



香港中文大學
The Chinese University of Hong Kong



香港中文大學醫學院
Faculty of Medicine
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The Function of Invasive Bacterial Pathogens in the Etiology of Human Diseases

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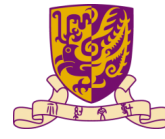
1st year PhD

Supervisor: Prof. Zigui CHEN

Graduate Student Seminar 11 Dec. 2024

Presentation Outline

1. Introduction
2. Mechanisms
3. Challenges
4. Conclusion



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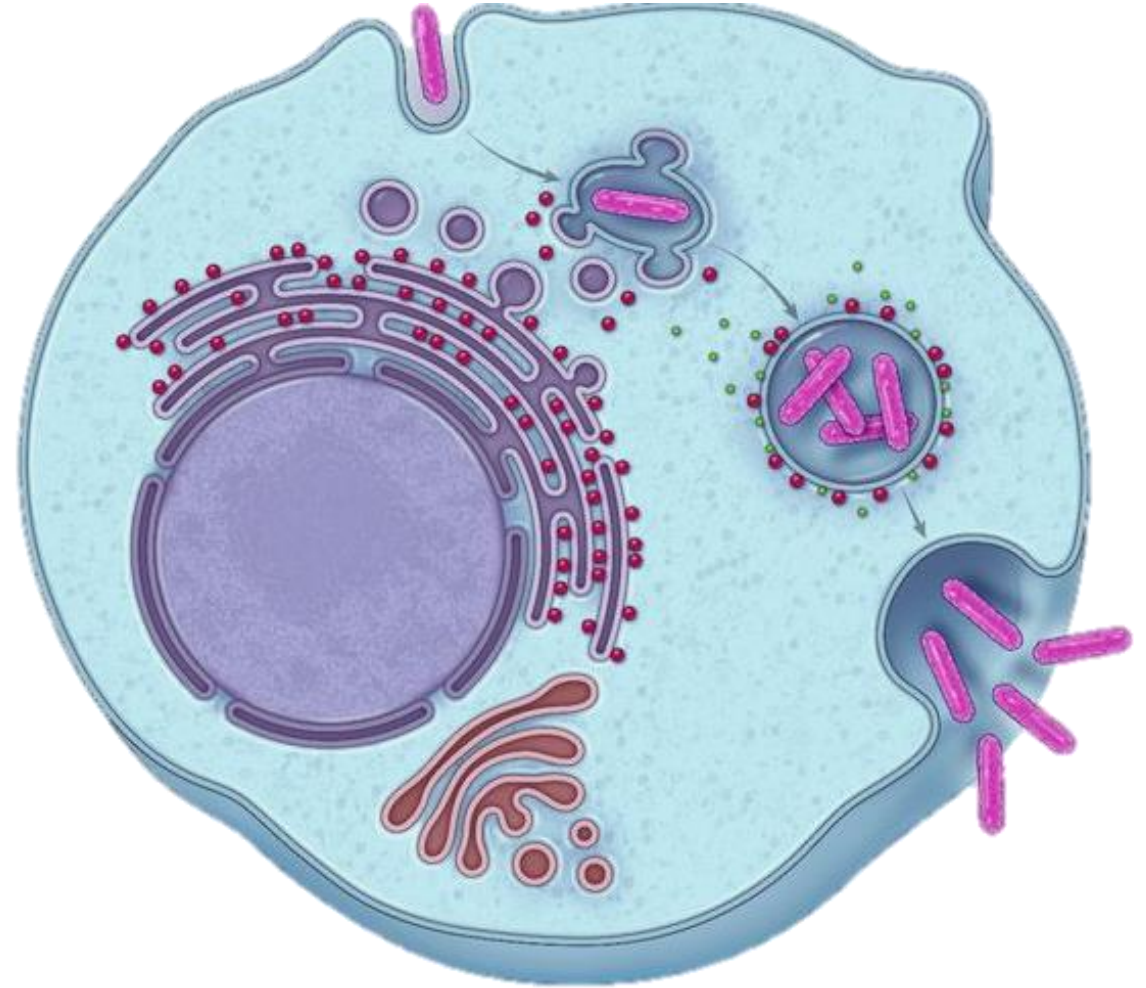


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Introduction

Invasive bacteria

- Microorganisms penetrate host tissues (eg. bloodstream)
- Small percentage
- Most are pathogenic



