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Differential diagnosis of strep A and C

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Background: Sore throat caused by *Streptococcus pyogenes* group A (Strep A) may warrant antibiotic treatment due to risk of complications. Other Streptococci (group C) have been associated with sore throat but there is insufficient evidence that they cause complications. We evaluated disease severity in patients with streptococcal and non-streptococcal sore throat, and the effect of flurbiprofen 8.75 mg lozenge on symptoms prior to any antibiotic administration.

Methods & Materials: Adults with sore throat < 4 days were evaluated for findings of pharyngitis using the Tonsillo-Pharyngitis Assessment (TPA) and pharyngeal inflammation using the Practitioner's Assessment of Inflammation and randomly assigned flurbiprofen or placebo lozenges under double-blind conditions. They rated their sore throat pain on the Throat Pain Scale and pain on swallowing (odynophagia) on the Sore Throat Pain Intensity Scale (STPIS) at baseline and over 7 days. Antibiotics could be administrated at the investigator's discretion once a diagnosis was made by throat culture (at ~48 hours).

Results: Of 204 patients, 32 (16%) had Strep A and 52 (25%) had Strep C. Both types of Strep patients had similar physical features, although pharyngeal inflammation was slightly more severe for Strep A (18.8%) than Strep C and non-Strep patients (11.5% and 11.7%, respectively, both p = NS). 62.5% of Strep A patients described relatively more severe odynophagia compared with 34.6% of Strep C ($p < 0.05$) and 44.2% of non-Strep patients ($p = 0.064$). The mean TPA scores were similar irrespective of cause, indicating the difficulty in making a diagnosis based on physical findings. Irrespective of cause, patients taking flurbiprofen lozenges reported -473.7 mm*h decrease in STPIS scores over the first (pre-antibiotic) 24 hours compared with -322.3 mm*h on placebo (i.e. 47% more relief with flurbiprofen versus placebo, $p < 0.05$). By 48 hours, mean lozenge consumption per day had decreased in both treatment groups regardless of etiology, indicating the natural resolution of symptoms with time.

Conclusion: Patients with Strep A appear to have more severe pain and inflammation than those with Strep C or non-streptococcal infection, although their clinical features are not distinct on physical examination. Sore throat, irrespective of cause, is a self-limiting condition but symptoms benefit from treatment with flurbiprofen lozenge.

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A novel mechanism of host cell death by ESAT-6 like protein of *Mycobacterium tuberculosis*

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Background: *Mycobacterium tuberculosis* (*Mtb*), causative agent of human tuberculosis (TB), manipulates the host immune responses for its survival. Several secretary proteins exported through ESX secretion system modulate the antibacterial effector functions of macrophages. Here we attempted to functionally elucidate the role of one of the previously uncharacterized ESAT-6 family protein in *Mtb* pathogenesis.

Methods & Materials: *Mtb* gene is cloned and expressed in *Mycobacterium smegmatis*. Invasion assay is performed in HeLa cells where as survival assays were carried out in both mouse and human macrophages. Survival mechanisms were studied by quantifying free radicals formation and host survival rate. Induction of autophagic pathway is studied by the expression of LC3. Nuclear and chromosomal aberrations were studied using micronucleus assay. The level of cytokine expressions were measured using qPCR.

Results: Recombinant *Mycobacterium smegmatis* strain expressing ESAT-6 family protein showed more invasion in human epithelial cells (HeLa) and survival in mouse macrophages (RAW264.7) and human monocyte derived macrophages (THP-1). The survival mechanistic studies revealed, infection induced host cell death and also up regulation of the level of nitric oxide, inducible nitric oxide synthase, reactive oxygen species, superoxide dismutase and catalase activities. Moreover, *Mycobacterium smegmatis* expressing ESAT-6 infection reduced T-cell survival, caused loss of mitochondrial membrane integrity, activated autophagy and also induced the expression of NF-κB and late endosomal markers such as Rab10, LAMP-2, Cathepsin-B and Cathepsin-Z in macrophages. An up regulation of both pro-inflammatory (TNF-α, IL-12) and anti-inflammatory (IL-10, TGF-β) cytokines was also observed after infection in macrophages. Genome stability studies showed that recombinant *Mycobacterium smegmatis* strain expressing ESAT-6 family protein infection led to several chromosomal abnormalities such as micronuclei formation in cytokinesis blocked cells, chromosomal malsegregation and nuclear fragmentation.

Conclusion: We envision that this study offers a novel mechanism of host cell death by *Mtb* infection. Taken together, this study has identified a novel ESAT-6 like family protein that acts as virulence as well as an immunomodulatory factor to evade killing by host, and thus it may provide a novel drug target.

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