INFECTIOUS DISEASE:
OVERVIEW AND UPDATE

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OBJECTIVES

- Understand the difference between bacteria, viruses, and fungi, and parasites
- Understand how the immune system responds to pathogens
- Review different types of vaccines
- Understand which pathogens are most concerning for corneal transplant
- Apply understanding of infectious diseases to the review of medical charts
INFECTIONS

Bacteria, fungus, virus, parasite...what's the difference and should I care?
Bacteria

- Large group of single-celled organisms
- Ubiquitous
- Vital to ecosystem
- Prokaryote (bacterial DNA floats freely within the cell)
- Structure: 5 basic shapes:

  - Spherical (cocci)
  - Rod (bacilli)
  - Spiral (spirilla)
  - Comma (vibrios)
  - Corkscrew (spirochetes)
Bacteria

• Humans/other animals carry vast numbers of bacteria, most in gut
• Most are harmless, many beneficial
• Many species are pathogenic or have the potential to be pathogenic
Common Bacterial Pathogens (Worldwide)

- Mycobacterium tuberculosis
- Staphylococcus
- Streptococcus
- Pseudomonas
- Shigella
- Campylobacter
- Typhoid
- Diptheria

BACTERIAL VIRULENCE FACTORS

- Toxin production
- Structure of bacteria
- Enzymes

TREATMENT

- Antibiotics – typically active against bacteria ONLY
- Mechanism—kill OR inhibit growth
- Resistance—evolutionary process caused by drug pressure selecting for resistant strains; overuse/misuse contributing factor
- Misuse—antibiotics are often prescribed for VIRAL infections and/or fungal infections
Fungi

• Can be single-celled or complex multi-celled organisms
• Ubiquitous but most live in soil or plant material
• 6 million species, more than 600 associated with humans

• Commensals (e.g. part of our microbiome)
• Pathogens (disease-producing, most often in immunocompromised hosts)
Fungi

• Sub-divided based on their life cycle:

1. Multicellular filamentous molds
2. Single-celled microscopic yeasts
3. Macroscopic filamentous fungi (mushrooms)
Structure of Fungal Cell

- Cell wall and cell membrane provide structural rigidity and stability
- More complex than bacterial cell
Fungal Pathogens

Common
• Candida albicans (non-invasive), found on skin and in gut

Associated with specific regions
• Blastomycosis
• Coccidiomycosis
• Cryptococcus
• Histoplasmosis

Immunocompromised
• Aspergillus
• Candida spp (invasive)
• Mucormycosis

Many fungal infections are self-limited in immunocompetent host and are non-invasive
Fungal Eye Infections

- **Candida** species (in gut, skin, ubiquitous)
- **Fusarium** (lives in soil)
- **Aspergillus** (common fungus in environment)
FUNGAL VIRULENCE FACTORS

- Structural (cell wall)
- Morphological transition
- Adherence to surfaces
- Toxins
- Enzymes
Key Virulence Factors of *Candida albicans*

- **Metabolic Flexibility:** Efficient use of alternate carbon sources, stress resistance, cell surface changes
- **Hydolytic Enzymes:** Saps, Lip, Pep; Degradation of host connective tissues, cleavage of host immune factors, nutrient acquisition
- **Evasion from host immune system:** Changes in cell wall architecture and composition, masking of PAMPs
- **Escape from phagocytosis:** Vomimosis, hyphal lysis of host cells, phagolysosomal neutralization, pyroploids
- **Candidalysin:** Secretory cytolytic peptide damaging host immune cells
- **Phenotypic Switching:** Opaque cells resistant to neutrophil engulfment
- **Countering Host Nutritional Immunity:** Micronutrient uptake transporters and redundant proteins with alternate collections
- **Wast to Hyphal Morphogenesis:** In response to temperature, serum, alkaline pH, nutrient starvation, CO₂
- **Biofilm formation:** Resistant to antifungals and host immune defence
- **Adherence to Host Surfaces:** Expression of adhesins

Current Opinion in Microbiology

TREATMENT

- Damage cell membrane or inhibit cell wall synthesis
- Topical, oral, IV

Challenges:
- Eukaryotic animal cells and fungal cells share many of the same cell structures and targets—leads to severe side effects
- Resistance is common

https://musculoskeletalkey.com/antifungal-therapy/
CANDIDA AURIS

- Species of genus Candida, grows as yeast
- First identified in 2009
- Multiple drug resistance
- Easily misidentified as other candida species
- Mortality with bloodstream infection due to C. auris 30%-60%
Viruses