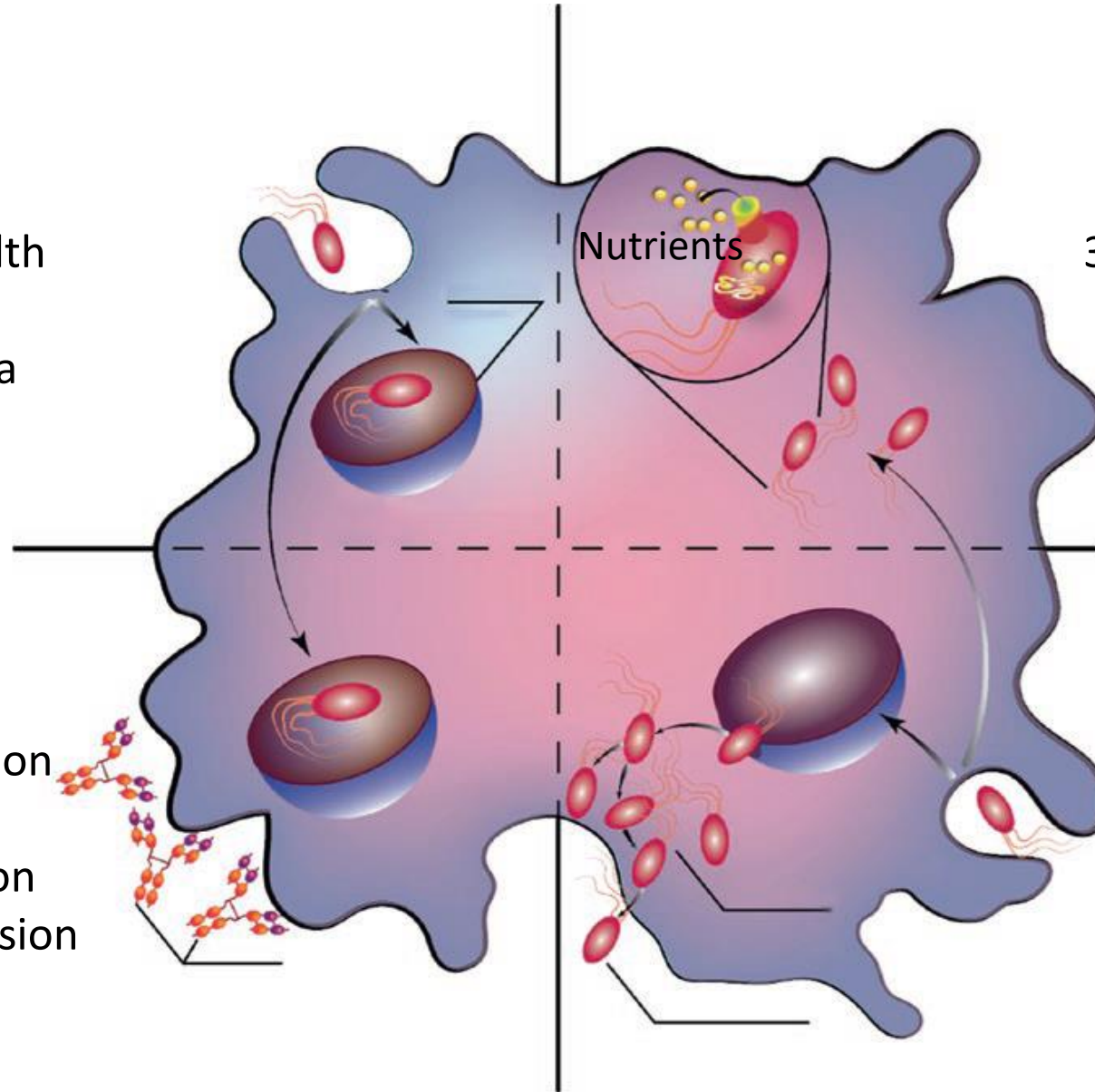
Features of invasive bacteria

1. Immunological Stealth (Hide)

- Surrounded by a capsule
- Hibernation

2. Immunological evasion (Block)

- Antigenic variation
- Immune suppression



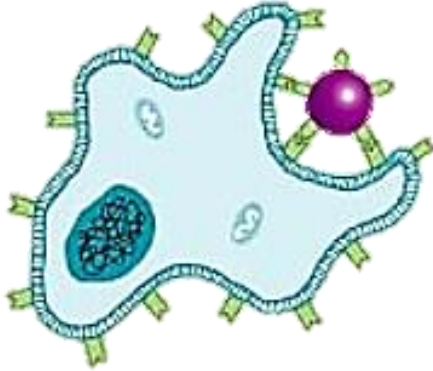
3. Nutritional Acquisition

Nutrition privilege in the host cytosol

4. Replication and spread

Invade and spread through mobile, phagocytic cells

Invasive bacteria



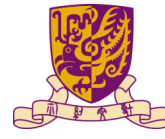
- Multiply within host cells
- Severe systemic diseases
- Develop immune evasion

Non-invasive bacteria



vs.

- Live on body surfaces
- Milder, Localized infections
- Rely on adherence, less evasion



Mechanisms and Functions

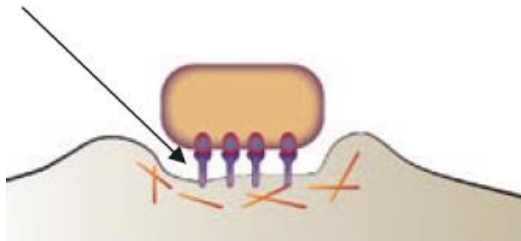
- Zipper mechanism
- Trigger mechanism

1.

Zipper mechanism of invasion

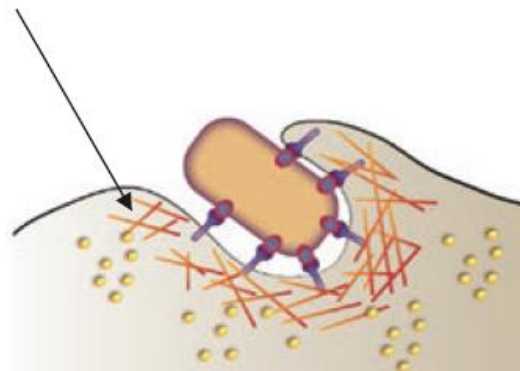
1. Binding

1. A bacterial adhesin binds a host receptor.



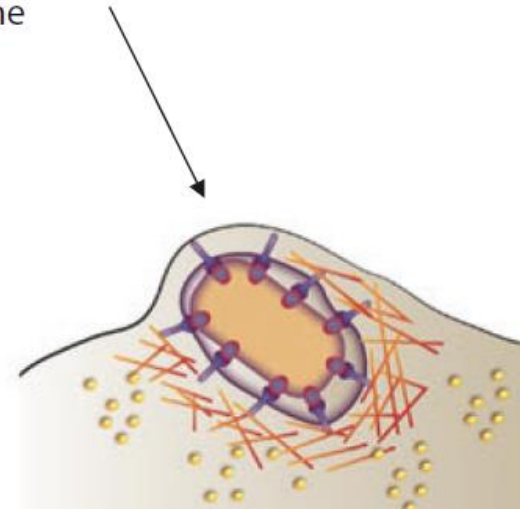
2. Ligation

2. The ligation of the receptor induces downstream signaling events that culminate in the invagination of the host membrane and extension of actin filaments around the bacterium.



