Multidrug Resistant
*Pseudomonas aeruginosa*

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**Pseudomonas aeruginosa**

- Not a member of human microbiome
  - Inhabitant of soil and moist environments
- Opportunistic bacterial pathogen in people
  - Self-resolving in healthy individuals
  - Link to immunocompromised individuals
- Common nosocomial (i.e. hospital-acquired) infectious agent
  - Persists on medical equipment, particularly water sources and surgical tubing
  - Commonly isolated pathogen from patients with ventilator associated pneumonia.
- Multiple sites of infection
  - Respiratory tract, urinary tract, skin and soft skin tissue, ocular tissue, outer ear

https://slideplayer.com/slide/6281123/21/images/63/Diverse+sites+of+infection+by+P+aeruginosa.jpg
Risk assessment

• Accumulation of antimicrobial resistance
  • Natural resistance to carbapenem antibiotics, drugs of last resort reserved for multidrug-resistant bacterial infections
  • High risk of adaptive resistance due to incorrect MIC
  • Multidrug resistant (MDR) or extensive drug resistance (XDR)

• High morbidity and mortality rates in immunocompromised individuals
  • 60-80% morbidity in patients with cystic fibrosis (CF), 30% mortality in patients with ventilator associated pneumonia

• Progression to chronic infections
  • More than 20 years in CF patients
  • Rapid exacerbation of existing condition and/or gradual but relentless deterioration of infected organ

http://www.omafra.gov.on.ca/english/livestock/animalcare/amr/facts/17-017.htm
Diseases linked to *P. aeruginosa*

- Common link – damage to lung tissues and/or immune response mechanisms
  - Bronchiectasis
  - Chronic obstructive pulmonary disease
  - Cystic fibrosis


Cystic fibrosis and *P. aeruginosa*

- Of CF patients, 60-80% colonized by *P. aeruginosa*
- Most information about association with *P. aeruginosa*
- Patients suffer continuous damage to lung tissues
- *P. aeruginosa* adapts to CF host conditions

Population structure

• Genotyping
  • Subspecies differentiation to identify evolutionary history, in epidemiology used to track transmission events

• Some *P. aeruginosa* subtypes are widespread (e.g. ST235, ST111, ST175)
Population structure

• Some *P. aeruginosa* subtypes are linked to specific areas or people
  • ST277 associated with Brazil
  • ST146 with CF patients

• “Non-clonal epidemic” structure
  • Populations contain many subtypes
  • Limited number of dominant subtypes
  • Subtypes undergo mutation and recombine with each other
  • Result = rapid development and sharing of acquired resistance factors

Which *P. aeruginosa* subtypes become high-risk?

- Many MDR/XDR subtypes exist, but few are widespread
- Study of association of biological parameters as factors of high-risk subtypes
  - Motility
  - Biofilm-forming capacity
  - Iron acquisition
  - Pyocyanin toxin (persistence-related)
  - Competitive growth
- High risk clones have reduced motility and increased mutation frequencies and biofilm formation
  - Is survival and persistence prioritized over growth and virulence?

Pathogenesis – initial infection (acute phase)

• Motility

• Adherence

• Exotoxins
  • Cell death
  • Increased permeability
  • Reduced wound healing

• Type 3 secretion system
  • Four effector proteins (ExoS, ExoT, ExoU, ExoY)

• Inhibited immune response

Virulent motility

• Flagellum and pili perform motility and adherence function

• Motility mechanism matters
  • Swimming uses only flagellum and takes place in liquid
  • Twitching uses only pili and takes place on solid (but moist) surface
  • Swarming uses flagellum and pili and takes place on semi-solid surface

Pathogenesis – host response (acute phase)

- Detection by toll-like receptors
- Response by macrophages
- Secretion of cytokines and chemokines (especially IL8) to recruit neutrophils for phagocytosis
- Activation of dendritic cells to signal adaptive immune response

Pathogenesis – colonization (chronic phase)

- *P. aeruginosa* infection is no cleared in immunocompromised
  - biofilm formation and upregulation of evasion and survival factors.
- Suppression of host cell adaptive immune signaling activity
- Constant host immune dysregulation leading to inflammatory damage over time
  - In CF patients, neutrophils do not clear infection but continue to be recruited, which leads to inflammatory damage.

Biofilm formation

- Substrate adherent, protective coating
- Reduced virulence, increased evasion factors and signaling activity
- Impacts *P. aeruginosa* survival and antimicrobial resistance
Quorum sensing

- Population-level detection and response
- Autoinducer molecules released by individual cells until threshold is reached
- Critical for regulation of complex shifts between phenotypes

Antimicrobial resistance

- Intrinsic
  - Blockage of entry
  - Beta lactamases
  - Efflux pumps

- Acquired
  - Transposon and plasmids
    - New gene or a gene copy
  - Genetic mutation
    - Alter target structure or change regulation of factor

- Adaptive
  - Biofilm formation
  - Loss of motility structures
  - Reduced membrane permeability

Treatment issues and solutions

• Utilize older drugs
  • Used less often, so lower chance of pre-existing resistance
  • Somewhat effective, but many have toxic side effects

• Combine multiple antibiotics
  • Greater chance of completely clearing infection
  • Toll on patient, risk of adaptive resistance may remain

• Develop adjuvants that boost antibiotic effectiveness

• Directly target biofilm in combination with antibiotic against bacterial cell

• Shift treatment towards a focus on limiting *P. aeruginosa* virulence

• Bacteriophage therapy
  • Shows promise
  • Pathogen can develop phage resistance, host may inhibit phage activity, hyper-specificity toward species or subtype may be too limited
Conclusion

• Many mechanisms and interactions between *P. aeruginosa*, host cells, and the microbiome have yet to be elucidated

• Current therapies for *P. aeruginosa* are a temporary measure (at best) and will not remain effective, but new approaches may succeed where traditional antibiotic development has failed

• *P. aeruginosa* is a powerful example of the antimicrobial “arms race” taking place between high-risk bacterial pathogens and humanity
Questions?