- Submicroscopic infectious particle that can only replicate in living cell
- Cannot exist outside of cell
- All contain nucleic acid (DNA or RNA), encodes unique genetic information
- Almost all have a shell (capsid)
- Most have other proteins
- Infect all life forms (plants, animals, bacteria)
VIRAL PARTICLE (VIRION)
VIRAL PATHOGENS/DISEASES

- Respiratory Viruses
  - Rhinovirus (one of the causes of common cold)
  - Influenza
  - SARS-CoV-2 (causes COVID)
  - Measles
- Emerging pathogens
  - Ebola
  - Mpox (formerly monkeypox)
- Zoonosis
  - Rabies
  - West Nile Virus
  - Yellow Fever
- Other
  - Chickenpox and shingles
  - Human Immunodeficiency Virus (HIV)
  - Cytomegalovirus (CMV)
  - Hepatitis (A, B, C)
  - Human Papillomavirus (HPV)
Ocular Viral Infections

- Human herpes viruses (HSV type 1 and HSV type 2)
- Cytomegalovirus (CMV)
- Adenovirus
TREATMENT

- Antiviral medication available for **some** viral pathogens
- Mechanism: block any step in viral replication, sometimes multiple medications must be used (e.g. HIV) and suppress but do not eliminate the virus from the host
- **Challenges:**
  - Viruses rely on human cells to replicate—need to stop virus without damaging host cells
  - For acute viral illnesses, Must be delivered in early viral replication phase of illness
  - Viruses often replicate rapidly and mutate rapidly, enabling them to become resistance to medications

https://knowablemagazine.org/article/health-disease/2021/challenges-antiviral-treatments
Parasites

Organisms that lives on or in host organism

3 main classes:

1. **Protozoa**—microscopic, one-celled (e.g. giardia, malarial parasites)

2. **Helminths**—large, multicellular, visible worms (e.g. flatworms)

3. **Ectoparasite**—large, multicellular (ticks, fleas, lice, mites). Also vectors for other pathogens
<table>
<thead>
<tr>
<th>Parasite (Synonym)</th>
<th>Disease or Common Name</th>
<th>Estimated Worldwide Prevalence</th>
<th>Estimated Mortality Rank</th>
<th>Relative U.S. Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. falciparum</em></td>
<td>Malaria</td>
<td>&gt;500 million</td>
<td>Low</td>
<td>Rare</td>
</tr>
<tr>
<td><em>T. cruzi</em></td>
<td>Chagas disease</td>
<td>15-20 million</td>
<td>Low</td>
<td>Common</td>
</tr>
<tr>
<td><em>H. contortus</em></td>
<td>Hookworm disease</td>
<td>800-900 million</td>
<td>Very low</td>
<td>Low</td>
</tr>
<tr>
<td><em>T. brucei</em></td>
<td>African sleeping sickness</td>
<td>37 million</td>
<td>Very low</td>
<td>Very low</td>
</tr>
<tr>
<td><em>A. lumbricoides</em></td>
<td>Roundworm</td>
<td>1-2.5 billion</td>
<td>Very low</td>
<td>Very low</td>
</tr>
<tr>
<td><em>H. nana</em></td>
<td>Necator americanus</td>
<td>800-900 million</td>
<td>Very low</td>
<td>Low</td>
</tr>
<tr>
<td><em>T. solium</em></td>
<td>Taenia solium</td>
<td>200-300 million</td>
<td>No. 1</td>
<td>Common</td>
</tr>
<tr>
<td><em>D. latum</em></td>
<td>Schistosomiasis</td>
<td>200-300 million</td>
<td>No. 1</td>
<td>Common</td>
</tr>
<tr>
<td><em>H. Magnusia</em></td>
<td>Ascariasis</td>
<td>0-5 million</td>
<td>Very low</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

H. enterobius vermicularis (Enterobius vermicularis) | Common, an estimate | Very low | Common |

4. Rates of positive testing in U.S. residents have been reported to be as high as 25% in 13% (data not available). 5. The prevalence of parasitic infections in women is lower because female-only programs may be less effective. 6. Acute symptoms of parasitic diseases are often asymptomatic or mildly symptomatic and may be long-lasting. 7. Mortality and prevalence may vary widely depending upon species and regional resistance patterns. 8. Hookworm disease is a major cause of anemia, particularly in children. 9. The data on the geographic distribution of hookworm disease are not complete. 10. The prevalence of parasitic infections in men is lower because female-only programs may be less effective. 11. The data on the geographic distribution of hookworm disease are not complete. 12. The prevalence of parasitic infections in men is lower because female-only programs may be less effective. 13. The data on the geographic distribution of hookworm disease are not complete. 14. The prevalence of parasitic infections in men is lower because female-only programs may be less effective. 15. The data on the geographic distribution of hookworm disease are not complete. 16. The prevalence of parasitic infections in men is lower because female-only programs may be less effective.
EXAMPLES OF PARASITES OF CONCERN

