BACTERIAL PATHOGENESIS

INDIGENOUS/COMMENSAL AND PATHOGENIC MICROBIAL FLORA IN HUMANS

MICROORGANISMS PLAY A CRITICAL ROLE IN HUMAN SURVIVAL

THE NORMAL COMMENSAL POPULATION OF MICROBES:

- PARTICIPATES IN THE METABOLISM OF FOOD PRODUCTS
- PROVIDES ESSENTIAL GROWTH FACTORS
- PROTECTS AGAINST INFECTIONS WITH HIGHLY VIRULENT MICROORGANISMS
- STIMULATES THE IMMUNE RESPONSE

MICROBIAL FLORA IN & ON THE HUMAN BODY IS IN A CONTINUAL STATE OF FLUX

DETERMINED BY: AGE, DIET, HORMONAL STATE, HEALTH, AND PERSONAL HYGIENE

- INFANT'S SKIN IS COLONIZED FIRST, FOLLOWED BY THE OROPHARYNX, GASTROINTESTINAL TRACT, AND OTHER MUCOSAL SURFACES.

- THROUGHOUT THE LIFE OF AN HUMAN BEING, THE MICROBIAL POPULATION CONTINUES TO CHANGE

- CHANGES IN HEALTH CAN DRASTICALLY DISRUPT THE DELICATE BALANCE THAT IS MAINTAINED AMONG THE HETEROGENEUS ORGANISMS COEXISTING WITHIN US
  (HOSPITALIZATION, ANTIBIOTICS → REPLACEMENT OF NORMALLY AVIRULENT ORGANISMS WITH OTHERS THAT CAN INVADE THE HOST TISSUES)

EXPOSURE TO AN INDIVIDUAL TO AN ORGANISM CAN LEAD TO ONE OF THREE OUTCOMES

A) THE ORGANISM CAN TRANSIENTLY COLONIZE THE PERSON

B) THE ORGANISM CAN PERMANENTLY COLONIZE THE PERSON

C) THE ORGANISM CAN PRODUCE DISEASE

- A + B: DO NOT INTERFERE WITH NORMAL BODY FUNCTIONS
- C: THE INTERACTION BETWEEN MICROBE AND HUMAN LEADS TO A PATHOLOGIC PROCESS CHARACTERIZED BY DAMAGE TO THE HUMAN HOST

CLASSES OF MICROBES AND THEIR PROPENSITY FOR CAUSING DISEASE

A) STRICT PATHOGENS:

*ALWAYS ASSOCIATED WITH HUMAN DISEASES

* e.g., *Mycobacterium tuberculosis*, *Neisseria gonorrhoeae*, *Plasmodium* spp.

B) OPPORTUNISTIC PATHOGENS:

* TYPICALLY MEMBERS OF THE PATIENT'S NORMAL MICROBIAL FLORA

* DO NOT PRODUCE DISEASE IN THEIR NORMAL SETTING BUT ESTABLISH DISEASE WHEN THEY ARE INTRODUCED INTO UNPROTECTED SITES (BLOOD, TISSUES)

* e.g., *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*

MOST COMMON MICROBES THAT COLONIZE THE UPPER RESPIRATORY TRACT. I

A) MOUTH, OROPHARYNX, AND NASOPHARINX:

*THE MOST COMMON ANAEROBIC BACTERIA ARE: *Peptostreptococcus* and related anaerobic cocci, *Veillonella*, *Actinomyces*, and *Fusobacterium* spp.

* THE MOST COMMON AEROBIC BACTERIA ARE: *Streptococcus*, *Haemophilus*, and *Neisseria* spp.

* MOST OF THE COMMON ORGANISMS IN THE UPPER RESPIRATORY TRACT ARE RELATIVELY AVIRULENT AND RARELY ASSOCIATED WITH DISEASES UNLESS THEY ARE INTRODUCED INTO NORMALLY STERILE SITES (e.g., sinuses, middle ear, brain).

* POTENTIALLY PATHOGENIC ORGANISMS CAN ALSO BE FOUND IN THE UPPER AIRWAYS: *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Enterobacteriaceae*

B) EAR: THE MOST COMMON ORGANISM IS coagulase-negative *Staphylococcus*

C) EYE: THE SURFACE IS COLONIZED WITH coagulase-negative staphylococci.

