Bacterial Pathogenesis

How do bacteria cause disease?

***S. aureus* - Epidemiology**

- **The anterior nares is the primary site of colonization**
- **Colonization occurs in 20-40% of "normals"**
- **Infections are increased in colonized subjects usually with the colonizing strain**
  - **Colonization increased in IVDU, diabetics, HIV-infected**
  - **Elimination of carriage in high risk patients has been shown to reduce infection rates**
- **Most infections result from autoinoculation**
  - **82-86% of cases *S. aureus* bacteremias (Von Eiff *et al*., 2001)**

Which bacteria cause disease?

Commensal flora - oral streptococci

Pathogens - Group A Streptococcus
Pharyngitis
Impetigo
Rheumatic disease - secondary to immune response to the organism - cross reactive Abs

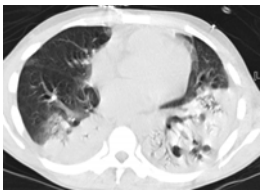
Commensal flora - *E. coli* - acquire virulence genes

E.coli -0157:H7 - toxigenic - hemolytic uremic syndrome

This is an official
CDC HEALTH ADVISORY

Distributed via Health Alert Network
Wednesday, January 30, 2008, 19:17 EST (07:17 PM EST)
CDCHAN-00268-2008-01-30-ADV-N

Influenza-Associated Pediatric Mortality and *Staphylococcus aureus* co-infection



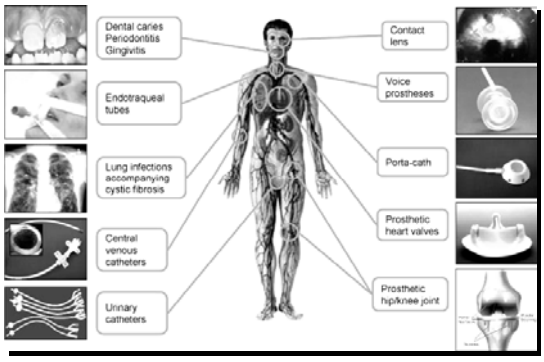
- **5 fold increase in pediatric influenza associated deaths 2006-07 due *S. aureus* bacteremia/pneumonia**
- **Of the 22 deaths associated with *S. aureus* 15 were caused by MRSA**
- **Similar data reported by *Hageman et al.* 2003-2004 influenza season**

Or is it the host response to the bacteria ?

Depends upon the host:
Coagulase negative Staphylococci - skin flora

Colonize catheters, prosthetic devices, neonates

Location of the organism:
Invasion into a normally sterile site:
S. aureus on the skin - colonization
bloodstream - bacteremia/sepsis



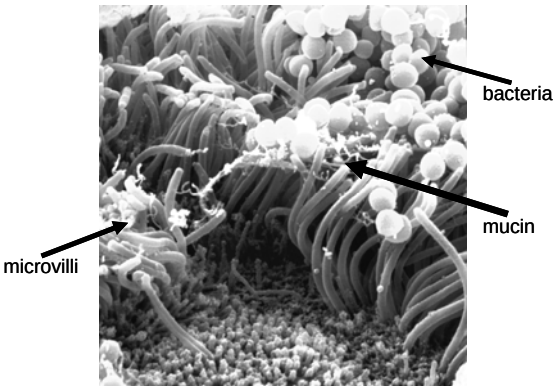
How do bacteria cause disease ?

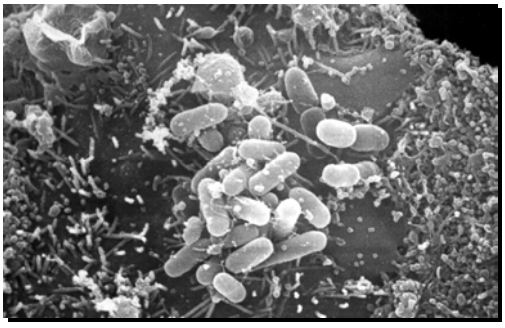
1 - Attachment

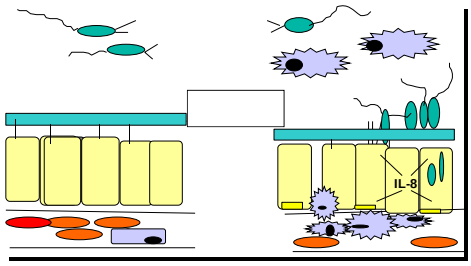
2 - Toxin expression

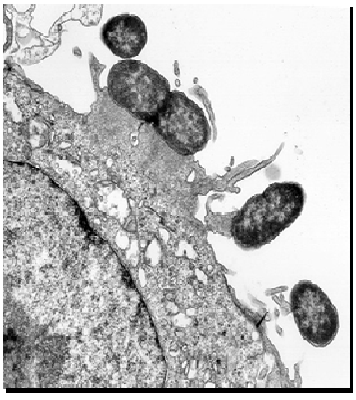
3 - Direct damage

4 - Activate host genes to cause damage
- avoid immune recognition
- look like the host