- Malaria
- Toxoplasmosis
- Acanthamoeba
- Leishmania
- Chagas (T. cruzi)

Many have latent phase of disease, particular concern with immunosuppression

TREATMENT

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prevention/Use</th>
<th>Treatment/Use</th>
<th>Notes on Treatment</th>
<th>Notes on PrEP/preventive maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>300 mg orally weekly</td>
<td>300 mg orally twice 5 days, 500 mg at R. 24, and 48 hr</td>
<td>Prevented over re-exposure is 100% effective, efficacy and toxicity measures given. Prevention dosage is equivalent to 100 mg at L. 24, and 48 hr.</td>
<td>300 mg orally twice at a minimum, start 6 days before arrival to minimal relapse probability.</td>
</tr>
<tr>
<td>Quinine</td>
<td>400 mg orally daily</td>
<td>7 days, followed by 2 days, duration is 2 days</td>
<td>The basis of therapy in most countries is 5-day chloroquine-resistant areas. Given daily as quinidine for severe malaria.</td>
<td>Requires daily doses and long-term use can lead to development of drug-resistant organisms. Other preventive drugs are usually preferred.</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>300 mg orally weekly</td>
<td>1,350 mg orally as a single dose</td>
<td>Successful therapy can be administered to a large single dose. Effective against some chloroquine-resistant strains.</td>
<td>Alternatively, can also be given as a loading dose starting 4 days before travel.</td>
</tr>
<tr>
<td>Primaquine</td>
<td>30 mg orally daily</td>
<td>7 days before departure and continue for 7 days after leaving malaria area</td>
<td>First-line standard of treatment is used in areas with chloroquine-resistant malaria. Chloroquine is used as treatment for secondary prevention for severe malaria.</td>
<td>Rarely used as first-line treatment due to its toxicity and risk of drug-resistant development. May be used as prevention of any malaria species but only logical in areas with high incidence of drug-resistant strains.</td>
</tr>
<tr>
<td>Sulfadoxine-pyrimethamine</td>
<td>Not recommended for treatment during pregnancy</td>
<td>Usually a single oral dose is recommended for 5-7 mg pyrimethamine/150 mg sulfadoxine.</td>
<td>Relatively a lower dose of malaria due to its toxicity and risk of sulfadoxine resistance.</td>
<td>No known contraindication for prevention or treatment of P. falciparum in areas of Africa due to resistance.</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg orally daily</td>
<td>10 days, 100 mg orally twice daily, 7 days before departure and continue for 7 days after leaving malaria area</td>
<td>Treatment is complicated by its toxicity and risk of sulfadoxine resistance.</td>
<td>Highly effective for prophylaxis. Although a lower dose should be considered for 4 weeks after leaving area.</td>
</tr>
<tr>
<td>Atovaquone-proguanil</td>
<td>1 tablet (200 mg/400 mg) or 1 tablet (150 mg/300 mg) orally daily</td>
<td>4 tablets daily, 1 tablet (500 mg/500 mg) daily for 3 days</td>
<td>Appropriate for chloroquine-resistant P. falciparum. Not recommended for treatment.</td>
<td>Primary use is for prophylaxis. Efficacy is sufficient to consider this agent for only 7 days after returning.</td>
</tr>
<tr>
<td>Artemether-lumefantrine</td>
<td>Not routinely used for malaria prevention</td>
<td>Artemether-lumefantrine is available in a fixed-dose combination.</td>
<td>Rarely used for prophylaxis or treatment.</td>
<td>Not recommended.</td>
</tr>
</tbody>
</table>

Challenges:

- Life cycle of organism can be complex
- Resistance to medications (e.g. malaria treatment)

References:

IDENTIFYING PATHOGENS

**Bacteria**
- Culture (fluid or tissue)
- Tissue histology

**Virus**
- PCR
- Histopathology (e.g. CMV)

**Fungus**
- Culture
- Histopathology

**Parasite**
- Serology
- Histopathology, microscopic examination of blood/fluid
MECHANISM OF INFECTION AND DISEASE
Host Pathogen Interaction

- Pathogens
- Host Susceptibility
- Modes of Pathogen Shedding
- Modes of Transmission
- Routes of Entry
- Reservoir Host

https://microbenotes.com/factors-affecting-bacterial-pathogenicity/
HOST BARRIERS TO INFECTION

