Microbe-host interactions

Nov 15, 2006
Ch. 21
Antimicrobial drug resistance

- Acquired ability to resist effects of a chemotherapeutic to which it is normally susceptible
- **Common mechanisms**
  1. Lack structure drug targets
  2. May be impermeable to drug
  3. Organism may be able to modify drug to an inactive form
  4. Organism may modify the target itself
  5. Organism may develop a new pathway
  6. Organism may be able to pump out the drug
**R factors**

- Most drug resistant bacteria isolated from patients contain drug resistance genes on plasmids
- Many of these plasmids encode enzymes that inactivate drugs
- Multi-drug resistance plasmids predate medical use of antibiotics
- Widespread emergence of multi-drug resistance
Resistance to all known drugs...

- **Methicillin-resistant** *Staphylococcus aureus* (MRSA)
- **Vancomycin-resistant** *Enterococcus* (VRE)

Figure by MIT OCW.
Healthcare-associated infections

- Healthcare-associated infections (HAIs) are infections that patients acquire during the course of receiving treatment for other conditions
- In hospitals alone, HAIs account for an estimated 2 million infections, 90,000 deaths, and $4.5 billion in excess healthcare costs annually

http://www.cdc.gov/ncidod/dhqp/healthDis.html
Changing patterns for HAIs

- 1950s to 1960s gram positive bacteria were a major problem (*Streptococcus pyogenes* and *Staphylococcus aureus*)
- 1970s and 1980s gram negative bacteria became a major problem (*E. coli* and *Pseudomonas* spp.)
- Currently, gram positive bacteria are again emerging as a major problem (*S. aureus* and *Enterococcus* spp.)
Methicillin-resistant
Staphylococcus aureus N315

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Terminology

• Normal microbial “flora” or “microflora”
  - Better term is microbiota
  - Commensal (at the same table)

• Pathogen
  - Infection versus disease

• Virulence

• Opportunistic pathogen
Indigenous microbiota

- Microorganisms that inhabit body sites in which surfaces and cavities are open to the environment
- Skin, oral cavity, upper respiratory tract, gastrointestinal (GI) tract, and vagina
- Each habitat can be considered a separate ecosystem
- For every cell in human body ($10^{13}$) there are 10 viable indigenous bacteria in the GI tract
- The GI tract ($10^{14}$) harbors 100-fold more bacteria than the skin ($10^{12}$)
Major bacteria present
- Prevotella
- Streptococcus
- Veillonella
- Helicobacter
- Enterococci
- Lactobacilli
- Bacteroides
- Bifidobacterium
- Clostridium
- Enterobacteria
- Enterococcus
- Escherichia
- Eubacterium
- Klebsiella
- Lactobacillus
- Peptococcus
- Peptostreptococcus
- Proteus
- Ruminococcus
- Staphylococcus
- Streptococcus

Major physiological processes

- **Esophagus**
  - pH 1-2
  - Esophagus

- **Stomach**
  - pH 1-2
  - Gastric juice (HCl)
  - Helicobacter
  - Digestion of macromolecules

- **Duodenum**
  - pH 6-7
  - Bile secretion
  - Enterococci
  - Lactobacilli

- **Small intestine**
  - pH 4-5
  - Absorption of monosaccharides, amino acids, fatty acids, water
  - Jejunum
  - Ileum

- **Large intestine**
  - pH 7
  - Absorption of bile acids, vitamin B₁₂
  - Colon

Figure by MIT OCW.
Defining the GI microbiota

- **Autochthonous microbiota**
  - Present during the evolution of an animal and therefore present in every member of a species

- **Normal microbiota**
  - Common and perhaps even present in every individual in a given geographic area/community, but not in every member of the species

- **True pathogens**
  - Acquired accidentally and therefore not normally present in all members of a community of an animal species

Ecological principles

• In a stable GI ecosystem, all available habitats are occupied by indigenous microbiota
• Transient species derived from food, water, or even another part of the GI tract or the skin will not establish (colonize)
• Habitats are physical spaces in the GI tract normally occupied by a climax community of indigenous microbiota
• Population levels and species composition are stable and not easily disrupted
Succession & climax populations

- Lactic acid bacteria and coliforms predominate in infant human and animal GI tracts
- During weaning the microbiota changes drastically and obligate anaerobic bacteria become predominant
- The indigenous GI microbiota of adults consists of climax communities that are remarkably stable
- Each region of the GI tract has a characteristic population of microbes, in terms of complexity and population density
Model systems

- Germ free animals
- Delivered by Cesarean section into sterile plastic-film isolators
- Maintained free of all bacteria, fungi, protozoa, viruses, and other detectible life forms
- Introducing microorganisms is called association or colonization
- Contamination is accidental introduction of unwanted microorganisms
- Germ free animals can be monoassociated with a single species or poly associated with multiple species
ASF 361 → Lactobacillus animalis
Lactobacillus murinus
Lactobacillus mali
Lactobacillus salivarius
ASF 360 → Lactobacillus acidophilus
Lactobacillus lactis
ASF 500 → Clostridium propionicum
Clostridium neopropionicum
ASF 356 → Clostridium piliforme
Ruminococcus gnavus
Eubacterium contortum
Roseburia cecicola
ASF 502 → Catonella morbi
Acetitomaculum ruminis
ASF 492 → Eubacterium plexicaudatum
Johnsonella ignava
Flexistipes sinusarabic
Deferrribacter thermophilus
Geovibrio ferrireducens
Colobus Monkey sp.
ASF 457 → Rodent sp. 1
Rodent sp. 2
Rodent sp. 3
(Bacteroides) mordae
(Bacteroides) distasonis
ASF 519 → (Bacteroides) forsythus
CDC DF-3

Figures by MIT OCW.
Human colonic microbiota

- Highest cell densities recorded for any ecosystem
- Diversity at the division level is among the lowest
- Only 8 of the 55 known bacterial divisions have been identified in colonic bacteria to date
- 2 division dominate
  - Cytophaga-Flavobacterium-Bacteroides (CFB)
  - Firmicutes (genera Clostridium and Eubacterium)
- Proteobacteria are common, but not dominant
- Compare to many soil communities, where ≥ 20 bacterial division can be present
Diversity

- > 200,000 16S rRNA sequence in GenBank
- 1,822 from human gut
- 1,689 are uncultured
- Look at 495 with length > 900 bp
- ~ 800 species
- > 7,000 strains


Figure by MIT OCW.

Incidence diagram of Helicobacter pylori disease in the world today
Gastritis and peptic ulcer

The proteins encoded by these genes assemble to form a complex type IV secretion apparatus capable of delivering CagA from the bacterium into host cells.

- HP0524 (VirD4)
- HP0525 (VirB11)
- HP0527 (VirB10)
- HP0528 (VirB9)
- HP0544 (VirB4)

Translocation of CagA into gastric epithelial cells
Phosphorylation of CagA by host-cell kinases c-Src and Lyn
Binding to and activation of cellular phosphatase SHP-2
Growth factor-like response in host cell, cytoskeletal rearrangements

Figure by MIT OCW.

http://www.cdc.gov/ulcer/
H. pylori and gastritis

Images of Helicobacter pylori removed due to copyright restrictions.

Helicobacter pylori on gastric epithelial cells (false-color SEM)