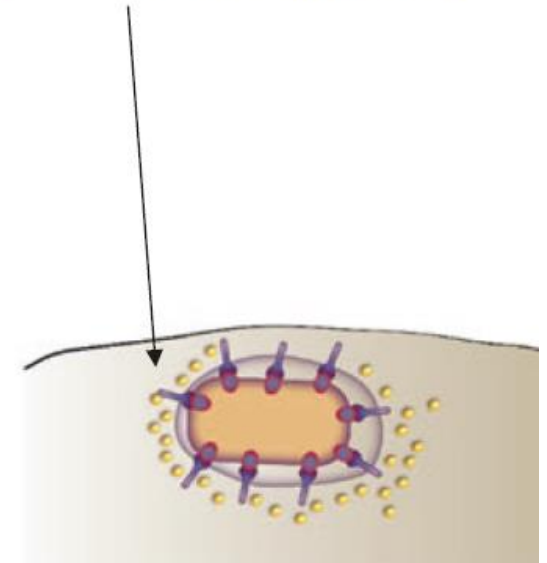
3. Fusion

3. The membrane fuses with the now enclosed bacterium in a vacuole.



4. Collapse

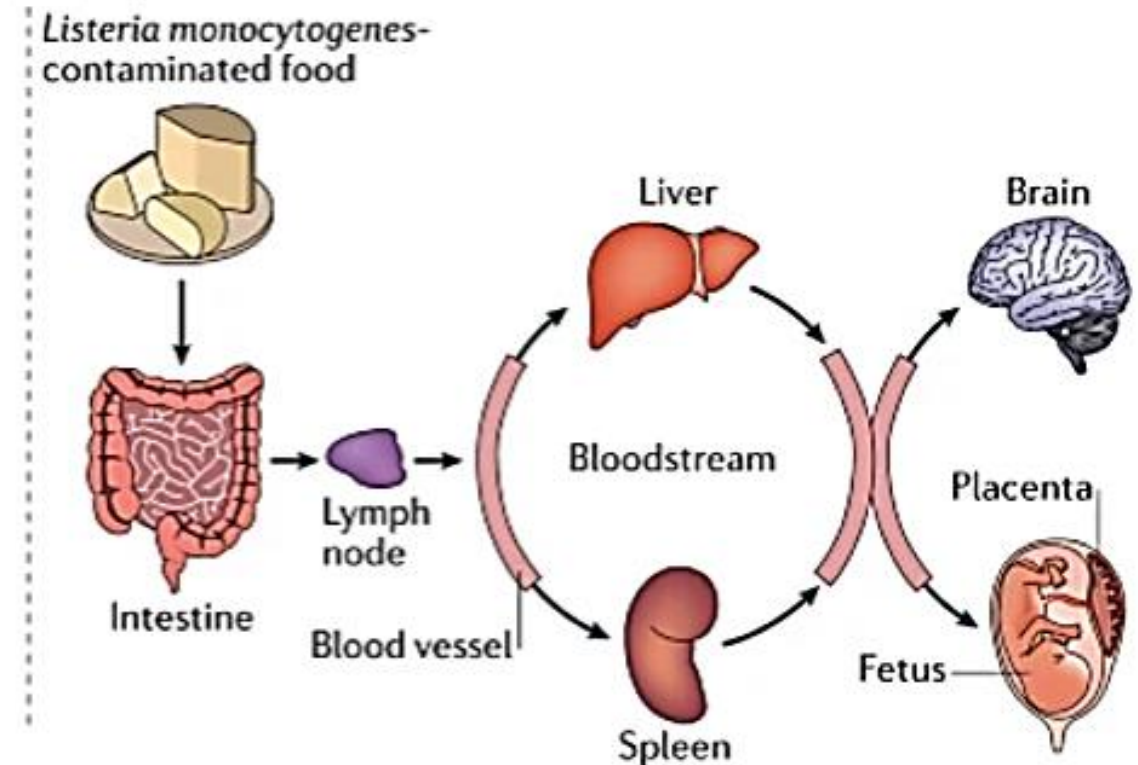
4. Collapse of the actin restores the host surface.



Example

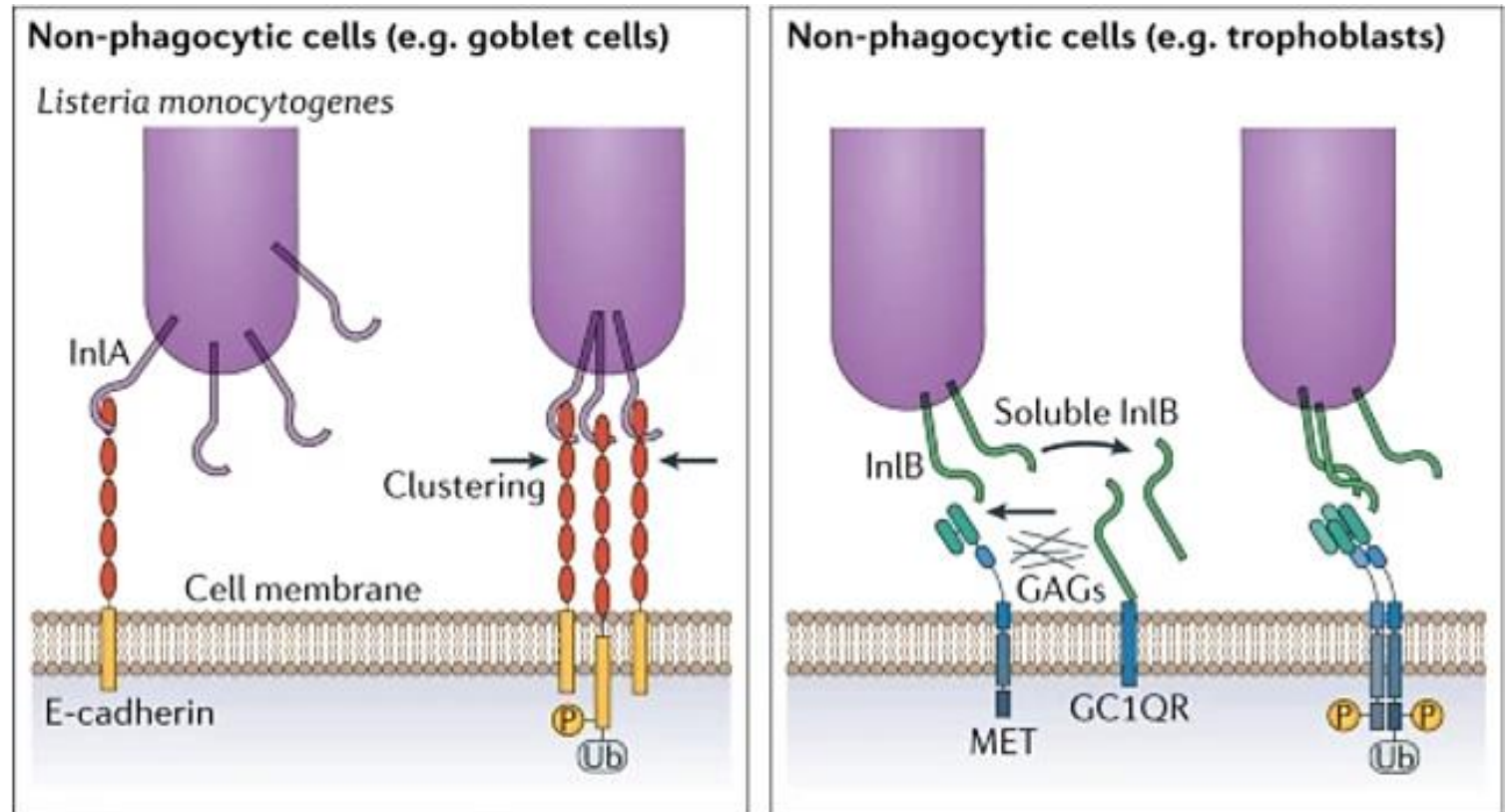
Listeria monocytogenes associated infection