- **Natural Barriers**
  - **Skin** (if disrupted, microorganisms can enter) + cornea
  - **Mucous membranes** (tears, trapping action of mucus)
  - **Respiratory tract**
    - Upper airway filters (mucociliary epithelium)
  - **Gastrointestinal tract**
    - Acid pH of stomach
    - Antibacterial activity of pancreatic enzymes, bile, intestinal secretions
  - **Bacteria** on surface of skin, in GI tract
INNATE IMMUNITY

- Immediate, does not require prior exposure to pathogen
  - Macrophages phagocytize pathogen
  - Release of cytokines by macrophages (chemical signals)
    - Attract neutrophils
    - Initiate inflammation (cause swelling, fever, pain etc)
    - Initiate complement system which enhances killing of pathogens
  - Activate the adaptive immune system
ADAPTIVE IMMUNITY

• Highly specific to particular pathogen that has previously been encountered
• Macrophage ingests pathogen and presents antigen
  • Antigen = molecular structure that is on surface of pathogen (can be protein, peptide, lipid, nucleic acid)
• Stimulates:
  • Humoral immunity (B-cells, antibodies specific to antigen + memory B-cells)
  • Cell-mediated immunity (T-cells)
• Creates immunological memory after an initial response to a pathogen
  • Memory B- and T-cells
Processes in the primary immune response

- **Pathogen**: i.e., a virus "Antigen"
- **Macrophage**: adopts the pathogen (Phagocytosis)
- **Macrophage presents components of the pathogen to a T-lymphocyte**
- **T-lymphocyte**: Activation
  - **First specific antibodies against the antigen**
  - **Plasma cells produce specific antibodies**
  - **B-lymphocyte**: Proliferation
- **Cytotoxic T cell destroys infected body cell**
  - "Killer Cell"
  - **Macrophages phagocytize and digest**
- **Antigen-antibody complexes**

Memory cells can later induce the secondary immune response upon renewed contact with the same pathogen.
Acquired Immunity

Immunity that develops during your lifetime

Active Immunity

Develops in response to an infection or vaccination

Natural
Antibodies developed in response to an infection

Artificial
Antibodies developed in response to a vaccination

Passive Immunity

Develops after you receive antibodies from someone or somewhere else

Natural
Antibodies received from mother, e.g., through breast milk

Artificial
Antibodies received from a medicine, e.g., from a gamma globulin injection or infusion
VACCINES
VACCINES

Definition:
Biological product that can be used to safely induce an immune response to confer protection against infection and/or exposure to pathogen

Essential component:
One or more protein or polysaccharide antigens that induce immune responses

## VACCINE TECHNOLOGY

### Classification

<table>
<thead>
<tr>
<th>Type of Vaccine</th>
<th>Licensed Vaccines using this technology</th>
<th>First Introduced</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live (attenuated)</strong></td>
<td>Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster</td>
<td>1798 (smallpox)</td>
</tr>
<tr>
<td><strong>Killed whole organism</strong></td>
<td>Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies</td>
<td>1896 (typhoid)</td>
</tr>
<tr>
<td><strong>Toxoid</strong></td>
<td>Diphtheria, tetanus</td>
<td>1923 (diphtheria)</td>
</tr>
<tr>
<td><strong>Subunit (purified protein, recombinant protein, polysaccharide, peptide)</strong></td>
<td>Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A</td>
<td>1970 (anthrax)</td>
</tr>
<tr>
<td><strong>Virus-like particle</strong></td>
<td>Human papillomavirus</td>
<td>1986 (hepatitis B)</td>
</tr>
<tr>
<td><strong>Outer membrane vesicle</strong></td>
<td>Pathogen-antigen</td>
<td>1987 (group B meningococcal)</td>
</tr>
<tr>
<td><strong>Protein-polysaccharide conjugate</strong></td>
<td>Carrier protein</td>
<td>1987 (H. influenzae type b)</td>
</tr>
<tr>
<td><strong>Viral vectored</strong></td>
<td>Pathogen gene, viral vector genes</td>
<td>Ebola 2019 (Ebola)</td>
</tr>
<tr>
<td><strong>Nucleic acid vaccine</strong></td>
<td>DNA, mRNA, RNA-lipid coat</td>
<td>SARS-CoV-2 2020 (SARS-CoV-2)</td>
</tr>
<tr>
<td><strong>Bacterial vectored</strong></td>
<td>Pathogen gene, bacterial vector</td>
<td>Experimental –</td>
</tr>
<tr>
<td><strong>Antigen-presenting cell</strong></td>
<td>Pathogen-antigen MHC</td>
<td>Experimental –</td>
</tr>
</tbody>
</table>

