Toxic shock and Septic shock syndromes

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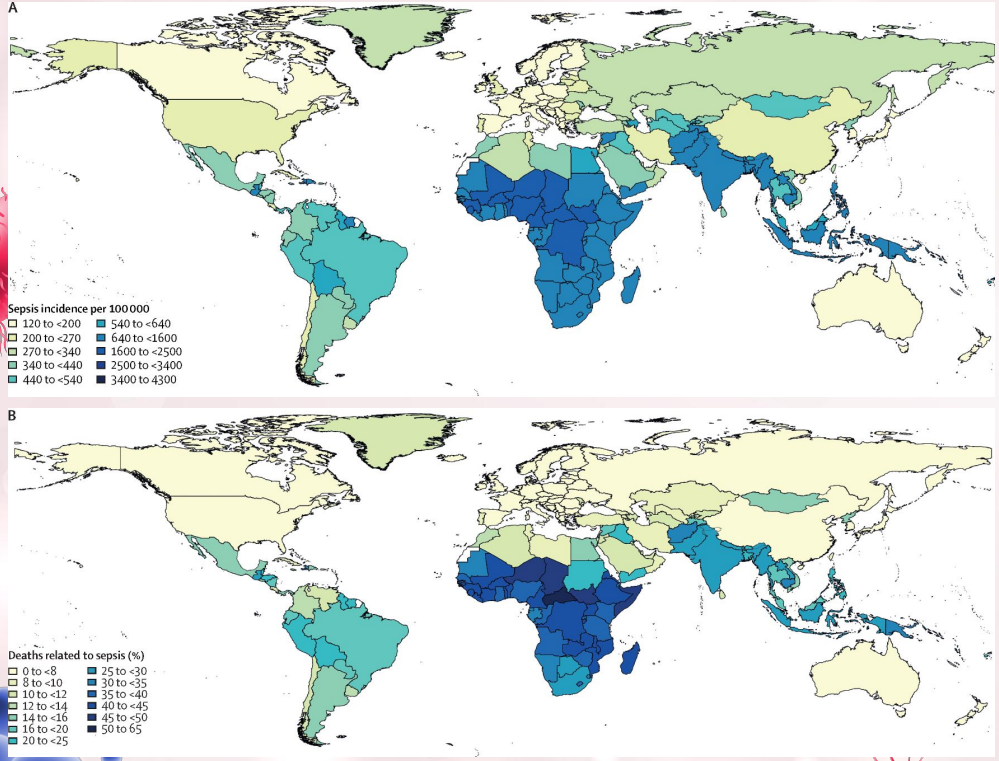
Recap: what is sepsis?

Sepsis is a life-threatening organ dysfunction caused by dysregulated **systemic** inflammatory and immune responses to microbial infections.

Progression of sepsis is is more complex than simply inflammation or pathogen vs. host interactions, as it involves:

- ➔ Immune dysregulation (activation vs. suppression)
- ➔ endothelial dysfunction
- ➔ coagulation and neurological disturbances