- Gram-positive
- Infect through contaminated food
- Traverse the intestinal barrier and spread into the bloodstream
- Cross the blood–brain barrier or fetoplacental barrier
- Meningitis, sepsis, premature birth or abortion



Invasin-based invasion of *L. monocytogenes*

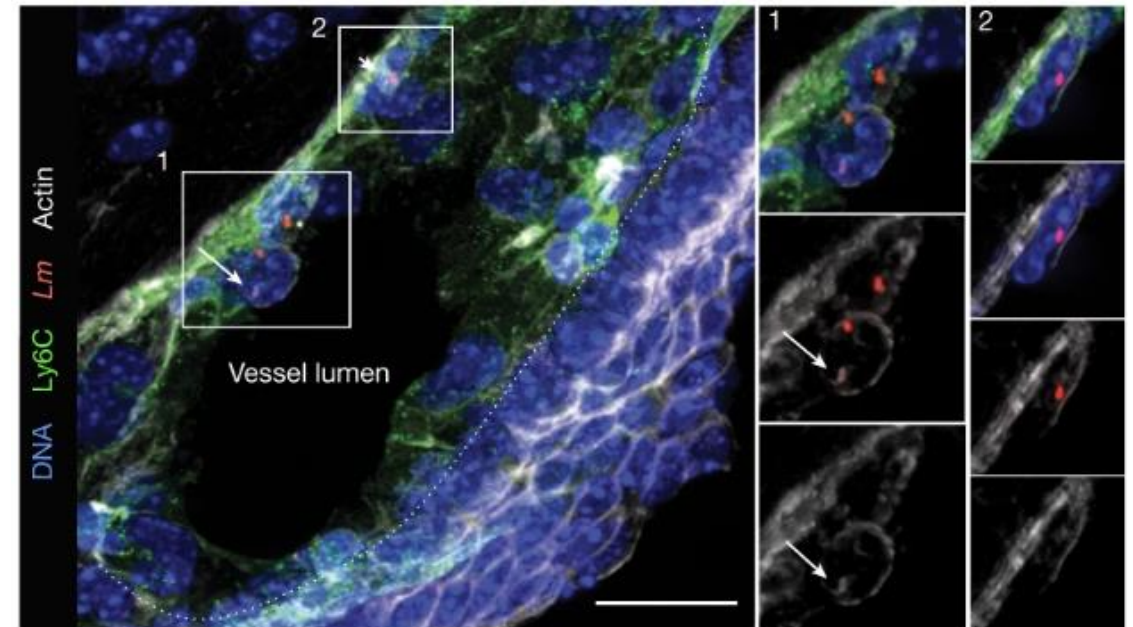
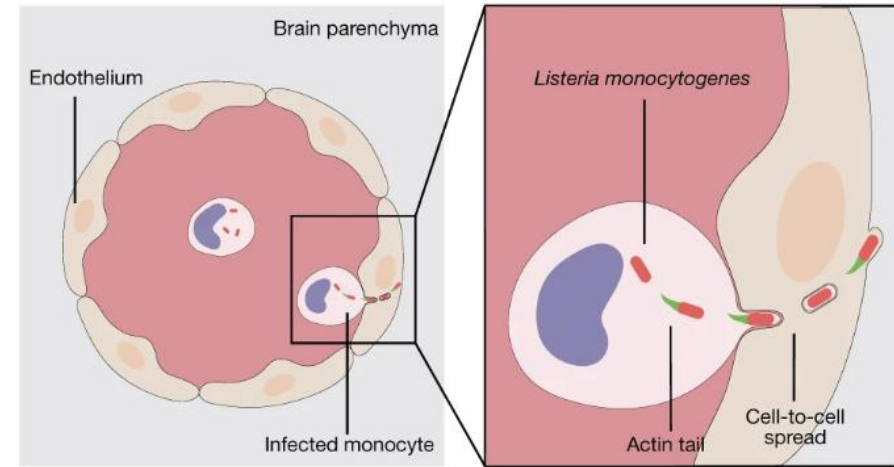
- Internalized in both phagocytic and **non-phagocytic** cells
- Internalin A (InlA) bind to E-cadherin
- Internalin B (InlB) bind to Met
- Stimulate actin extension
Inducing bacterial uptake



GC1QR (Complement component 1 Q subcomponent-binding protein)
GAG (glycosaminoglycans)