### Adjuvant: can be added to inactivated vaccines to improved immunogenicity of the vaccine

- **Live (attenuated)**
  Contains a weakened replicating strain of an organism

- **Inactivated**
  Contains only components of a pathogen or killed whole organisms

- **Subunit**
  Made from a piece of a pathogen, not the whole organism

- **Viral vectored**
  Uses harmless virus to deliver to the host cells the genetic code of the antigen

- **Toxoid**
  Uses inactivated toxins to target toxic activity created by bacteria

- **mRNA**
  Uses mRNA (genetic material) that “teaches” our cells to make a harmless piece of the pathogen and triggers and immune response
Longevity of Protection

- Antibody levels wane over time
- Interplay between time of re-exposure, incubation of pathogen, rapidity of memory cell response
- Prevention of infection vs disease
LIVE VACCINES

Examples:
- MMR (measles, mumps, rubella)
- Yellow Fever vaccine
- Oral polio

Risk of live vaccines:
- Benign in most patients
- In immunocompromised individuals, risk of reversion to virulence
- Contraindicated in certain populations, including solid organ transplant (receiving systemic immunosuppression)

CORNEAL TRANSPLANT
Mechanisms of immune privilege:

1. Lack of vascular supply in lens and central cornea prevents innate and adaptive immune system from interfering
2. Vascular barrier in the eye helps keep clear from inflammation
3. 90% aqueous humor does not drain to lymph nodes
4. Scarcity of antigen presenting cells (less inflammation)
INFECTION RISK CORNEAL TRANSPLANT

- Risk of graft rejection
  - 2 year survival > 90%, but 25-70% in recipients with high-risk factors for rejection
- Causes of rejection/graft failure:
  - Immune rejection (immunologic response to graft)
  - Infection

https://www.ncbi.nlm.nih.gov/books/NBK519043/
POST-TRANSPLANT INFECTION RISK

- **Solid Organ**
  - Highest risk due to immunosuppression of recipients and vascularization of organs

- **Tissue**
  - Lower risk may reflect host’s normal inflammatory and immune function as well as graft disinfection with tissue allografts

- **Cornea**
  - Lowest risk due to fact that cornea is avascular and recipients not usually immunosuppressed
CORNEAL TRANSPLANT INFECTIONS

- Important source of post-transplant infection is donor tissue

- Potential consequences transmitted infection:
  - Endophthalmitis
  - Graft rejection
  - Loss of vision
  - Systemic illness
The following communicable diseases and disease agents are relevant for ocular tissue (§ 1271.3(r)(1)(i)):

i. Human immunodeficiency virus (HIV), types 1 and 2;
ii. Hepatitis B virus (HBV);
iii. Hepatitis C virus (HCV);
iv. Human transmissible spongiform encephalopathy (TSE); including Creutzfeldt-Jakob disease (CJD); and
v. Treponema pallidum (syphilis)
II. A communicable disease agent or disease meeting the criteria described in § 1271.3(r)(2), but not specifically listed in § 1271.3(r)(1), is relevant if it is one:

- For which there may be a risk of transmission by ocular tissue
- That could be fatal or life-threatening
- For which appropriate screening measures have been developed

Examples of RCDADs not specifically listed in § 1271.3(r)(1) as relevant include, but are not limited to:

- West Nile Virus
- Sepsis
- Vaccinia
- Zika Virus
CHART REVIEW

Systemic Symptoms

- Fevers
- Hemodynamic instability

Positive cultures (bacteria, fungus)

- Growth in a normally sterile site (e.g. blood, urine, CSF)
- Colonization vs infection

Viral data

- PCR

Parasite data

- Serology
- Tissue pathology
CHART REVIEW

**History**
- Travel history
- Other important medical history

**Hospital course**
- Antibiotic/antifungal treatment
- Sepsis
- Repeat blood cultures?

**Cause of death**
- What role (if any) did infection play?
CHART REVIEW

Organism of Concern per EBAA
Example: West Nile Virus, Hepatitis B virus
Reject

Colonization or treated/cleared infection
Example: repeat blood cultures negative
Possibly accept

Evidence of disseminated or difficult to treat infection
Example: sepsis, repeat cultures positive, untreated infection
Reject
CONCLUSIONS

• Infection rates low in corneal transplant but still a risk

• Understanding range of pathogens, virulence, immune system responses, and treatment can help guide chart review when looking for suitable donors
QUESTIONS

Thank you

• EBAA
• Stacey Gardner
• Genevieve Magnuson
• The Eye-Bank for Sight Restoration
• Patricia Dahl
• Michelle Rhee, MD