E.coli

- tightly adherent
- type III toxin secretion

Bacterial life styles

Extracellular - Environment ⟶ Host

Relatively hardy - resistant to extremes in temperature, can deal with various growth conditions - not fussy some extracellular also are well adapted to live intracellularly- *Shigella*

Intracellular organisms (obligate) - *Chlamydia*

Predominantly intracellular - highly adapted to live within a macrophage - *Salmonella, Mycobacteria tuberculosis*

How do bacteria "sense" the environment?

? - extracellular versus intracellular
temperature, phosphate, glucose, magnesium etc.

Two component signal transduction

SENSOR COMPONENT - phosphorylation

→ Response regulator

Salmonella adaptation

phoP/phoQ - 2 component signaling
divalent cations

Changes in LPS

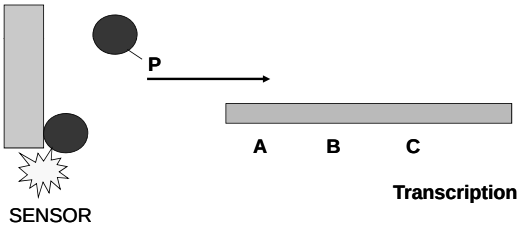
Affects susceptibility to antimicrobial peptides
And antigenicity

Intracellular - T cell recognition for clearance

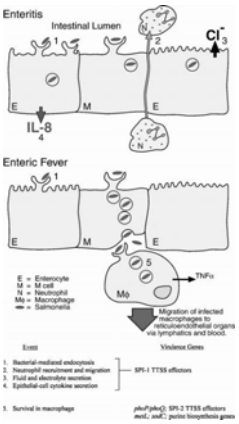
Two component signaling

Coordinate regulation of virulence genes

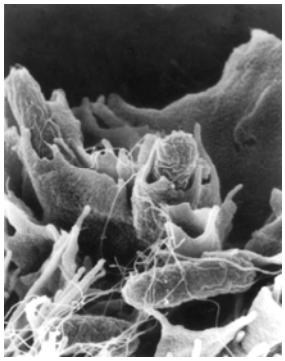
In response to a given environmental signal

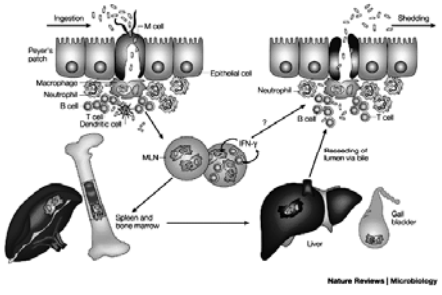


Pathogenesis of Salmonella infection



Salmonella invading a gut epithelial cell





Bacterial virulence factors

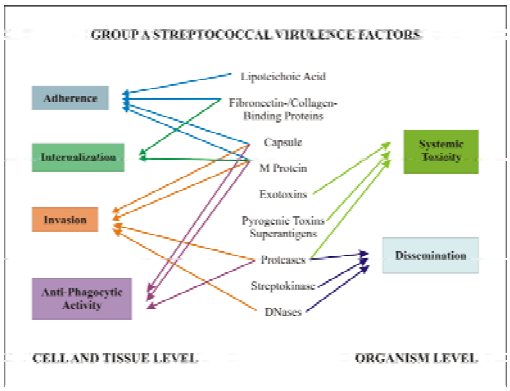
What is a virulence factor ?

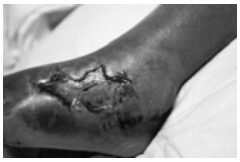
1 - Facilitate colonization – fimbriae, pili

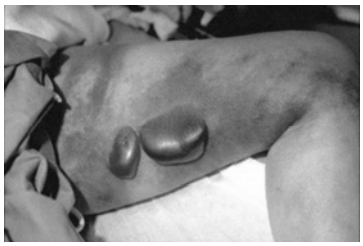
2 - Thwart immune response – capsule, IgG binding