Epidemiology of sepsis

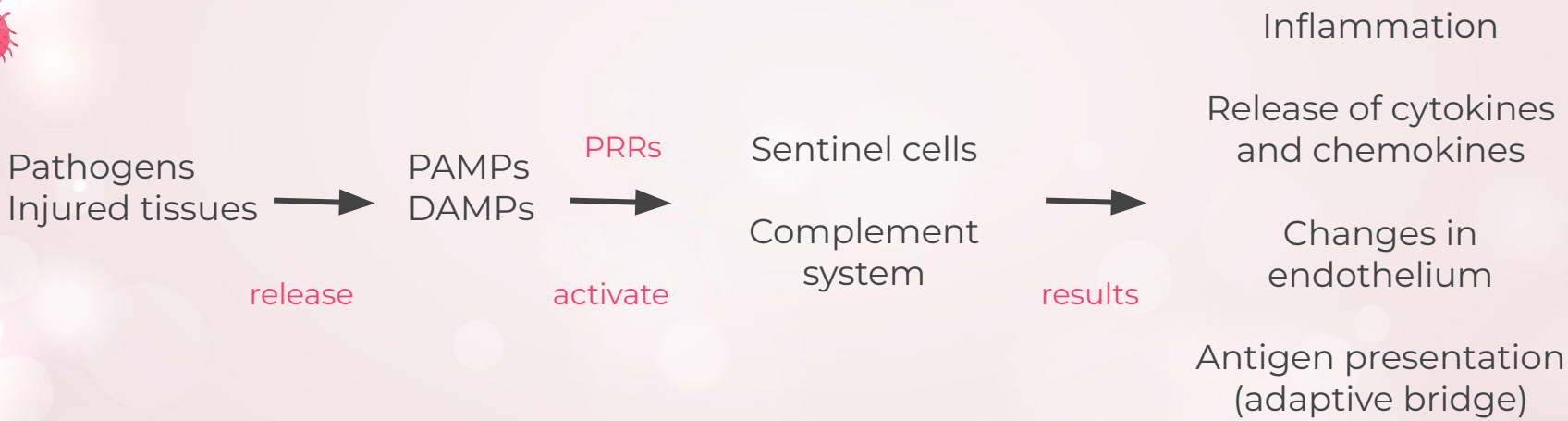


- Almost 50 million cases and 11 million deaths worldwide **(20% of all global deaths)**
- **Age** is a risk factor (children < 5y, elderly people)
- Other risk factors: pregnancy, hospitalized patients, immunosuppressed
- More prevalent in low and middle income countries

RUDD et al, 2020

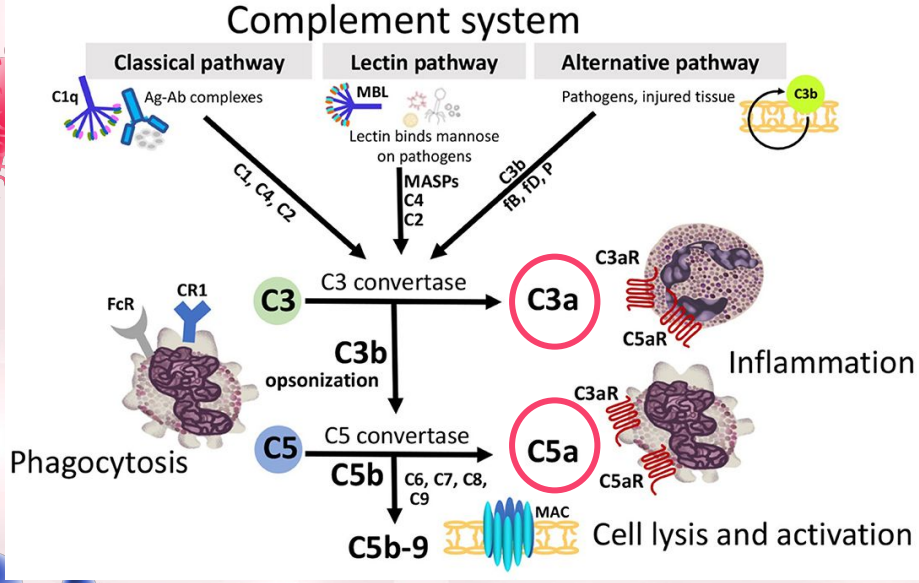
Mechanisms of sepsis

Initial inflammation - innate immunity



Mechanisms of sepsis

The Complement system ⟶



- Opsonization
- Formation of MAC
- **Release of chemotactic fragments (C3a and C5a)**

C5a and neutrophils:

➔ Trigger oxidative burst

➔ Release of ROS and granular enzymes

➔ Stimulates synthesis and release of inflammatory cytokines and chemokines

Responses are physiological, but may lead to neutrophil dysfunction, tissue damage and systemic inflammation.

GIRARDI et al, 2020

Mechanisms of sepsis

Immune suppression

If there is an active inflammation, how can immune suppression happen?
Persistent inflammation/ immunosuppression and catabolism syndrome (PICS)

Constant release of PAMPs and DAMPs as the infection is not cleared

Opportunistic infections (viral reactivation, changes in microbiota)

Immune exhaustion:

- Lymphopaenia
- Release of immature neutrophils
- MDSCs
- Loss of inflammatory cytokine production