MOST COMMON MICROBES THAT COLONIZE THE UPPER RESPIRATORY TRACT. II

D) LOWER RESPIRATORY TRACT:

*THE LARYNX, TRACHEA, BRONCHIOLES, AND LOWER AIRWAYS ARE GENERALLY STERILE, ALTHOUGH TRANSIENT COLONIZATION WITH SECRETIONS OF THE UPPER RESPIRATORY TRACT MAY OCCUR

* MORE VIRULENT BACTERIA PRESENT IN THE MOUTH CAUSE ACUTE DISEASE OF THE LOWER AIRWAY (e.g. *S. pneumoniae*, *S. aureus*, members of the family *Enterobacteriaceae*)

* CHRONIC ASPIRATION MAY LEAD TO A POLYMICROBIAL DISEASE IN WHICH ANAEROBES ARE THE PREDOMINANT PATHOGENS

MOST COMMON MICROBES THAT COLONIZE THE GASTROINTESTINAL TRACT

- COLONIZED AT BIRTH

- REMAINS THE HOME FOR A DIVERSE POPULATION OF ORGANISMS THROUGHOUT THE LIFE OF THE HOST

- THE POPULATION REMAINS RELATIVELY CONSTANT, UNLESS EXOGENOUS FACTORS SUCH AS ANTIBIOTIC TREATMENT DISRUPT THE BALANCED FLORA

A) ESOPHAGUS: Transient colonizers (Oropharyngeal bacteria and yeast, as well as the bacteria that colonize the stomach)

C) STOMACH: Acid-tolerant bacteria (lactic acid-producing bacteria such as *Lactobacillus* and *Streptococcus* spp and *Helicobacter pylori*, cause of gastritis and ulcerative disease)

MOST COMMON MICROBES THAT COLONIZE THE GASTROINTESTINAL TRACT. II

D) SMALL INTESTINE:

Colonized with different bacteria, fungi, and parasites. Most are anaerobes (Peptosterptococcus, Porphyromonas, and Prevotella)

E) LARGE INTESTINE:

* More than 10^{11} bacteria per gram of feces can be found, with anaerobic bacteria in excess by more than 1000-fold. The most common include *Bifidobacterium, Eubacterium, Bacteroides, Enterococcus*, and the *Enterobacteriaceae* family (*E. coli* is present in virtually all humans from birth until death))

* Various yeasts

* Nonpathogenic parasites

- ANTIBIOTIC TREATMENT: CAN RAPIDILY ALTER THE POPULATION, CAUSING PROLIFERATION OF ANTIBIOTIC-RESISTANT ORGANISMS (*Enterococcus*, *Pseudomonas*, and fungi, *C. difficile)*

MOST COMMON MICROBES THAT COLONIZE THE GASTROINTESTINAL TRACT

A) BACTERIA:

**Acinetobacter, Actinomyces, Bacteriodes, Bifidobacterium, Campylobacter, Clostridium, Corynebacterium, Eubacterium, Enterobacteriaceae, Enterococcus, Fusobacterium, Haemophilus, Helicobacter, Lactobacillus, Mobiluncus, Peptostreptococcus, Porphyromonas, Prevotella, Propionibacterium, Pseudomonas, Staphylococcus, Streptococcus, Veilonella.*

B) FUNGI:

** Candida*

C) PARASITES:

** Blastocystis, Chilomastix, Endolimax, Entamoeba, Iodamoeba, Trichomonas*

MOST COMMON MICROBES THAT COLONIZE THE GENITOURYNARY TRACT

- THE ANTERIOR URETHRA AND VAGINA:

  THE ONLY ANATOMIC AREAS OF THE GENITOURINARY SYSTEM PERMANENTLY COLONIZED WITH MICROBES

- THE URINARY BLADDER: CAN BE TRANSIENTLY COLONIZED WITH BACTERIA MIGRATING UPSTREAM FROM THE URETHRA, BUT SHOULD BE CLEARED RAPIDILY BY THE BACTERICIDAL ACTIVITY OF THE UROEPITHELIAL CELLS AND THE FLUSHING ACTION OF VOIDED URINE

ANTERIOR URETHRA:

- COMMENSAL POPULATION OF *lactobacilli*, *streptococci*, AND coagulase-negative *staphylococci* (RELATIVELY AVIRULENT)
- CAN BE COLONIZED TRANSIENTLY WITH FECAL ORGANISMS (*Enterococcus*, *Enterobacteriaceae*, AND *Candida*) AND LEAD TO SIGNIFICANT DISEASE.
  - PATHOGENS AS *N. gonorrhoeae* and *C. trachomatis* ARE COMMON CAUSES OF URETHRITIS AND CAN PERSIST AS ASYMPTOMATIC COLONIZERS.