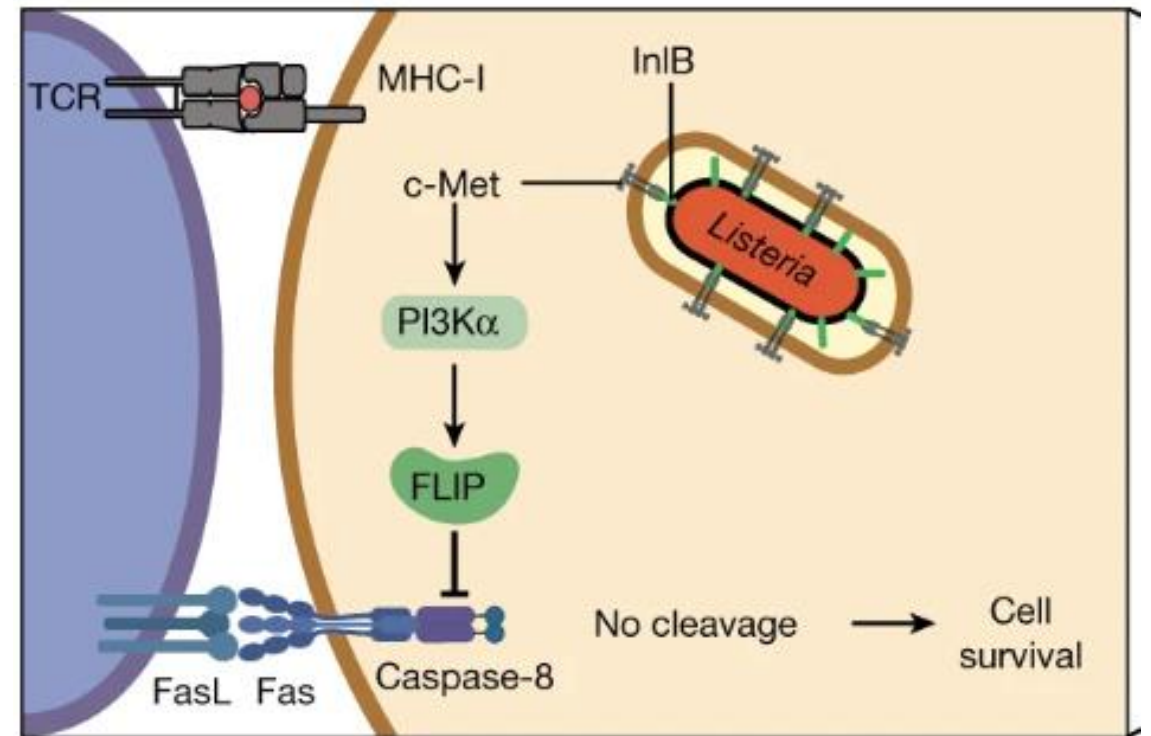
L. m infects Central Nervous System

- Oral delivered *L. monocytogenes* cross intestinal barrier and infect monocytes
- Infected monocytes transport the blood vessel in brain section
- Infected monocytes adhering to the blood vessels endothelium
- *Lm* polymerizes actin and infect neurons



Immunoinhibitory function of InIb

- InIb plays a major role in *Lm* neuroinvasion
- InIb promotes *Lm* neuroinvasion
- InIb blocks CD8+ T cell-mediated killing through c-Met–PI3K–FLIP



Diagnosis and treatment of *Lm*-associated meningitis

Diagnosis

- *Clinical Presentation*
 - Fever & Chills
 - Headache
 - Nausea and vomiting
- *Diagnostic Tests*
 - Blood Tests (First line)
 - Cerebrospinal fluid (CSF) Analysis
 - MRI (Magnetic resonance imaging) or CT (Computed tomography) scans
 - PCR on blood or CSF samples

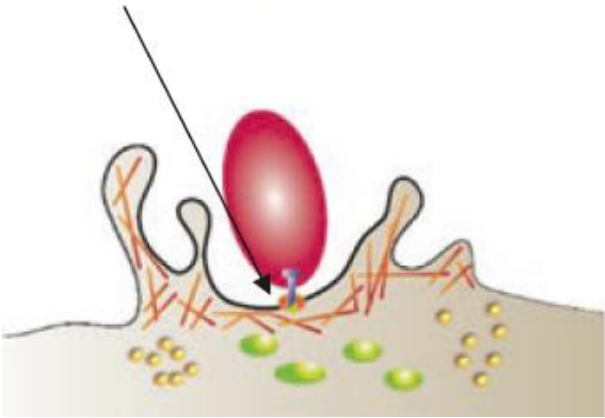
Treatment

- *Antibiotic Therapy*
 - Ampicillin
 - Trimethoprim-sulfamethoxazole
- *Duration of Therapy*
 - 10 to 21 days
 - Up to 8 weeks in severe cases

2.

