Immune compromise I

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Immune defects

- When any or all of these primary defenses are weakened, microflora is altered/increased and infection will often ensue.
Altered flow

- Flow occurs in blood vessels and lymphatics, cerebral ventricles, salivary glands, respiratory tract, heart, gastrointestinal tract, urinary tract, etc.

- Reduced flow or blockage in any of these areas will predispose to infection

- Such infections are usually caused by microflora (i.e. the patient's own bacteria)
Altered flow: examples

- A large endobronchial tumour predisposes to pneumonia: either relapsing (i.e. treatment failure) or recurrent (i.e. a new infection).

- Men with prostatic hypertrophy—with resultant reduced urinary outflow—are more predisposed to urinary tract infections; “dehydration” has a similar effect for both men and women.

- Women (mostly) with lymphedema following axillary lymph node dissection for breast cancer are predisposed to cellulitis.
Cancer of the right upper bronchus with post-obstruction pneumonia

PET images (A,B) and CT image (C): Image A shows uptake of 18F-FDG by the tumour and the pneumonia. Image B shows limited uptake of 18F-FLT by the tumour (and even less so by the pneumonia). Image C shows obstruction of the right upper bronchus (vertical arrow) with a post-obstructive pneumonia (horizontal arrow).

J Nuclear Medicine 2004;45:1680
Cellulitis with lymphangitis following breast cancer
Where there is no flow, infection will follow
Gravity & mobility

- recall that the mouth is mostly colonized with Gram-positives and (oral) anaerobes, whereas the colon is colonized with mostly Gram-negatives and (gut) anaerobes

- one of the major benefits of gravity and mobility is that faecal organisms don’t colonize our head-and-neck region

- being mobile allows us to shower and clean ourselves effectively, and to avoid bed sores (see ‘skin & mucosal integrity’)

Altered gravity & mobility: examples

- after being bed-ridden for several days, residents of long-term care institutions and hospitalized patients have their skin and oropharynx colonized with faecal organisms
- if they get a pneumonia, it is frequently due to faecal organisms (e.g. Gram-negatives)
- skin wounds are often infected by faecal organisms
Almost nobody defecates upwards

GOSH, FRED... SURE IS NICE OF YOU TO COME OVER TO SHOOT THE SHIT!!
pH and other chemical factors

- the stomach environment, by means of its acidity, kills most microbes it encounters
- the urinary tract has a variety of chemical which pass through it which serve to denature many microbes
- tears, saliva, and many other secreted fluids possess antimicrobial properties (e.g. lysozyme)
Altered pH and other chemical factors: examples

- Patients in the intensive care unit who are on a ventilator (i.e. “intubated”) are at risk from pneumonia and gastrointestinal bleeding.
  - Suppressing gastric acid reduces the risk of bleeding ... but increases the risk of pneumonia.
- Patients with a dry mouth (“xerostomia”) are at risk for cavities (caries, an infectious disease) and other oral infections.
Skin & mucosal integrity

- perhaps the most important parts of the immune system are the skin & mucosal physical barriers
- skin also plays host to functioning cells of the immune system (e.g. T lymphocytes, macrophages, Langerhans’ cells, etc.)
- mucosæ also secrete mucous (which trap and inactivate microorganisms), and often work with cilia to dispose of microorganisms
Altered skin & mucosal integrity: examples

- bed sores
- surgical site infections
- burn wounds
- intravenous drug use
- febrile neutropenia (more of this later)
Bed sores (decubitus or pressure ulcers)

- Christopher Reeve acted in 4 Superman movies.
- He was paralyzed in 1995 after a fall while horseback riding.
- He got the best medical care money could buy.
- He died of an infected decubitus ulcer.
Bed sores

- Bed sores result from prolonged pressure on one part of the body.
- "Dependent" (i.e. low) parts of the body are particularly prone: occiput, sacrum, heel.
- Prolonged compression results in relative ischaemia to the skin and underlying soft tissues, rendering them prone to necrosis/breakdown.
- Commensal flora usually infect necrotic soft tissue, causing local and/or systemic disease.
Surgical site infections