MOST COMMON MICROBES THAT COLONIZE THE GENITOURYNARY TRACT

VAGINA: DIVERSE MICROBIAL POPUPATION, DRAMATICALLY INFLUENCED BY HORMONAL FACTORS:

a) NEWBORN GIRLS ARE COLONIZED WITH *lactobacilli* AT BIRTH, PREDOMINATING FOR 6 WEEKS.

b) AT THAT TIME, THE LEVELS OF MATERNAL ESTROGEN HAVE DECLINED, AND THE VAGINAL FLORA CHANGES TO INCLUDE *staphylococci, streptococci, and Enterobacteriaceae.*

c) AT PUBERTY, WHEN THE ESTROGEN PRODUCTION IS INITIATED, *lactobacilli* REEMERGE AS THE PREDOMINANT ORGANISMS, AND MANY OTHER ORGANISMS ARE ALSO ISOLATED, INCLUDING *staphylococci, streptococci, enterococcus, Gardnerella, Mycoplasma, Ureaplasma, Enterobacteriaceae*, AND ANAEROBIC BACTERIA.

MOST COMMON MICROBES THAT COLONIZE THE GENITOURYNARY TRACT

* *N. gonorrhoeae* IS A COMMON CAUSE OF VAGINITIS
* WHEN THE BALANCE OF VAGINAL BACTERIA IS DISRUPTED:
  DECREASEMENT OF *lactobacilli*
  INCREASEMENT OF *Mobiluncus, Gardnerella, Trichomonas vaginalis, C. albicans, C. glabrata*

CERVIX: NOT NORMALLY COLONIZED WITH BACTERIA

- *N. gonorrhoeae* AND *C. trachomatis* ARE IMPORTANT CAUSES OF CERVICITIS
- *Actinomyces* CAN ALSO PRODUCE DISEASE AT THIS SITE

MOST COMMON MICROBES THAT COLONIZE THE SKIN

**** RELATIVELY HOSTILE ENVIRONMENT THAT DOES NOT SUPPORT THE SURVIVAL OF MOST ORGANISMS (e.g. THE VOLATILE FATTY ACIDS PRODUCED BY THE ANAEROBE *propionibacteria* ARE TOXIC FOR *streptococci*; THE SKIN IS TOO DRY FOR GRAM-NEGATIVE RODS WITH THE EXCEPTION OF *Acinetobacter*)

-THE MOST COMMON ORGANISMS FOUND ON THE SKIN SURFACE ARE:

- GRAM-POSITIVE BACTERIA: coagulase-negative *Staphylococcus*

- AND LESS COMMONLY, *S. aureus, corynebacteria, AND propionibacteria)*

VIRULENCE FACTORS

WHAT IS VIRULENCE?
INFECTION, DISEASE, AND VIRULENCE FACTORS

VIRULENCE OR PATHOGENICITY: ABILITY OF A BACTERIUM TO CAUSE INFECTION

VIRULENCE FACTORS: BACTERIAL PRODUCT OR STRATEGY THAT CONTRIBUTES TO VIRULENCE OR PATHOGENICITY:

- ability to adhere to mucosal cells
- ability to produce toxic proteins
- ability to obtain energy from sugar fermentation
- ability to acquire carbon and energy from the human body

CATEGORIES OF VIRULENCE FACTORS:

- THOSE THAT PROMOTE BACTERIAL COLONIZATION AND INVASION OF THE HOST
- THOSE THAT CAUSE DAMAGE TO THE HOST

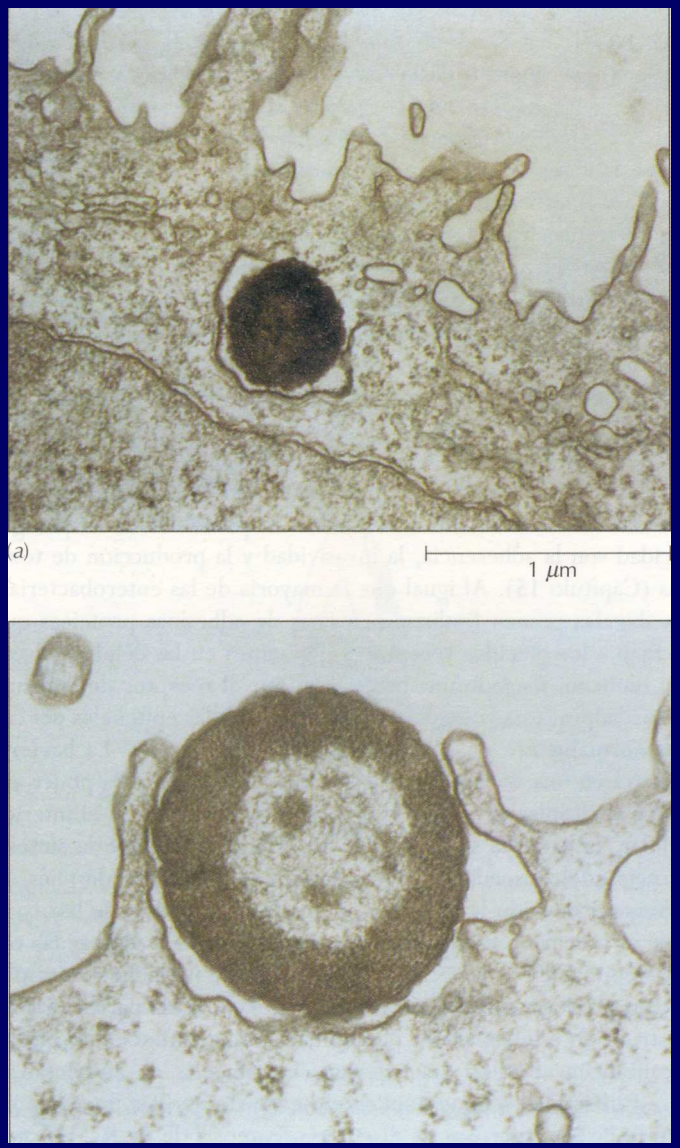
VIRULENCE FACTORS THAT PROMOTE COLONIZATION AND SURVIVAL OF INFECTING BACTERIA (I)

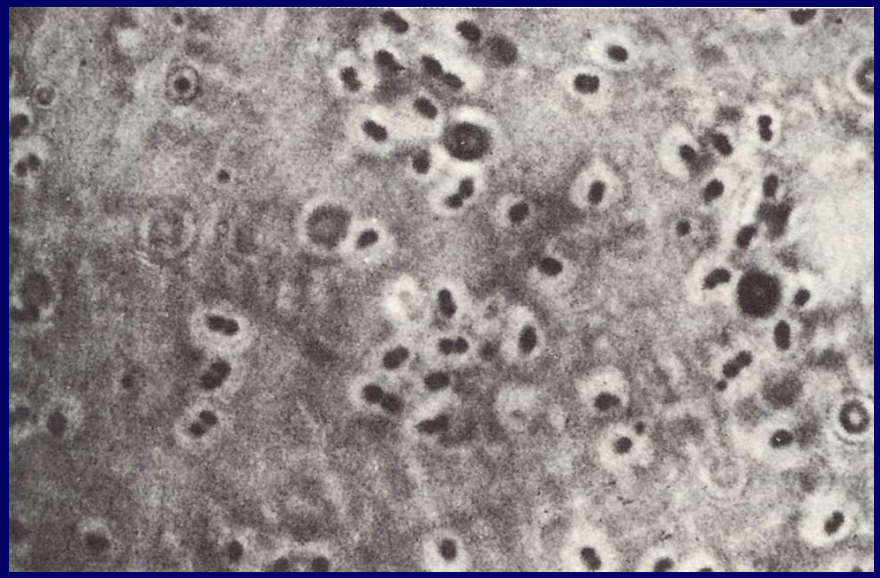
1. PILI: ADHERENCE TO MUCOSAL SURFACES
2. NONFIMBRIAL ADHESIN: TIGHT BINDING TO HOST CELLS
3. BACTERIAL TRIGGERING OF ACTIN REARRANGEMENT IN HOST CELLS: FORCED PHAGOCYTOSIS OF BACTERIA BY NORMALLY NONPHAGOCYTIC HOST CELLS; MOVEMENT WITHIN HOST CELLS OR FROM ONE HOST CELL TO ANOTHER
4. BINDING TO AND ENTRY OF M CELLS: M CELLS USED AS NATURAL PORT OF ENTRY INTO UNDERLYING TISSUE
5. MOTILITY AND CHEMOTAXIS: REACHING MUCOSAL SURFACES
6. sIgA PROTEASES: PREVENT TRAPPING OF BACTERIA