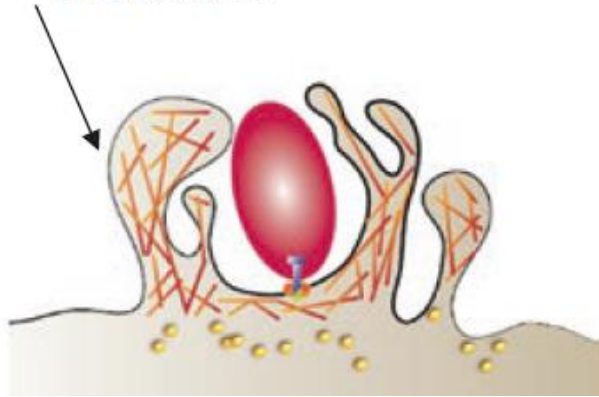
Trigger mechanism of invasion

1. Bacterium injects effectors that rearrange the actin cytoskeleton.



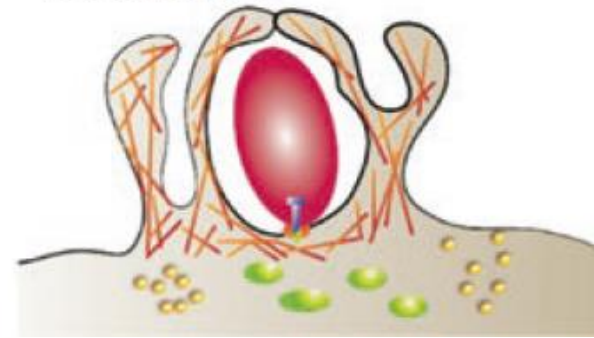
1. Injection

2. Actin filament extensions grow upwards pushing against the host cell membrane.



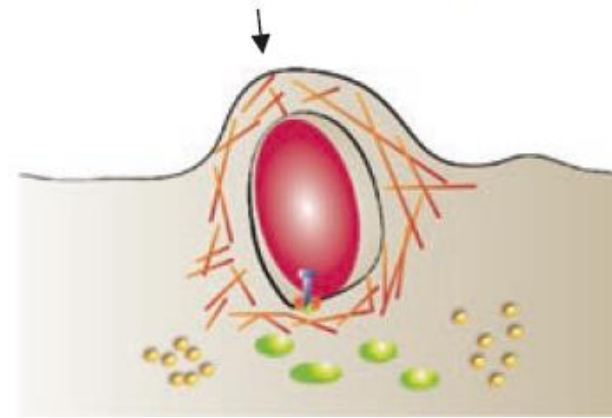
2. Extension

3. Actin-based extensions induce ruffling of the membrane which eventually encloses the bacterium.



3. Enclosing

4. The bacterium now is fully engulfed into a vacuole. The ruffles begin to collapse.

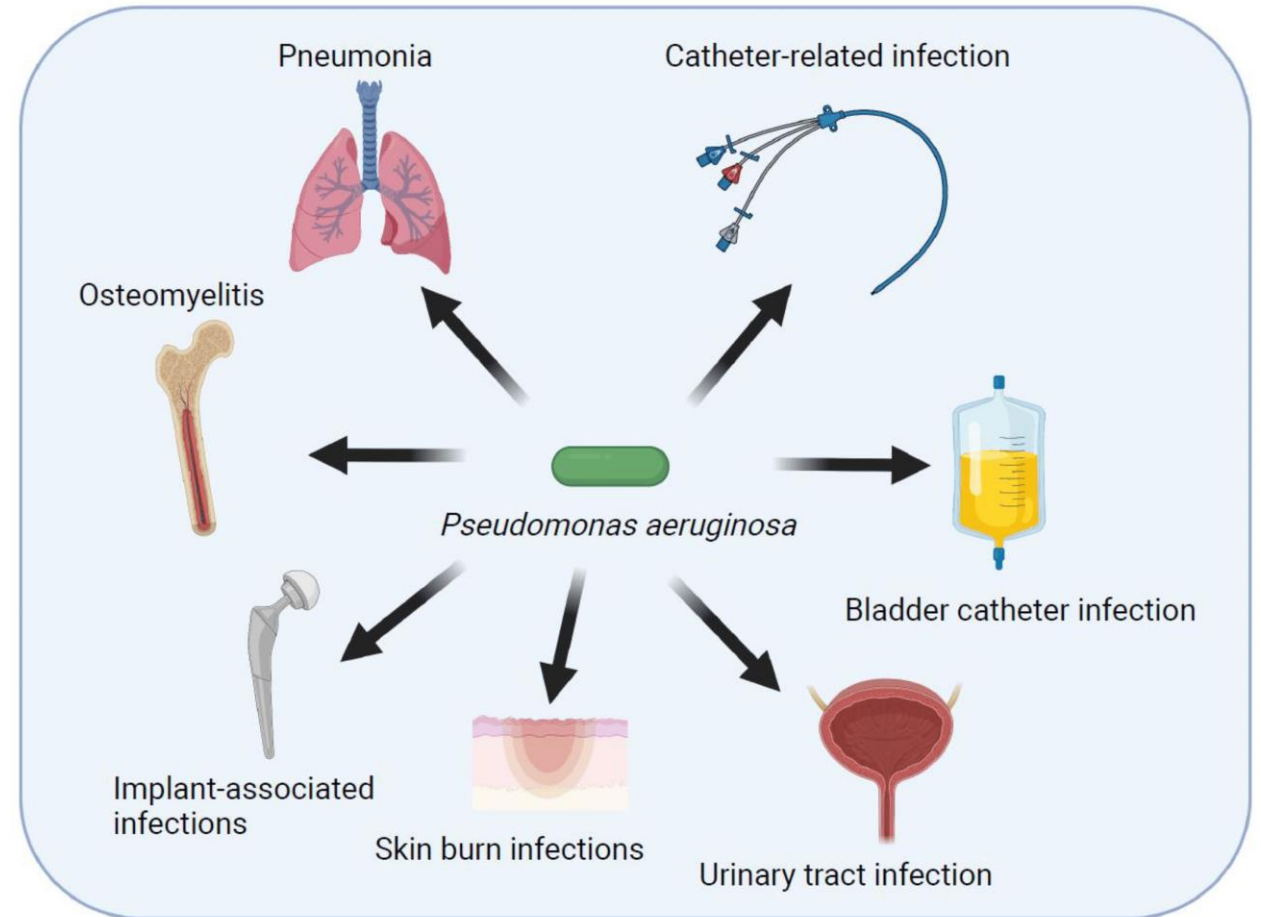


4. Engulfing

Example

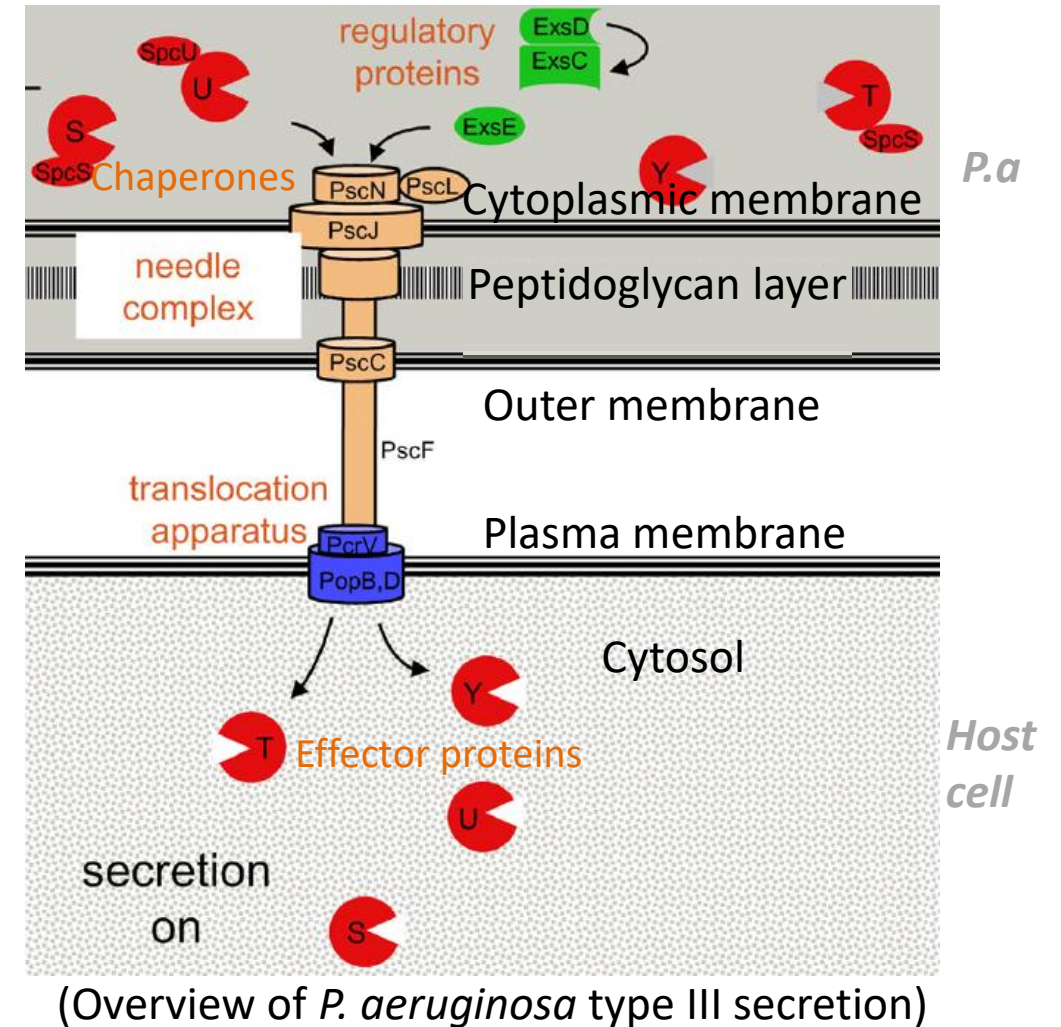
Pseudomonas aeruginosa associated infection