- Without appropriate measures, bacteria present on the surface of the skin, mucous membranes or hollow visci are introduced into deeper (usually sterile) sites.
- These relatively benign colonizers can cause disease, depending on bacterial “load” and “virulence”, and the host’s defenses.
- Before the mid-1800s, patients would commonly develop post-operative fever and infection, often resulting in death.
- Antisepsis (removing bacteria from surfaces) dramatically reduced surgical site infections.
Surgical site infections

Infect Control Hosp Epidemiol 1999;20:247-280
Burn mortality is related to age and affected body surface area (BSA)
## Chronology of Skin Infection in Burn Patients

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>1st wk</th>
<th>2nd wk</th>
<th>3rd wk</th>
<th>4th wk</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. faecalis</em></td>
<td>30%</td>
<td>14.3%</td>
<td>5.5%</td>
<td></td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>5%</td>
<td>11.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>A. baumanii</em></td>
<td>5%</td>
<td>34.3%</td>
<td>27.7%</td>
<td>50%</td>
</tr>
<tr>
<td>MRSA</td>
<td>10%</td>
<td>2.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSA</td>
<td>20%</td>
<td>5.7%</td>
<td>5.5%</td>
<td>10%</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>10%</td>
<td>5.7%</td>
<td>5.5%</td>
<td>19%</td>
</tr>
<tr>
<td><em>Ps. aeruginosa</em></td>
<td>10%</td>
<td>11.4%</td>
<td>22.2%</td>
<td>10%</td>
</tr>
<tr>
<td>β-haemolytic Strep.</td>
<td>5%</td>
<td>2.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Strep. pneumoniae</em></td>
<td>5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td></td>
<td></td>
<td>5.7%</td>
<td></td>
</tr>
</tbody>
</table>
Intravenous drug use

- Intravenous drug users have a very high risk of infection.

- Their risk of infection results primarily from the breach of skin barriers coupled with introduction of macroflora (although social factors, such as sex-trade work, also contribute to their infection risk).

- Infections from introduction of microflora (esp. Staph aureus) include local abscesses, cellulitis, and right-sided infective endocarditis.

- Hepatitis C and HIV are important infections caused by introduction of macroflora (via needle-sharing).
Normal flora

- Our micro flora is normally comprised of healthy, normal flora which protect us and keep us healthy.

- If our normal flora is destroyed or replaced, potentially pathogenic micro flora can cause disease.

- Antibiotics and poor infection control/public health measures are the most common causes of altered micro flora.
Altered normal flora: examples

- C. difficile-associated diarrhea
- Candida infection
C. difficile-associated diarrhea (CDAD)

- C. difficile is an anaerobic Gram-positive bacillus resistant to all but a few antibiotics.
- Approximately 2% of people, at any one time, will have detectable C. difficile in their colonic flora (although this number is higher for people in LTC institutions and even hospitals).
- When patients are receiving antibiotics, protective colonic microflora are eradicated (as innocent bystanders), allowing organisms such as C. difficile to proliferate.
- When it proliferates, C. difficile can cause diarrhea, colitis and other severe illness, and even death.
C. difficile-associated diarrhea (CDAD) and colitis

C. difficile vegetative cells produce toxins A and B and hydrolytic enzymes. Local production of toxins A and B leads to production of tumour necrosis factor-alpha and proinflammatory interleukins, increased vascular permeability, neutrophil and monocyte recruitment, opening of epithelial cell junctions and epithelial cell apoptosis. Local production of hydrolytic enzymes leads to connective tissue degradation, leading to colitis, pseudomembrane formation and watery diarrhea.
CDAD: infection control

- It is currently unclear how C. difficile is acquired, but it is largely felt to be via the faecal-oral route.
- The following appear to contribute to outbreaks of CDAD in hospitals (and, to a lesser extent) LTC institutions:
  - Failure to keep hospital rooms and wards clean
  - Poor hand hygiene
  - Failure to isolate patients with diarrheal illness
  - Overuse of antibiotics
Candida infection