Defective antimicrobial activity

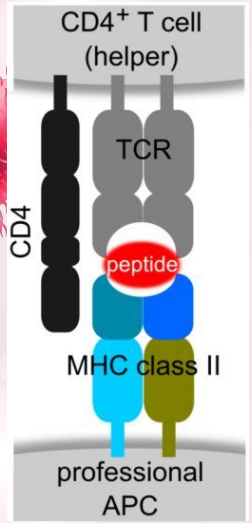
Poor NET formation

Production of IL-10

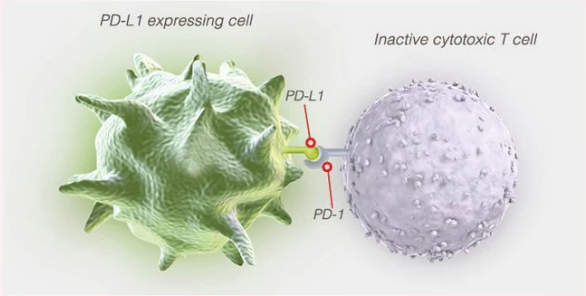
HOTCHKISS et al, 2016

Mechanisms of sepsis

Immune suppression



In sepsis, APCs have deficient expression of MHC class II, causing poor antigen presentation and breaking the innate-adaptive bridge.



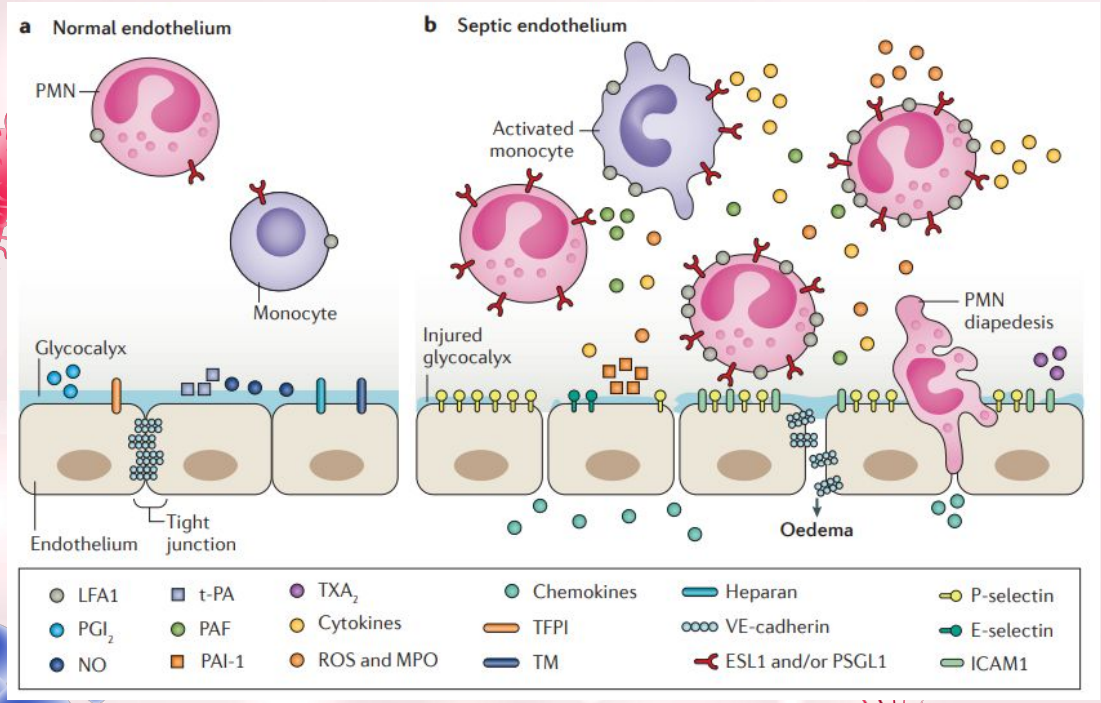
Sepsis causes APCs and stromal cells to have increased expression of PD-L1, further suppressing T cell activation.

Inhibition ligands
+
Loss of MHC class II
+
Anti-inflammatory cytokines
=
+Treg
T cell anergy
T cell and DC apoptosis

HOTCHKISS et al, 2016

Mechanisms of sepsis

Endothelial barrier dysfunction



Normally: **anticoagulant** (actin, tight junctions, proteins).

Sepsis: **procoagulant**, barrier disrupted by neutrophil and platelet adhesion, leakage of fluids

Glycocalyx: targeted by inflammatory mediators and leukocytes, damage becomes systemic

Vascular permeability > leaky capillaries > hypotension > hypoperfusion > shock

HOTCHKISS et al, 2016

Septic shock

The cascade of events in sepsis may lead to septic shock. The endothelium suffers injury and activates coagulation cascades, **exacerbating capillary injury and leakage**.

