

Observational Studies of Statins in Bacteremia

P. Kruger

Princess Alexandra Hospital, Brisbane, Australia

Statins have become the most widely used drugs for lowering cholesterol with at least 15% of patients requiring admission to hospital on established statin therapy, and this number is growing each year. However, statins have been postulated to have beneficial effects independent of their lipid lowering including anti-inflammatory and immunomodulatory roles. Evidence is emerging from observational studies and basic science research that HMG Co A Reductase inhibitors (statins) might be associated with a reduced mortality in sepsis.

A number of observational studies have suggested that patients on statins for heart disease are less likely to develop infections and that their infections are less likely to be severe or result in death. Not all studies support a benefit associated with statin therapy for patients with sepsis. Other studies have suggested that stopping statins in patients that present with infections (as suggested by current guidelines), may worsen outcomes.

The desire to incorporate the ever expanding potential of these agents into routine clinical practice for patients with sepsis must be tempered by the potential for adverse effects. There is a significant body of evidence that the side effects of statins may be more frequent and serious in the critically ill. A variety of less well known toxicities are being reported as these agents gain more widespread use.

This is a rapidly growing field of fascinating experimental biology that suggests an urgent need for the investigation of the pharmacology and a reappraisal of the therapeutic indications of these drugs in patients with sepsis. This may provide new insights to the role of lipids and the endothelium in the response to infection. The potential for statins as an adjuvant therapy in sepsis is a simple, inexpensive intervention that warrants further prospective investigation.

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6.004

Parasites as host cholesterol consumers: The special case of *Toxoplasma gondii*K.A. Joiner^{1,*}, I. Coppens²¹ *University of Arizona, Tucson, AZ, USA*² *Johns Hopkins University, Baltimore, MD, USA*

Background: All protozoan parasites pathogenic for humans are cholesterol auxotrophs and must acquire cholesterol from the host. Defining the acquisition process provides insights into pathogenesis and avenues for therapeutic intervention.

Results: The obligate intracellular protozoan parasite *Toxoplasma gondii* actively invades all nucleated mammalian cells and resides within a parasitophorous vacuole (PV), surrounded by a specialized membrane (PVM). From that location, parasites acquire host cell cholesterol endocytosed by the host cell LDL receptor pathway. The parasite actively recruits host microtubules, resulting in selective

delivery of host endolysosomes within the PV, where they are sequestered by a tubular coat. Blocking cholesterol exit from the endolysosomes inhibits parasite growth. Cholesterol transits the parasite plasma membrane in a protein-dependent fashion, then accumulates in the parasite interior, in a process augmented by the parasite Rab5. Neither statins nor disruption of the host cell endoplasmic reticulum or Golgi functions impair cholesterol delivery to *Toxoplasma*. With excess host fatty acids and LDL, cholesterol is rapidly esterified by a parasite acyl-cholesterol acyltransferase (ACAT), and accumulates in parasite lipid bodies. This process can be inhibited by selected ACAT inhibitors, that induce parasite plasma membrane destabilization and rupture. By contrast, malaria parasites residing in a PV within hepatocytes acquire needed cholesterol from both host plasma LDL and the host endogenous biosynthetic pathway. Pharmacological interference with the host mevalonate pathway reduces *Plasmodium* development in hepatocytes.

Conclusions: In combination, these results show how a series of unique parasite adaptations selectively drive parasite acquisition of cholesterol from the host cell. Depending upon the parasite and host cell, manipulations which impair cholesterol transport to the PV, cholesterol storage within the parasite, or host cell cholesterol synthesis, block parasite growth.

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Models of Tools for Optimizing Public Health Preparedness: The Case of Pandemic Influenza (invited)

8.001

Planning for Pandemics: Epidemiological Analysis in the Formulation of Public Health Policy

R. Anderson

Imperial College London, London, United Kingdom

Many new quantitative epidemiological tools have been developed in recent years to aid in the formulation of public health policy and to delineate optimal control interventions for epidemics of directly transmitted respiratory tract infections such as influenza A. The presentation will describe the range of methods that can be applied and their strengths and weaknesses for different situations. Specific applications will focus on SARS and influenza A. The current situation with H5N1 will be examined and various control interventions used alone or in combination will be analysed using simulation approaches. Novel methods to meld economic considerations of cost and benefit with those of transmission dynamics will be introduced and used to assess current country based pandemic plans. The paper will end with a discussion of the adequacy of currently published country wide and international plans for pandemic control with a focus on the presence or absence of detail in these plans and the importance of speed of implementation and logistics.

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