of cholera patients as well as in the severity of the disease has been observed. Globally, also there has been a substantial increase in the incidence of cholera and in the number of outbreaks of cholera.

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5.004

Rotavirus and Rotavirus Vaccines: Are We There Yet?

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Rotavirus vaccines currently licensed in more than 90 countries hold the promise of preventing more than 600,000 diarrhea deaths and many hospitalizations and doctor visits worldwide. The positive impact of vaccination programs is just becoming evident in US and middle income countries of Latin America and as yet, no major danger signs such as intussusception have clouded the horizon. At the same time, the efficacy of these new rotavirus vaccines has not been demonstrated in poor developing countries and some ominous signs are appearing that are cause for concern. The immune response to the GSK vaccine in infants in S. Africa and Bangladesh has been substantially less than that measured in studies in Latin America, the US and Finland and this difference may be reflected in lower efficacy. Trials now ongoing should determine the efficacy in two populations in Sub-Saharan Africa. The reasons for this impaired immune response are numerous - high titers of maternal antibody, breast feeding practices, and interfering gut flora, micronutrient deficiency- to name a few and ways to address these issues will be key to either improving these vaccines or to rejecting them should the results of ongoing field trials prove disappointing. To date, no serious discussion has been given to the level of efficacy that the international community would deem acceptable for rotavirus vaccines to receive a global recommendation from WHO. Research is needed today to identify the cause of the low immune responses and to identify strategies to improve this problem. Insurance policies to consider new vaccines should be considered as well so that alternative vaccine candidates are in the wings should they be needed.

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Beyond Cardiovascular Disease: Statins and Cholesterol in Infectious Diseases (invited)

6.001

Statins and Sepsis: Multiple Modifications at Multiple Levels

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Mortality from sepsis is a leading cause of death worldwide. Clinical observational studies of the effect of statins in reducing the morbidity and mortality of sepsis suggest a prevention, and possible treatment, effect. Effects at the transcriptional level lead to the reduced expression of various inflammatory mediators by leukocytes and endothelial cells. Heme oxygenase induction has anti-oxidant, anti-inflammatory, and cytoprotective effects. Direct blockade alters leukocyte-endothelial cell interaction, while reduced expression of MHC-II affects T-cell function. That statins do not target individual inflammatory mediators, but possibly reduce the overall magnitude of the systemic response, may prove an important distinguishing feature modulating the host response to septic insults.

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6.002

Statins in Animal Models of Infection

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Statins, are effective lipid lowering agents used extensively in medical practice. Recent statin studies have extended statin therapy to the acute manifestations of cardiovascular disease and have suggested cholesterol independent therapeutic benefits, termed ''pleiotropic'' effects, which have added a wide scope of potential targets for statin therapy. Since the approval for clinical use in humans of lovastatin as the first statin several statins have become commercially available including pravastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin (withdrawn in 2001), pitavastatin and rosuvastatin. While all these statins share HMG-CoA reductase inhibition as common mechanism of action, they differ in absorption, affinity, binding, solubility and excretion. Apart from causing variations in efficacy of cholesterol lowering between the agents, differences in these pharmacologic properties might also be relevant with respect to so called ''pleiotropic'' effects of statins. These ''pleiotropic'' effects include anti-inflammatory and antioxidative properties, improvement of endothelial function and increased nitric oxide bioavailability and thus might contribute to the benefit observed with statin therapy. Notably, these important immunomodulatory effects of statins have been demonstrated to be independent of lipid lowering and appear to be mediated via interference with the synthesis of mevalonate metabolites (nonsteroidal isoprenoid products). In addition, mechanisms for anti-inflammatory actions of statins have been revealed that are not related to the isoprenoid metabolism. For instance, it has been identified that some statins act as direct antagonists of LFA-1 due to their capacity to bind to the regulatory site in the LFA-1 i-domain. Several animal models of infection ranging from bacterial, and fungal to viral causative agents have been studied toward potential beneficial application of statins. The present talk will give an overview of animal models of infection with respect to effects of statin treatment.

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