Vasodilation, capillary leakage → loss of vascular fluids → hypotension → hypoperfusion

Septic shock is a type of **distributive shock**: the hypoperfusion is a consequence of systemic vasodilation.

~ 50% of septic shock patients suffer mortality, and others may have sequelae.

MAHAPATRA and HEFFNER, 2023
MAYR et al, 2010

Septic shock

Pathophysiology

1. Increased vascular permeability
2. Reduced peripheral resistance
3. Decreased venous return
4. **Initial compensatory increased heart rate** → **Warm shock**
5. **Increased peripheral vascular resistance** → **Cold shock**

Septic shock

Management and prognosis

- Fluid resuscitation **combined with vasoactive support** (dopamine, norepinephrine, phenylephrine)
- Suppression of infection
- Continuous monitoring of vital signs

Septic shock may be difficult to be interrupted because it “feedbacks itself”:

PAMPs/DAMPs > inflammation > tissue damage > endothelial dysfunction > hypoperfusion

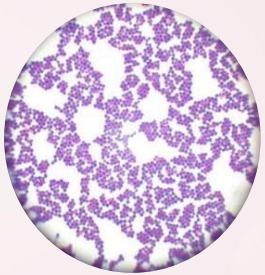
Even patients who survive septic shock may experience post-sepsis sequelae due to organ injury.

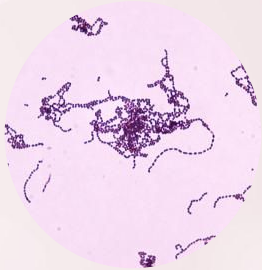
Toxic shock syndrome (TSS)

TSS is a condition caused by bacterial toxins, usually ***S. aureus* or *S. pyogenes***

Symptoms:

- ➔ Fever
- ➔ Hypotension
- ➔ Rash
- ➔ Organ failure



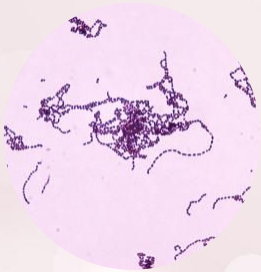


TSS was originally associated with the prolonged use of tampons, but can also be present in settings such as tissue infections, burns, post-cirurgical infections, etc. Importance in **nosocomial infections**.

ROSS and SHOFF, 2023

Toxic shock syndrome (TSS)

Pathophysiology



Superantigen toxin → Non-specific binding of MHC class II →

- Extreme activation of T cells
- Cytokine storm and systemic inflammation
- Distributive shock

ROSS and SHOFF, 2023

Nosocomial infections

Nosocomial infections are infections **acquired in a hospital environment**, that were **not present at the time of admission**.

Causative organisms: depend on healthcare facility location, setting and local population. **Bacteria** are the most frequent, followed by fungi and viruses.

- *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Clostridium difficile*
- ...

SIKORA and ZAHRA, 2023

Nosocomial infections

Transmission routes:

- Direct or indirect contact
- Droplets
- Airborne
- Catheter-associated
- Skin and soft tissue infection (surgery)
- Ventilation-associated

Complications:

- Diagnosis
- Antibiotic resistance
- Sepsis, septic shock and toxic shock
- Associated costs

What are some pathogens associated with infections that lead to shock and how does that happen?

