality in several clinical trials, including non-coronary mortality2 and recently pretreatment with simvastatin was shown to improve survival in a mouse model of sepsis.3 These observations may in part be explained through the anti-inflammatory effects of statins. In this cohort, severe sepsis developed in only 2.4% patients in the statin group compared to 19% in the no-statin group. Prior statin therapy was associated with a 16% reduction in risk of severe sepsis and a significantly lower ICU admission rate. Another important observation of this study was that blood cultures were positive six times more often in patients who developed severe sepsis than in patients who did not. Low serum albumin levels were also predictive of severe sepsis.

1. Almog Y. Prior statin therapy is associated with a decreased rate of severe sepsis. Circulation 2004;110:880-5.

2. [No authors listed] Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-9.

3. Merx MW.HMG-CoA reductase inhibitor simvastatin profoundly improves survival in a murine model of sepsis. Circulation 2004;109:2560-5.

'Immuno-biotic' for insect stings

A common misconception of both parents and physicians regarding allergic disorders such as asthma and reactions to insect stings is that all children outgrow their allergies. Goldman and colleagues1 followed 512 patients enrolled 20 to 25 years ago as children with diagnosis of allergy to insect stings. Venom immunotherapy was initially instituted to a group of these children. Forty-three percent of the patients received subsequent stings in roughly equal proportions in the immunotherapy treated and non-treated groups. The rate of systemic reactions was significantly greater in the untreated group (17%) compared to the treated group (3%). Systemic reactions developed in 32% of those who had an initial moderate-to-severe reaction compared to 13% of those who had a limited dermal reaction only. As shown for adults previously2, this study showed that those children who had an initial high intensity allergic reaction to insect sting were more likely to experience a similar severe reaction on subsequent exposure. This study also showed that even a decade or two after stopping venom immunotherapy, there was a significant reduction in the rate and intensity of systemic reactions in children who had initial moderate-to-severe reactions. Thus, the study recommends venom immunotherapy for children with initial moderate-to severe systemic reactions to insect stings but not for children with mild dermatologic manifestations only, which is also the case for adults.2

1. Golden DB. Outcomes of allergy to insect stings in children, with and without venom immunotherapy. N Engl J Med. 2004 Aug 12;351(7):668-74. Editorial comment: Gruchalla RS. Immunotherapy in allergy to insect stings in children. N Engl J Med 2004;351:707-9.

2. Reisman RE. Natural history of insect sting allergy: relationship of severity of symptoms of initial sting anaphylaxis to re-sting reactions. J Allergy Clin Immunol 1992;90:335-9.

Natural Antibiotic for H. pylori

Helicobacter pylori colonizes the gastric mucosa of about half of the world's population. However, a small proportion of the infected individuals develop peptic ulcer, gastric cancer and malignant lymphoma, suggesting host defense mechanisms against H. pylori pathogenesis. The bacterium is rarely found in the deeper portions of the gastric mucosa, which is lined by a different kind of mucin. Gland mucus cells produce mucins in the deeper layers of the gastric mucosa, having terminal a1,4-N-acetylglucosamine (NAG) residues attached to branched O-glycans. A Japanese group showed that synthetic NAG inhibited the log phase of H. pylori growth.1 Human gastric mucins from the gland cells suppressed H. pylori growth in a similar fashion, however, mucin derived from

the surface mucus cells stimulated growth instead. Morphological changes similar to those induced by b-lactam antibiotics were observed in H. pylori, suggesting disruption of peptidoglycan synthesis in the cell wall on treatment with NAG. H. pylori is dependent on exogenous cholesterol for the synthesis of its cell wall constituents. The study shows that NAG competitively inhibits enzymatic synthesis of cholesterol esters required for cell wall integrity leading to bacteriocidal effects on H. pylori.

1. Kawakubo M. Natural antibiotic function of a human gastric mucin against Helicobacter pylori infection. Science 2004;305:1003-6.

'Typhi-Tussle'

Salmonella typhi causes an estimated 16 million cases of typhoid worldwide each year. In the past 2 decades there have been several reports of the global emergence of multi-drug resistant S. typhi (MDR-St). Due to increased resistance to conventional antibiotics, extended spectrum cephalosporins and fluroquinolones have become drugs of choice for MDR-St. However alarmingly, resistant strains to imipenem in addition to both these antibiotics have also arisen. Of note is the finding that nalidixic acid resistance is a good predictor for reduced susceptibility to fluroquinolones in S. typhi, as resistance is predominantly mediated through mutations in the quinolone resistance-determining region (QRDR) of the DNA gyrase genes. Resistance to cephalosporins is generally due to the production of a variety of b-lactamases, genes for which are transmitted mostly in plasmids through conjugation. Overuse of antimicrobials in animal feed have contributed significantly to the emergence of MDR-St. Thus, food of animal origin is the primary source of MDR-St infections. In Denmark discontinuing the use of antimicrobials in animal food in 1999 resulted in a significant decline in antimicrobial resistance as well as pathogen load of food-borne bacteria, including MDR-St.1

