Infections

The Biological Conflict of Interest

HST.035
An Evolving Story …

<table>
<thead>
<tr>
<th>Year</th>
<th>Agent</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973</td>
<td>Rotavirus</td>
<td>Gastroenteritis</td>
</tr>
<tr>
<td>1977</td>
<td>Ebola virus</td>
<td>Epidemic hemorrhagic fever</td>
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<tr>
<td></td>
<td><em>Legionella pneumophila</em></td>
<td>Legionnaires disease</td>
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<tr>
<td></td>
<td><em>Campylobacter jejuni</em></td>
<td>Gastroenteritis</td>
</tr>
<tr>
<td>1981</td>
<td><em>Staphylococcus aureus</em></td>
<td>Toxic shock syndrome</td>
</tr>
<tr>
<td>1982</td>
<td><em>E. coli</em> O157:H7</td>
<td>Hemorrhagic colitis &amp; HUS</td>
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<tr>
<td></td>
<td><em>Borrelia burgdorferi</em></td>
<td>Lyme disease</td>
</tr>
<tr>
<td>1983</td>
<td>HIV</td>
<td>AIDS</td>
</tr>
<tr>
<td></td>
<td><em>Helicobacter pylori</em></td>
<td>Gastritis</td>
</tr>
<tr>
<td>1989</td>
<td>Hepatitis C</td>
<td>Chronic hepatitis</td>
</tr>
<tr>
<td>1992</td>
<td><em>Bartonella henselae</em></td>
<td>Cat scratch disease</td>
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<tr>
<td>1993</td>
<td>Hantaviruses</td>
<td>Hantavirus pulmonary syndrome</td>
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<tr>
<td>1995</td>
<td>HHV-8</td>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td>1999-2000</td>
<td>HHV-6 and HHV-7</td>
<td>Post-transplant disorders</td>
</tr>
</tbody>
</table>
With huge public health, economic, social and political implications
“Appalled and astounded” at the consequences that immigration to Boston had already produced, [Lemuel] Shattuck concluded [in 1850] that it was the immigrants - the poor and unwanted from England and Ireland - who were primarily responsible for bringing disease and impoverishment to an otherwise predominantly healthy and productive native stock: “Our own native inhabitants, who mingle with these recipients of their bounty, often themselves become contaminated with diseases, and sicken and die; and the physical and moral power of living is depreciated, and the healthy social and moral character we once enjoyed is liable to be forever lost.”

Barbara G. Rosenkrantz

Public Health and the State

“Tensions have been escalating in Mekambo [Gabon] and surrounding areas because of restrictions being placed on people regarding their movements and the sale of bushmeat and crops. Many local people are said to be blaming outsiders for their difficulties, while rumors have been running rampant that witchcraft and vampires are to blame for the people's deaths, not Ebola.”

UNWire, Jan 14, 2002.
We have won many battles, but why do we continue to struggle in the war against infectious diseases?
Because microorganisms have and will continue to evolve with us. They have and will continue to use every weapon in our possession as a weapon against us.
## What are human microbial pathogens?

<table>
<thead>
<tr>
<th>Class</th>
<th>Size</th>
<th>Site of Propagation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viruses</strong></td>
<td>20-30 nm</td>
<td>Obligate intracellular</td>
</tr>
<tr>
<td>Chlamydiae</td>
<td>200nm-1µm</td>
<td>Obligate intracellular</td>
</tr>
<tr>
<td>Rickettsiae</td>
<td>300nm-1.2µm</td>
<td>Obligate intracellular</td>
</tr>
<tr>
<td>Mycoplasmas</td>
<td>125-350nm</td>
<td>Extracellular</td>
</tr>
<tr>
<td>Bacteria (including spirochetes and mycobacteria)</td>
<td>800nm-15µm</td>
<td>Extracellular&lt;br&gt;Facultative intracellular</td>
</tr>
<tr>
<td>Fungi</td>
<td>2-200µm</td>
<td>Extracellular&lt;br&gt;Facultative intracellular</td>
</tr>
<tr>
<td>Protozoa</td>
<td>1-50mm</td>
<td>Extracellular&lt;br&gt;Facultative intracellular&lt;br&gt;Obligate intracellular</td>
</tr>
<tr>
<td>Helminths</td>
<td>3mm-10m</td>
<td>Extracellular</td>
</tr>
</tbody>
</table>
Viruses

• Only a few of the >400 viruses known to inhabit humans cause disease

• Viruses account for a major share of all human infections

• Individual viruses are too small to be seen by light microscopy, but many important pathogenic viruses result in intracellular **inclusion bodies** that can be seen on light microscopy