1

Staphylococcus aureus

Topics

The Bacteria

Virulence

Pathogenesis

Superantigens

Diagnosis

Treatment and Drug Resistance

Epidemiology

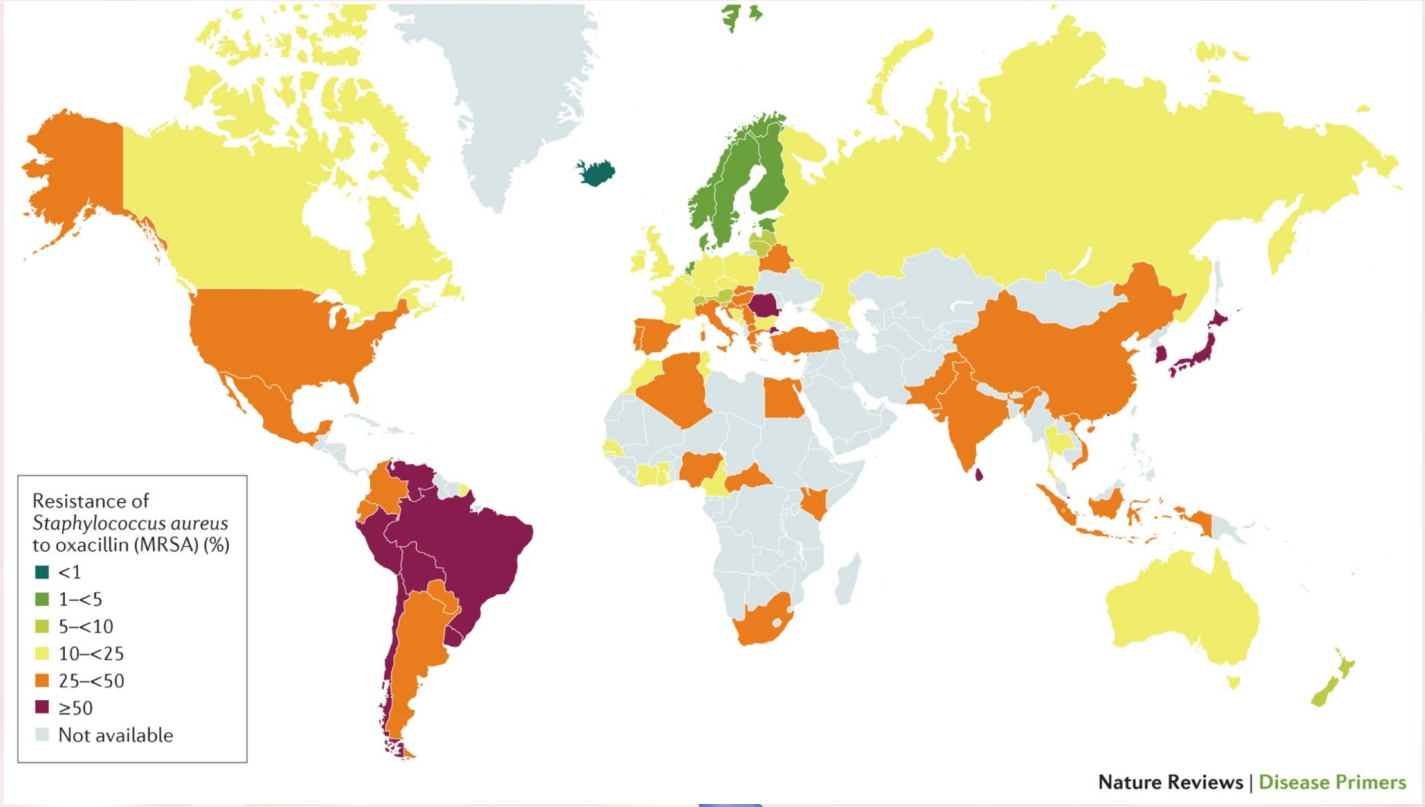


Figure 1: The percentage of *Staphylococcus aureus* isolates that are resistant to oxacillin