- Gram-negative
- Commonly found in most environments such as soil, water, and contaminated medical equipment
- **Hospital-acquired pneumonia**
- Skin and Soft Tissue Infections
- Eye infection
- Urinary Tract Infections



T3SS-based invasion of *P. a*

- Type III secretion system (T3SS):
 - Protein transport mechanism to inject effector proteins into the host cytoplasm
- Key proteins involved:
 - Needle complex
 - Translocation apparatus
 - Regulatory protein
 - Chaperones
 - Effector protein
- Cytoskeletal rearrangements and bacterial internalization

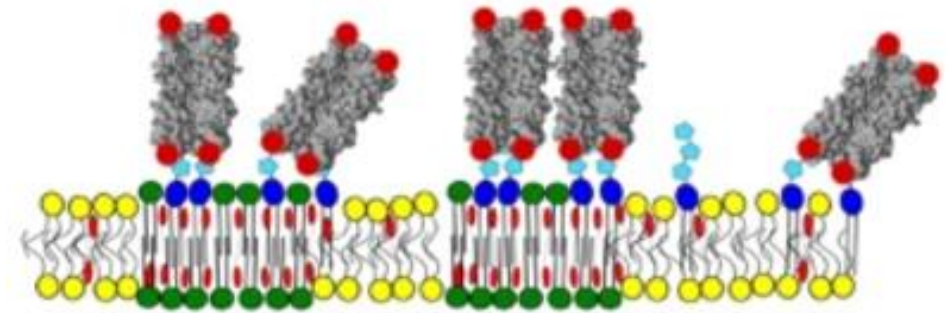
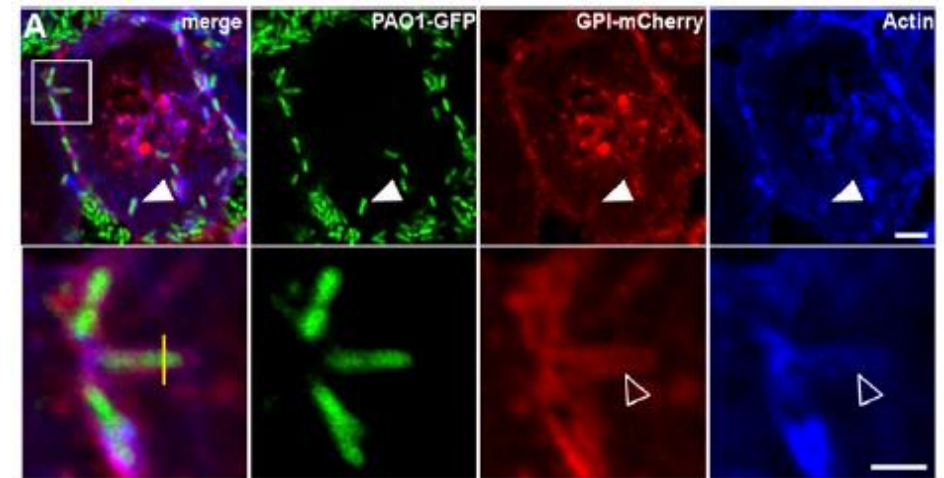


Zipper mechanism invasion of *P. aeruginosa*

- Bacterial surface lectin LecA and its cellular receptor, the glycosphingolipid Gb3
- Trigger plasma membrane bending by forming a lipid zipper