Ebola virus (EM from CDC)  Cytomegalovirus (LM)
Bacteria

• 10,000,000,000
• 1,000,000,000,000
• 100,000,000,000,000
• Pneumonia, cellulitis, sepsis, meningitis, gonorrhea, UTIs, endocarditis, dental caries, whooping cough, legionnaires, wound infections, typhoid fever, food poisoning, gastroenteritis, tetanus, botulism, anthrax, bubonic plague, tularemia, brucellosis, cat scratch disease, syphilis, cholera, tuberculosis, leprosy, …
Chlamydiae, Rickettsiae, and Mycoplasmas

- These infectious agents share many similarities with bacteria, but lack certain structures (e.g., cell wall) or metabolic capacity (e.g., ATP synthesis)
- Chlamydiae and rickettsiae are obligate intracellular parasites that replicate in phagosomes of epithelial cells or cytoplasm of endothelial cells
- Rickettsiae are transmitted by arthropods and classically cause a hemorrhagic vasculitis
- Mycoplasma spread in respiratory aerosols and cause pneumonia

Please see http://www.who.int/en/

150 Million people suffer from active trachoma as a result on Infection by C. trachomatis, the same organism that is also the leading infectious cause of female sterility.
Fungi

• Fungi grow as “perfect” forms (sexually reproducing) *in vitro* and as “imperfect” forms (budding yeast and branching hyphae) *in vivo*

• Opportunistic fungi (such as candida, aspergillus, cryptococcus) are ubiquitous, while others such as coccidiodies (Far West) and histoplasma (Ohio River Valley) are geographically limited

• Fungal infections range from minor superficial infections (such as Tinea infections) to devastating deep fungal infections that destroy vital organs in immunocompromised patients
Protozoal Parasites

- Protozoa are motile, single-cell eukaryotes
- Infections are among the leading causes of morbidity and mortality in the world (e.g., ~10^6 deaths/yr from *Plasmodium falciparum*)
- Protozoa may be (1) extracellular (*Giardia, Trichomonas*), (2) intra-cellular (*T. cruzi*), or live in the blood (*P. falciparum, T. brucei*)
- The life-cycle of protozoa is often shared between humans and other vectors
The Helminths

• Parasitic worms are highly differentiated organisms with complex life cycles involving humans and other vectors

• Roundworms (nematodes) such as Ascaris and the filariae have a collagenous tegument and a non-segmented body

• Flatworms (cestodes) such as meat tapeworms are gutless worms made of a scolex (head) and a ribbon of flat segments (proglottids)

• Flukes (trematodes) such as liver and lung flukes are primitive leaf-like worms with a syncytial integument

Lymphatic filariasis affects 120M people worldwide (40M seriously)

Image from CDC as posted on the NIAID (NIH) website, accessed on 2/18/2003.
How do they get away with it?
To kill or be killed:  
*Viral control of cell death*

The Apoptotic Machinery: 
*Intrinsic and Extrinsic Pathways*

Please see Figure 1 of *Nat Immunol*. 2002 Nov;3(11):1013-8.

To kill or be killed: viral evasion of apoptosis.

Benedict CA, Norris PS, Ware CF.
Viral evasion of apoptosis: p53 inactivation

- The physiological role of p53 is to induce apoptosis or cell cycle arrest in response to damaged DNA
- p53-deficient mice are prone to viral infections
- p53 up-regulates death receptors (TRAIL and Fas)
- p53 up-regulates pro-apoptotic proteins Bax, Bak1, ...
- p53 up-regulate anti-apoptotic protein Bcl-2
- SV40 large T antigen and hepatitis B pX protein bind and inactivate p53
- HPV-E6 and adenovirus E1B-55k promote ubiquination and degradation of p53
Viral evasion of apoptosis: Bcl-2 mimicry

• The physiological role of Bcl-2 is to antagonize Bax and Bak

• Adenovirus E1B-19K has is structurally homologous to Bcl-2 and inhibits Bax oligomerization

• Epstein-Barr virus (EBV) and Kaposi’s sarcoma-associated herpesvirus use Bcl-2 orthologs to prevent cytochrome C release

• Cytomegalovirus (CMV) UL37 gene product is not homologous to Bcl-2, but resides in mitochondria and inhibits Fas-mediated apoptosis
Viral evasion of apoptosis: Caspase regulation

• Caspases play a central role in regulation and execution of apoptosis

• The enzymatic activity of caspases is regulated by a variety of Inhibitors of Apoptosis Proteins (IAPs)

• Inhibition of apoptosis by regulation of caspases is used infrequently in human viral infections, with the exception of some poxviruses
Viral evasion of apoptosis: Modulation of TNFR

- Members of TNF-receptor (TNFR) superfamily, including Fas, TNFR1 and TRAILR2, are potent inducers of apoptosis, and are targeted by many viruses.