LEE et al, 2018

Characteristics

1

Gram Positive

Cell wall with high concentration of peptidoglycan

2

Microbiota

Live in our skin and mucosal surfaces

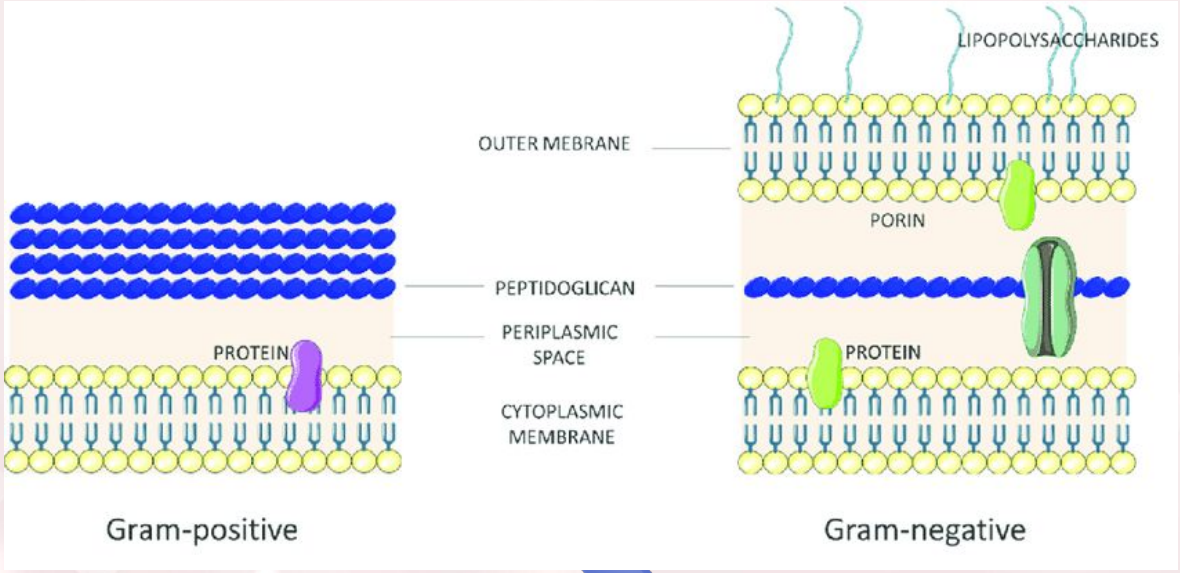


Figure 2: Scheme of gram positive and gram negative bacterial cell wall

ARTASENSI et al, 2021

Virulence

01

Capsule and Protein A

Prevent the bacteria from being phagocytosed

02

Biofilm

Protection, adherence and survival on surfaces

03

Enzymes

Extracellular enzymes such as coagulase, proteases, catalase

04

Toxins

δ-toxins, leukocidin, exfoliative toxins and superantigens

Pathogenesis

01

Superficial or Deep

Bacteria can come from the environment or the microbiota

02