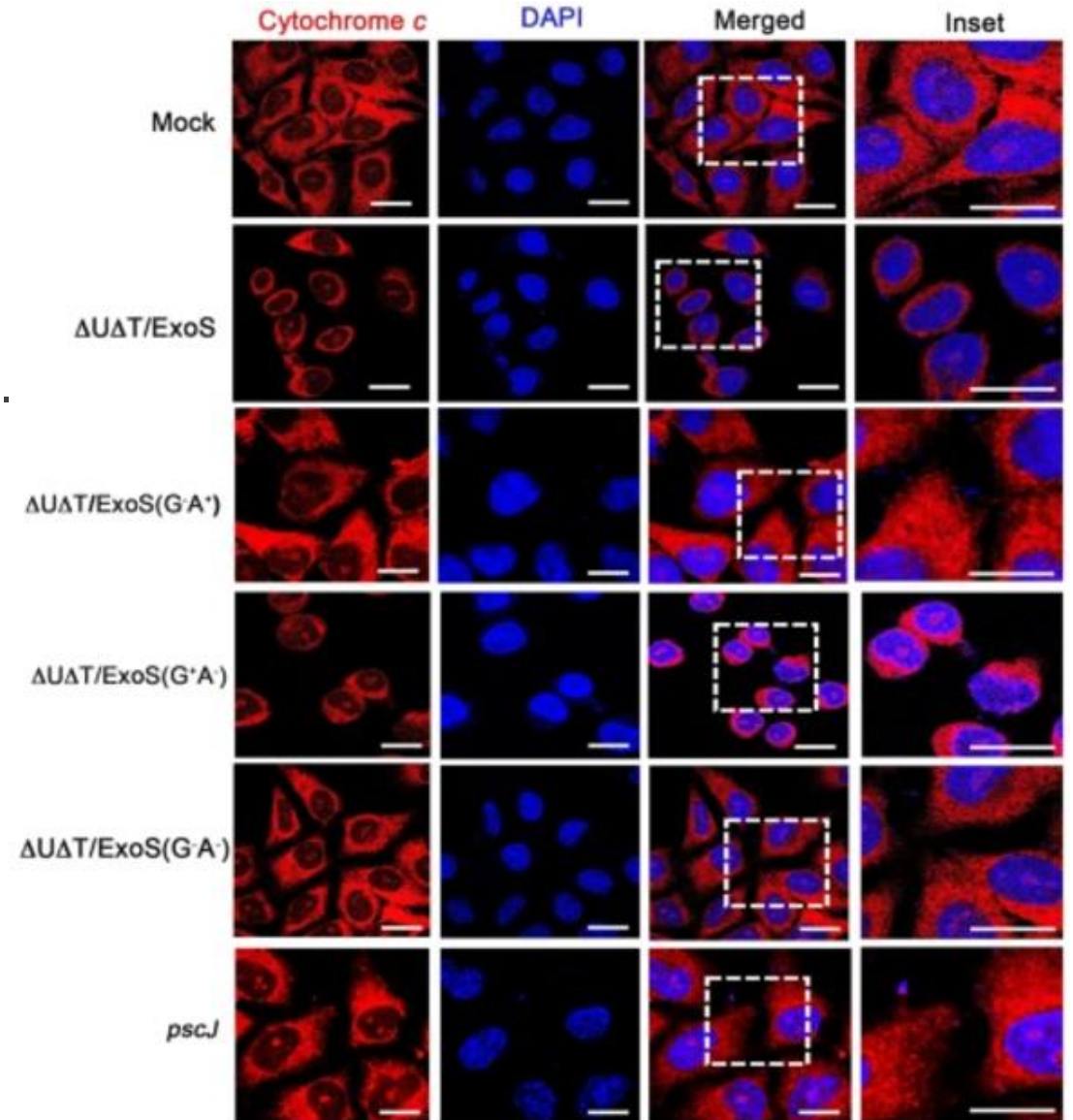
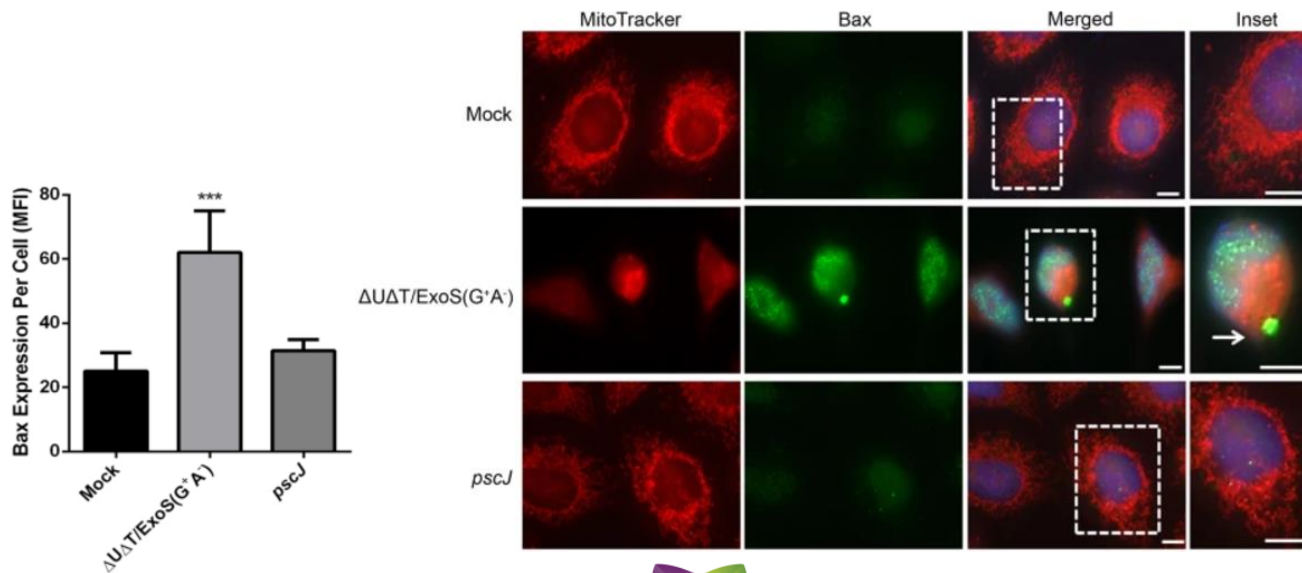
GFP marked
P. aeruginosa

plasma
membrane
marker



Pa ExoS Induces Intrinsic cell Apoptosis

- Exoenzyme S (ExoS)
 - GTPase Activating Protein
 - ADP-ribosyltransferase
- Induce host mitochondrial disruption
- Up regulation and mobilization of pro-apoptotic proteins to mitochondrial membrane



Diagnosis and treatment of *Pa*-associated pneumonia

Diagnosis

- *Clinical Presentation*
 - Fever & Chills
 - Dyspnea
 - Cyanosis
 - Productive cough
- *Diagnostic Tests*
 - Chest X-ray
 - CT scan
 - Sputum culture
 - Bronchoscopy

Treatment

- *Antibiotic Therapy*
 - Ceftazidime
 - Cefepime
 - Meropenem or Imipenem
- *Duration of Therapy*
 - 7 to 14 days
- *Supportive Care*
 - Oxygen therapy and mechanical ventilation



Challenges

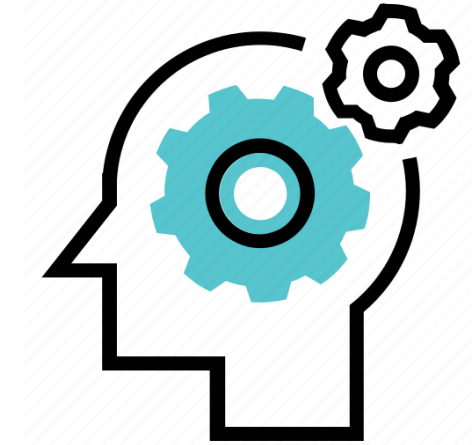
Challenges

- Diagnostic Challenges
 - Nonspecific symptoms result in delayed diagnosis
- Treatment Challenges
 - High risk groups (The elderly, pregnant women, and individuals with weakened immune systems)



Conclusion

- Invasive bacteria are microorganisms penetrate host tissues
- Zipper mechanism of invasion
 - Invasin dependent invasion
 - *Eg. Listeria monocytogenes*
- Trigger mechanism of invasion
 - Effectors injection dependent invasion
 - *Eg. Pseudomonas aeruginosa*
- Treatment through antibiotics is the first line
- Challenges of Early diagnosis and suitable treatment for high risk population



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A close-up photograph of a petri dish containing numerous bacterial colonies of varying sizes and colors, including yellow, orange, and red. A gloved hand is visible on the right side of the dish, holding a small, clear, circular object. The background is a blurred laboratory setting with a yellow biohazard sign.

Thank you!