○ Candida are yeasts (i.e. fungi that are predominantly unicellular)

○ Candida, mostly C. albicans, are normal microflora of humans (i.e. commensals)

○ they are found on the skin, throughout the GI tract, in sputum, and in the female genital tract

○ their growth is held in check by other microflora, mostly bacteria
Mucosal candidiasis

- although cell-mediated immunity plays a role in controlling mucosal candida growth, alteration in normal flora can allow overgrowth of Candida

- women given antibiotics are very prone to vaginal yeast infections (i.e. Candidal vaginitis)

- men may also get genital yeast infections from antibiotics (i.e. Candidal balanitis)

- thrush (or oral candidiasis) results from altered oral flora, usually in concert with altered cell-mediated immunity
Candidæmia

- candidæmia (or blood infection due to Candida species) is an increasingly important problem in hospitalized patients

- the major risk factors for candidæmia are:
  - broad-spectrum antibiotic use
  - indwelling central venous catheters

- what do you suspect is the pathogenesis of candidæmia
Prosthetic devices

- in general, prosthetic devices are either:
  - permanent or temporary
  - intravascular or extravascular
- prosthetic devices have become one of the most important risk factors for infection
- temporary prosthetic devices are usually percutaneous (i.e. through an opening in the skin)
Biofilm formation

- A feature of virtually all prosthetic devices is their predisposition to infection with coagulase-negative staphylococci, which tend to form biofilms.

- Biofilm formation is a two-step process:
  - First, the bacteria rapidly adhere to the polymer material.
  - Subsequently, the bacteria proliferate to form multilayered cell clusters on the polymer surface, which are embedded in extracellular material.

Lancet Infect Dis 2002;2:677–85
Percutaneous intravascular devices

- Central venous catheters (inserted for only days) and PICC (Peripherally Inserted Central Catheter) lines are tremendously prone to infection.
- Such infections usually result from microflora tracking along the catheter from the skin surface into the bloodstream.
- The most common infecting organisms are skin commensals: Staph. aureus, coagulase-negative Staphylococci, and Candida species.
- Broad-spectrum antibiotics, immobility (and other immunosuppression) increase the probability that a Gram-negative or yeast causes the infection.
Percutaneous intravascular devices

1. Attachment to unmodified polymer surface:
van der Waal’s forces, hydrophobic interactions,
SSP-1/SSP-2, AtIE, PSA/A, Bhp?

2. Attachment to polymer surface coated with
extracellular matrix proteins: transcutaneous migration
and/or hematogeneous seeding from distant site:
AtIE, Fbe (SdrG), teichoic acid

3. Proliferation and accumulation in multilayered cell clusters:
PIA, PS/A, AAP, Bhp?

Conditioning film:
fibrin, fibrinogen, fibronectin, vitronectin, thrombospondin, von Willebrand factor

Lancet Infect Dis 2002;2:677–85
Permanent intravascular devices

- pacemakers, artificial heart valves, and vascular grafts are examples of permanent intravascular devices.

- although they may get infected during insertion, they remain at risk for infection (usually by Staphylococci) for as long as they are exposed to blood.

- pacemakers, tissue valves and vascular grafts are covered by endothelium (they are not exposed to blood) within weeks.
Permanent extravascular devices

- orthopaedic hardware (e.g. spinal rods, prosthetic joints) are the most common permanent extravascular devices

- when such devices become infected, it is usually at the time of surgery

- skin flora—usually Staph. aureus and coagulase-negative staphylococci—are the usual organisms infecting these devices
Prosthetic devices

- because most infection of prosthetic devices occurs at the time of insertion, infection control (antisepsis and sterile surgical technique) is the most effective means of preventing such infections
Having altered or dysfunctional anatomical and mechanical barriers are the most common and most important forms of immunocompromise ... yet they are largely ignored by physicians.

Having commensals altered (primarily by antibiotics) puts people at risk for antibiotic-resistant infections.

Foreign bodies, which are increasingly prevalent, put patients at risk for infections, primarily from microflora.