A recent review of CDC data (1994-1999) reported 1400 cases of S. typhi in US, 74% of which were travel associated.2 Most were young male (54%) adults (median age 22 years) visiting family (80%) in the Indian subcontinent (53%). Pakistan contributed a staggering 13% of the cases. Only 4% of the cases reported having been vaccinated for S. typhi. Duration of stay of less than a week also resulted in contracting the infection, though longer periods of stay were associated with greater chances of infection. The paper additionally reports the general safety of the typhoid vaccine (particularly Typhim Vi capsular polysaccharide vaccine). Thus, vaccination for travelers to high risk countries like Pakistan is strongly recommended.3

1. Su LH. Antimicrobial resistance in nontyphoid Salmonella serotypes: a global challenge. Clin Infect Dis 2004;39:546-51.
2. Steinberg EB. Typhoid fever in travelers: who should be targeted for prevention? Clin Infect Dis 2004;39:186-91.
3. http://www.cdc.gov/travel/diseases/typhoid.htm

Antifungals for Aspergillosis

Invasive aspergillosis (IA) is a major cause of mortality in immunocompromised patients such as cancer patients and transplant recipients. Recently newer antifungal agents such as triazoles (e.g. voriconazole, posaconazole and ravuconazole) and echinocandins (e.g. caspofungin, micafungin and anidulafungin) have become available to treat this life- threatening infection.1,2 These two antifungal classes target the cell membrane and cell wall respectively and should theoretically work synergistically. Monotherapy with these agents have had limited success rates as has been the case with classical agents like amphotericin B. Marr et al. investigated combination therapy with voriconazole and caspofungin versus voriconazole alone for IA.2 Their pilot observational study showed marginally improved survival in combination therapy group, however this difference may mean a lot to the severely ill patients. A large double-blind randomized controlled trial of caspofungin vs liposomal amphotericin B showed that caspofungin is as effective as and generally better tolerated than liposomal amphotericin B when given as empirical antifungal therapy in patients with persistent fever and neutropenia.3

1. Herbrecht R.Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347:408-15.
2. Marr KA. Combination antifungal therapy for invasive aspergillosis. Clin Infect Dis 2004;39:797-802.
3. Walsh TJ.Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med 2004;351:1391-402.

Natural Killer Cell against Hepatitis C

Salim Khakoo et al. carried out a large scale genetic association study investigating the role of HLA and KIR (killer cell immunoglobulin-like receptors) genes in the resolution of HCV infection.1 They report that HLA-C1C1 genotype was associated with resolution of HCV infection, whereas HLA-C2C2 genotype predisposed to viral persistence. KIR2DL3 homozygous genotype had a synergistic protective effect with HLA-C1C1 and did not affect the HCV outcome independent of HLA-C1 genotype. This protective association disappeared when patients were stratified according to transfusion status. Since contracting HCV infection due to transfusion as opposed to needle-stick injury would have resulted in higher dose of the innoculum, the authors propose a dose-response relationship of the protective effect of the HLA-C and KIR2. This study identifies the role of NK-cells

as well as HLA and KIR genes in hepatitis C.

1. Khakoo SI. HLA and NK cell inhibitory receptor genes in resolving hepatitis C virus infection. Science 2004;305:872-4.

Farewell Francis Crick!

This year, on the 28th of July, a leading personality in science passed away. Trained as a physicist, he was among the founders, premier theorists, and most influential biologists of this century.

His colleagues and close friends (Horace Judson, Leslie Orgel, Alexander Rich and Charles Stevens) summarized the life, personality and work of Francis Crick in articles published in several journals since his death. They describe him as: relentless, committed, immersed and brutally candid. Among his greatest achievement was the unraveling of the double helical structure of DNA (1953), using X-ray diffraction patterns. The diffraction patterns were taken by Rosalind Franklin, coupled with James Watson's intuitive attempts to pair nucleotide bases, facilitated by Jerry Donahue's critical intervention regarding their correct structure. He was honored, along with Watson, with the Nobel Prize in Physiology or Medicine in 1962.

In the latter half of his career his switched his focus to the understanding of consciousness, believing that this was the most important goal in neuroscience and that the time was ripe for an experimental approach. Although he was not able to make any significant contribution to this field, his presence gave this field importance and attracted several competent scientists to it.

He battled colon cancer till the end, devoting his last minutes to science, writing papers, thinking ideas and talking to colleagues. The life and works of Francis Crick will remain a source of inspiration for generations to come. Farewell!