3 - Directly damage host tissues

Streptococcus pyogenes – Group A Strep







TOXINS

Modify host components - ADP ribosylating enzymes

Activate the cells - cytokine expression

Alter tight junctions - allows invasion

Stop protein synthesis

Activate secretory systems - adenyl cyclase
Vibrio cholera

Induce apoptosis - airway epithelium – *Pertussis*

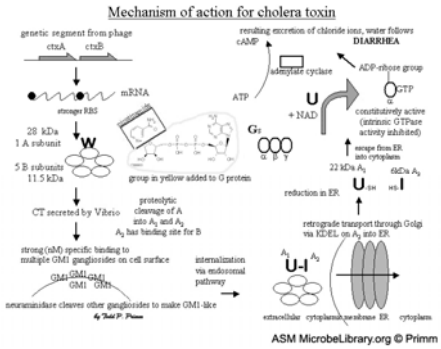
Stop protein synthesis

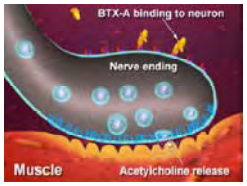
Toxins - Recognize eukaryotic receptors

Cholera toxin
- Activates Chloride (and H_20) secretion
- Via cAMP activation

Clostridium botulinum toxin - motor end plates
- Spores - resistant to sterilization
- soil contaminants

- Organic honey - infants ingest organisms - grows - produces toxin -
- Become floppy, lethargic -
- Infant botulism





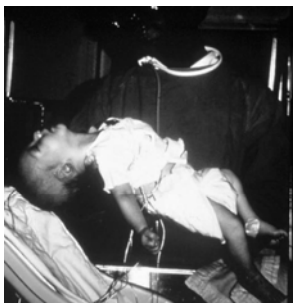
Activation of host immune signaling

Innate immune responses

Toll like receptors and many others

Activation of TLRs -
- Conserved signaling cascades
- Initiate inflammation

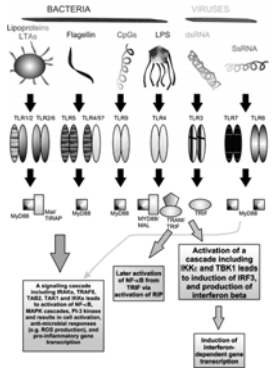
TLR polymorphisms -
- Genetic effects on disease susceptibility



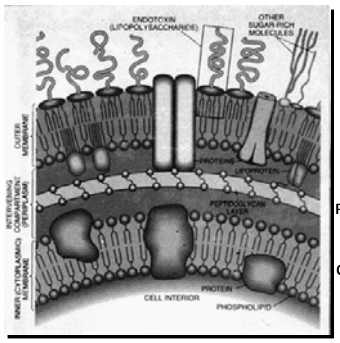
Infant botulism

Toxin prevents acetylcholine release

Toll like receptors - pattern recognition receptors



LPS



Peptidoglycan

Cytoplasmic membrane

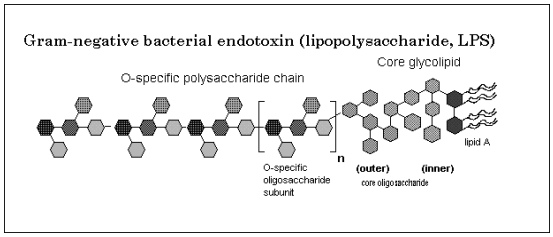
How do commensal flora cause disease?

Pattern recgonition receptors -

Immuno-reactivity of shared bacterial components

Innate immune response -

If disordered - ? Role in autoimmune diseases
inflammatory bowel disease



TLR4 polymorphisms

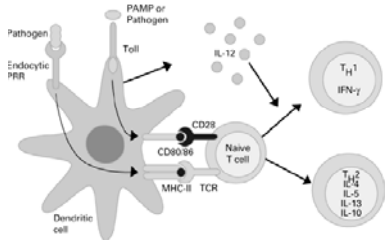
Proc Natl Acad Sci U S A. 2007 Oct 16;104(42):16645-50.
TLR4 polymorphisms, infectious diseases, and evolutionary pressure during migration of modern humans.

Ferwerda B, McCall MB, Alonso S, Giamarellos-Bourboulis EJ, Mouktaroudi M, Izagirre N, Syafruddin D, Kibiki G, Cristea T, Hijmans A, Hamann L, Israel S, ElGhazali G, Troye-Blomberg M, Kumpf O, Maiga B, Dolo A, Doumbo O, Hermsen CC, Stalenhoef AF, van Crevel R, Brunner HG, Oh DY, Schumann RR, de la Rúa C, Sauerwein R, Kullberg BJ, van der Ven AJ, van der Meer JW, Netea MG.
Department of Internal Medicine, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands.

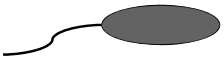
Polymorphisms in Toll-like receptor 4 (TLR4) have been related to susceptibility to Gram-negative infections and septic shock. Here we show that two polymorphisms of TLR4, Asp299Gly and Thr399Ile, have unique distributions in populations from Africa, Asia, and Europe. Asp299Gly has evolved as a protective allele against malaria, explaining its high prevalence in sub Saharan Africa. However, the same allele could have been disadvantageous after migration of modern humans into Eurasia, putatively because of increased susceptibility to severe bacterial infections. In contrast, the Asp299Gly allele, when present in co-segregation with Thr399Ile to form the Asp299Gly/Thr399Ile haplotype, shows selective neutrality.