- Many poxviruses (including smallpox) neutralize TNF by producing soluble decoy TNFR-like proteins (vaccinia, the attenuated form of smallpox, has a mutated TNFR decoy with reduced activity).

- Herpesvirus entry mediator (HVEM) of HSV-1 is designed to induce apoptosis in T cells and block maturation of APC’s.

- LMP1, the major transforming protein in EBV, activated anti-apoptotic proteins through its interactions with TNFR adaptors.

- The E3 region of adenoviruses clear the surface of host cells from death receptors (Fas, TRAILR1 and TRAILR2) by interfering with endocytic trafficking of receptors.

- And, so on …
Bacterial Strategies for Evading Host Defenses
Attachment and Colonization Strategies

• Motility and attachment factor (adhesins) are essential for withstanding mucosal clearing strategies.

• *Vibrio cholera* “toxin-coregulated pili” and *Bordetella pertussis* ciliostatic toxins are critical virulence factors.

• Biofilm formation by *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*, as well as the “curli” surface fibers of *Escherichia coli* shield bacteria from hostile environments and host removal mechanisms.
Modulation of Immune Recognition

• Proteolytic degradation of secretory immunoglobulins by *Haemophilus influenzae*

• Shielding and/or modification of “Pathogen-Associated Molecular Patterns” such as bacterial DNA, lipopolysaccharides (LPS) in the bacterial wall, and flagella (e.g., flagellar down-regulation by *Salmonella enterica* serovar Typhimurium)

• In contrast, overstimulation of the immune system is used as a surface-disrupting mechanism by *Shigella dysenteriae*
Evasion of Epithelial Antimicrobial Peptides

- *Staphylococcus aureus* reduces the net negative charge on its outer membrane (by addition of lysines and D-alanines) to reduce binding to positively charged antimicrobial peptides.

- *S. enterica* Typhimurium extensively modifies its surface to decrease susceptibility to α-helical antimicrobial peptides.

- Bacterial proteases may degrade antimicrobial peptides.
Strategies for Epithelial Invasion

• *S. enterica* Typhimurium uses a type III secretion system to transfer two bacterial products (SopE and SopE2) that act as nucleotide exchange factors that activate small GTP-binding proteins CDC42 and Rac, reorganize the actin cytoskeleton, and induce bacterial endocytosis

• *Shigella flexneri* secretes IpaB which mediates lysis of phagosomes, and expresses IcsA which promotes intracytoplasmic bacterial movement using the actin cytoskeleton

• *Salmonella* and *Shigella* spp. invade the intestinal barrier through the M-cells

• *S. pyogenes* and *C. perfringens* enter pre-existing epithelial injuries and enzymatically degrade the ECM for deep penetration
Escape from the Phagocytic Response

- Phagocytes are equipped with a number of receptors that detect (opsonized) microbial surfaces.

- *Salmonella* and *Shigella* stimulate the apoptotic pathway to circumvent phagocytic activation and immune response to infected cells (caspase-1-def. mice are resistant to Salmonella).

- *Yersinia enterolitica* and *Y. pseudotuberculosis* inhibit phagocytosis by disorganizing the host cell actin cytoskeleton by activation of small GTPases.

- Listeriolysin of *Listeria monocytogenes* disrupts endosomal membranes and allows bacterial escape into the cytosol.

- *Mycobacterium tuberculosis* inhibits phagosomal maturation by depleting $H^+$ ATPase molecules from the endosomal membrane.
Modulation of Cytokine Production

• Mycobacteria-infected macrophages produce IL-6, which inhibits T cell activation, as well as immunosuppressive cytokines IL-10 and TGF-β, which inhibit macrophage activation, production of reactive oxygen species, and antigen presentation.

• *Bordetella pertussis* and *Yersinia enterolitica* induce IL-10 secretion by dendritic cells and macrophages, respectively.
Inhibition of B and T Cell Effector Function

• *Helicobacter pylori* Cag pathogenicity island-encoded genes induce Fas-mediated apoptosis of T cells

• *Yersinia pseudotuberculosis* suppresses antigen-specific T cell activation by inhibiting tyrosine phosphorylation of the components of TCR

• *Neisseria gonorrhoeae* OPA proteins bind a lymphocyte-specific CD66 receptor, resulting in the inhibition of activation and proliferation of CD4+ T cells