VIRULENCE FACTORS THAT PROMOTE COLONIZATION AND SURVIVAL OF INFECTING BACTERIA (II)

7. SIDEROPHORES, SURFACE PROTEINS BINDING TO TRANSFERRIN, LACTOFERRIN… : IRON ACQUISITION
8. CAPSULES (USUALLY POLYSACHARIDAE): PREVENT PHAGOCYTIC UPTAKE; REDUCE COMPLEMEMNT ACTIVATION
9. ALTERED LPS O ANTIGEN: MAC NOT FORMED; SERUM RESISTANCE
10. C5a PEPTIDASE: INTERFERES WITH SIGNALING FUNCTION OF COMPLEMENT
11. TOXIC PROTEINS: KILL PHAGOCYTES; REDUCE STRENGTH OF OXIDATIVE BURST
12. VARIATIONS IN SURFACE ANTIGENS: EVADE ANTIBODY RESPONSE

***S. pyogenes*, invasion**





S. pneumoniae, capsule

STABLISHMENT OF INFECTION

1. COLONIZATION : INITIAL INTERACTION WITH HOST TISSUES AT MUCOSAL SURFACE

   - ADHESION: SURFACE INTERACTIONS BETWEEN SPECIFIC RECEPTORS ON THE CELL MEMBARNE AND LIGANDS ON THE BACTERIAL SURFACE

   - FIMBRIAL AND NON-FIMBRIAL ADHESINS

   BINDING TO FIBRONECTIN

2. INVASION: BACTERIA EXERT THEIR PATHOGENIC EFFECTS WITHOUT PENETRATING THE TISSUES OF THE HOST: TOXINS, OTHER AGGRESSINS AND INDUCTION OF INTRACELLULAR SIGNALLING PATHWAYS MEDIATE TISSUE DAMAGE

   - UPTAKE INTO HOST CELLS

   - ROLE OF CELL RECEPTORS

3. SURVIVAL AND MULTIPLICATION

STABLISHMENT OF INFECTION

4. AVOIDANCE OF HOST DEFENSE MECHANISMS : CAPSULES, SPREPTOCOCAL PROTEIN M, RESISTANCE TO KILLING BY PHAGOCYTIC CELLS, ANTIGEN VARIATION

5. DAMAGE OR DYSFUNCTION:

- TOXINS:
  - * ENDOTOXINS (LIPOPOLYSACCHARIDE): ANCHORED INTO THE OUTER MEMBRANE THROUGH A UNIQUE MOLECULE TERMED LIPID A THAT IS LINKED TO O ANTIGEN.
- EXOTOXINS:
  - * TYPE I (MEMBRANE ACTING): STIMULATE TRANSMEMBRANE SIGNALS, AND INCLUDE SUPERANTIGENS
  - * TYPE II (MEMBRANE DAMAGING): FORMING PORES OR DISRUPTING LIPID BILAYERS
  - *TYPE III (INTRACELLULAR EFFECTOR): TRANSLOCATE AN ACTIVE ENZYMATIC COMPONENT INTO THE CELL AND MODIFY AN INTRACELLULAR TARGET MOLECULE
- SYSTEMIC EFFECTS OF TOXINS
- OTHER AGGRESSINS: UREASES, MUCINASES, PHOSPHOLIPASES, COLLAGENASES, HYALURONIDASES