Toll like receptors

- activating an innate immune response



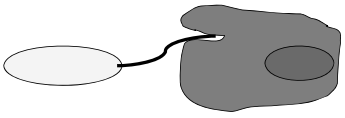
Flagella



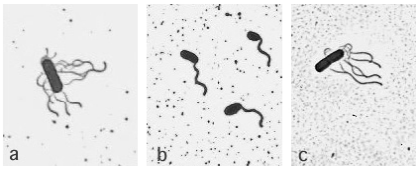
Motility - swim toward a desired carbohydrate
Ligands - for mucins

clearance

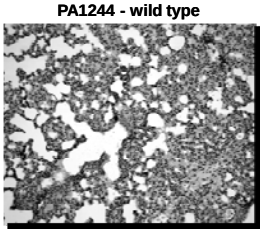
Ligand for macrophages -



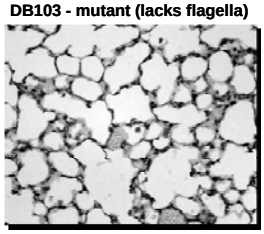
Flagella



PA1244 - wild type



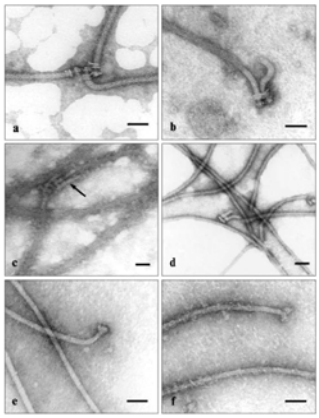
DB103 - mutant (lacks flagella)



Analysis of these pathways – Identify mutants

Flagella

Electron micrograph



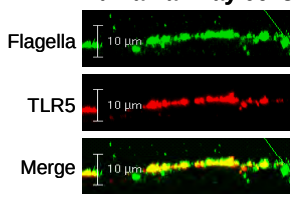
TLR5 Polymorphisms

J Exp Med. 2003 Nov 17;198(10):1563-72.
A common dominant TLR5 stop codon polymorphism abolishes flagellin signaling and is associated with susceptibility to legionnaires' disease.

Hawn TR, Verbon A, Lettinga KD, Zhao LP, Li SS, Laws RJ, Skerrett SJ, Beutler B, Schroeder L, Nachman A, Ozinsky A, Smith KD, Aderem A.
Institute for Systems Biology, 1441 N. 34th St., Seattle, WA 98103, USA.

We show that a common stop codon polymorphism in the ligand-binding domain of TLR5 (TLR5392STOP) is unable to mediate flagellin signaling, acts in a dominant fashion, and is associated with susceptibility to pneumonia caused by Legionella pneumophila, a flagellated bacterium.

Human airway cells



Airway - superficial stimulus is sufficient to activate inflammation
Apical display of the toll-like receptors

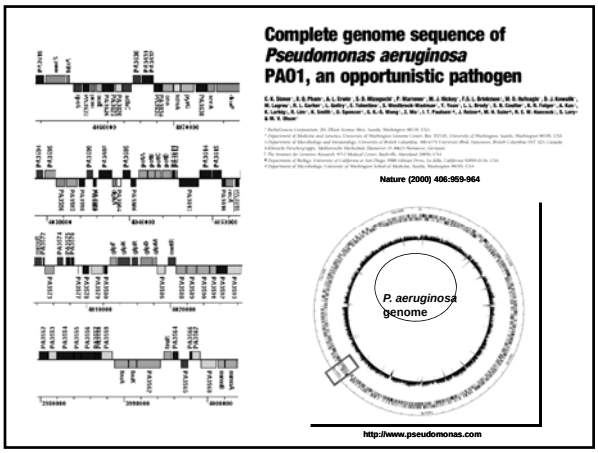
Mutations in TLRs - associated with increased susceptibility to specific bacterial infections

Opportunistic pathogens

Pseudomonas aeruginosa
- Genetically versatile bacteria
- Few growth requirements
- Rarely pathogenic in the normal host

- Major pathogens in immunocompromised patients
- Special settings - cystic fibrosis

Genomic sequencing - compare genetic organization of pathogens and non-pathogens



Virulence factors - *Pseudomonas aeruginosa*

1 - Turn on one group of genes in response to the environment
to **ESTABLISH** an infection

Flagella - motility
immune activation

Hemolysins - Phospholipases - cleave host components

Proteases -

Siderophores - pigments - scavenge iron

2 - Persistence - turn ON genes to adapt to host immune response