Accession , Evasion and Injury factors

Adhesins, capsule, protein A, toxins and enzymes

03

Abscess

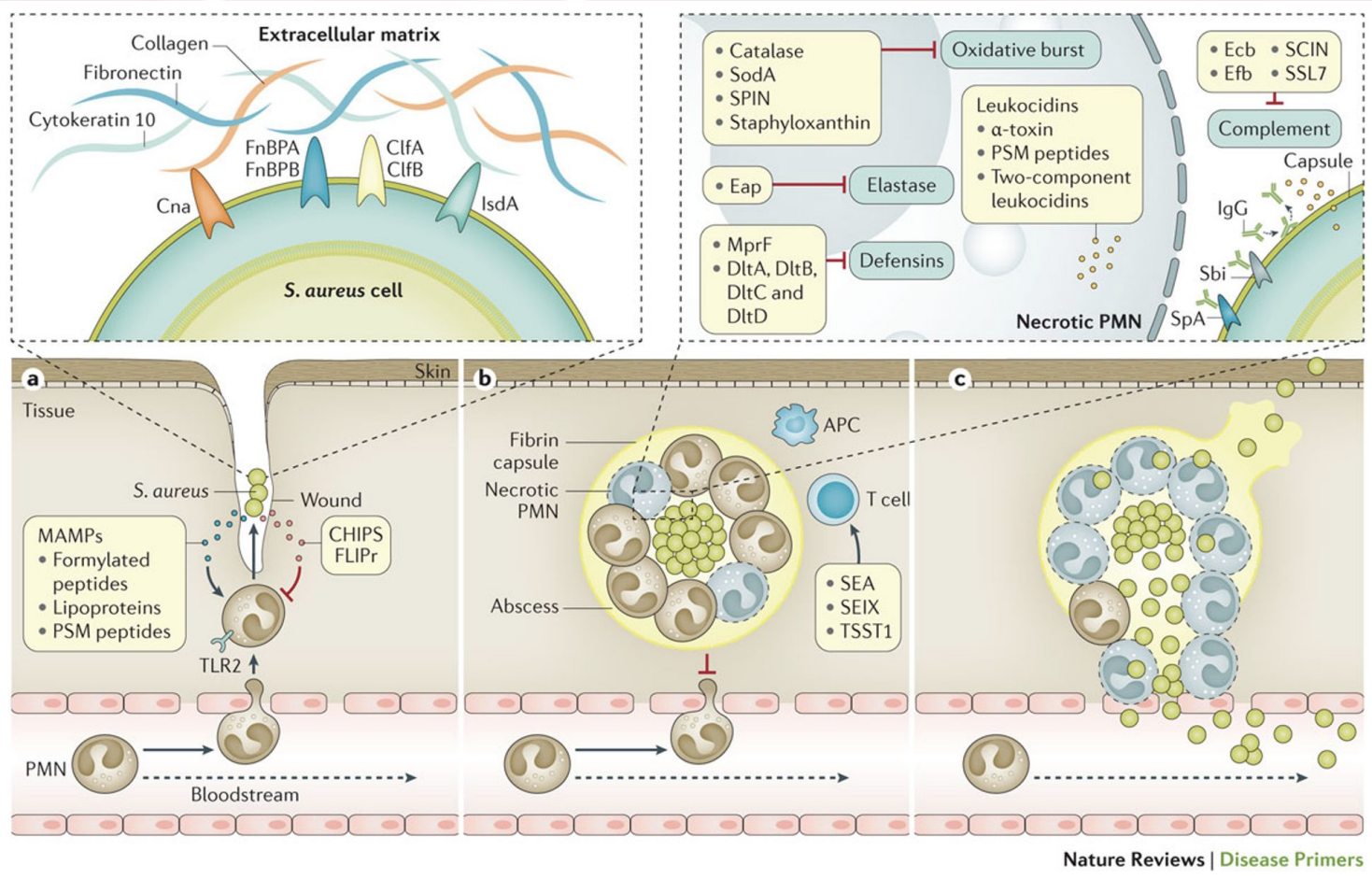
Purulent exudate

04

Toxic Shock Syndrome

Structural components, TSST-1

Pathogenesis



LEE et al, 2018

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Superantigens

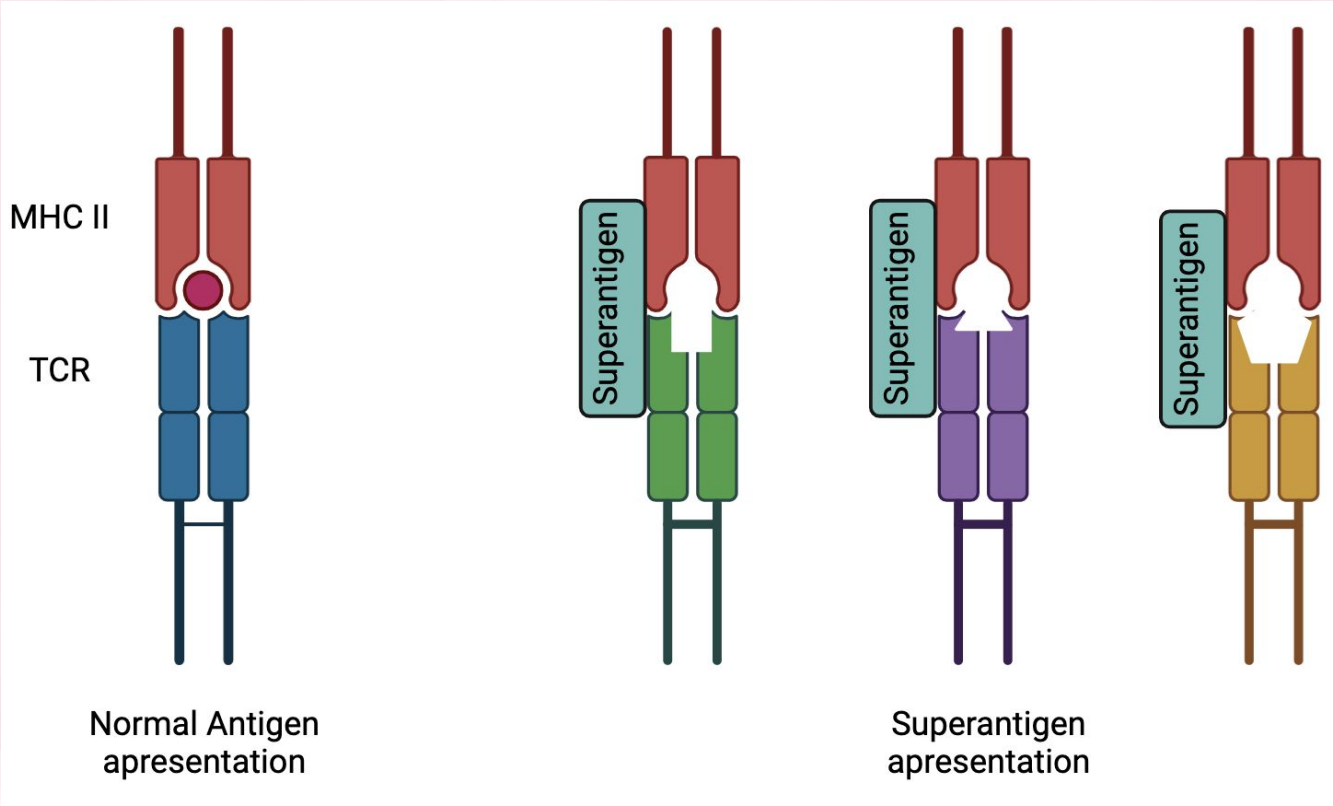


Figure 3: Made with biorender to illustrate the role of superantigen in the binding of MHC class two and the TCR

Diagnosis

01 Tests for coagulase and clumping factor

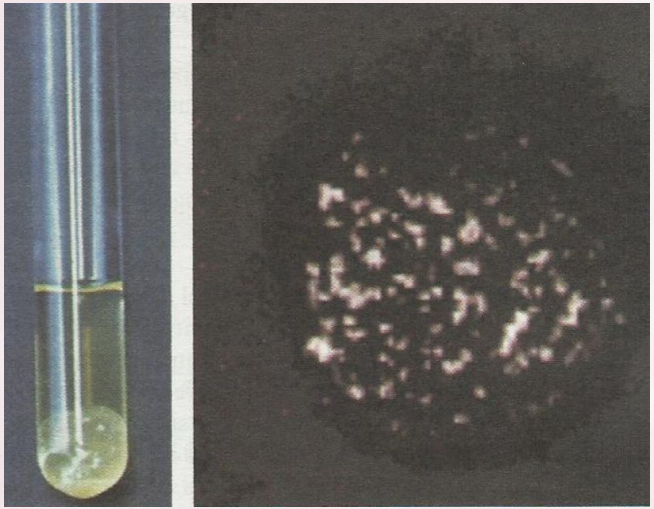


Figure 4: Coagulase positive test and clumping factor positive test

02 Bacterial Culture

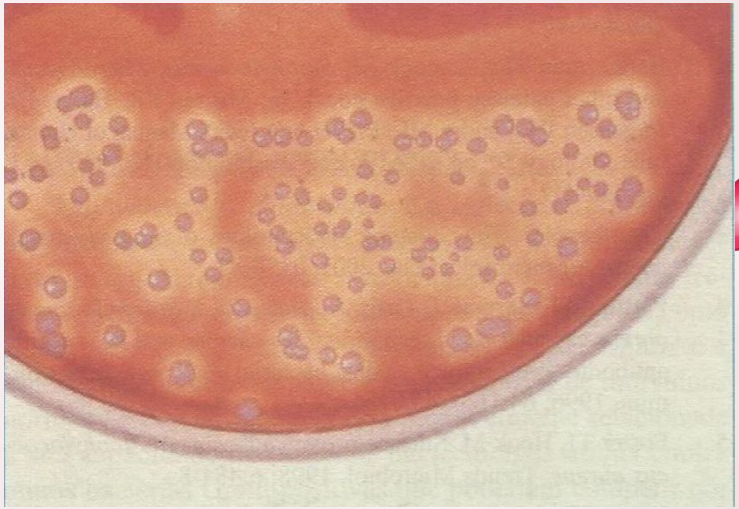


Figure 5: Patients secretion culture in Blood agar

TRABULSI et al, 2008

Treatment and Drug Resistance

01

Susceptible for various drugs?

Penicillin, Cephalosporin, Erythromycin, Aminoglycosides..

02

Multiple Resistance

Gene mutation and/or Gene acquisition

03

Susceptibility tests

Testing a wide spectrum of antibiotics with a patient's sample

04

MRSA

Methicillin-resistant *Staphylococcus aureus*

2 *Pseudomonas aeruginosa*

Characteristics

Gram-negative

Peptidoglycan layer in the periplasmic space

X

Aerobic

Non-fermentative bacterium, uses the glycolytic pathway for glucose degradation

X

Bacillus

With a single flagellum

X

Opportunistic pathogen

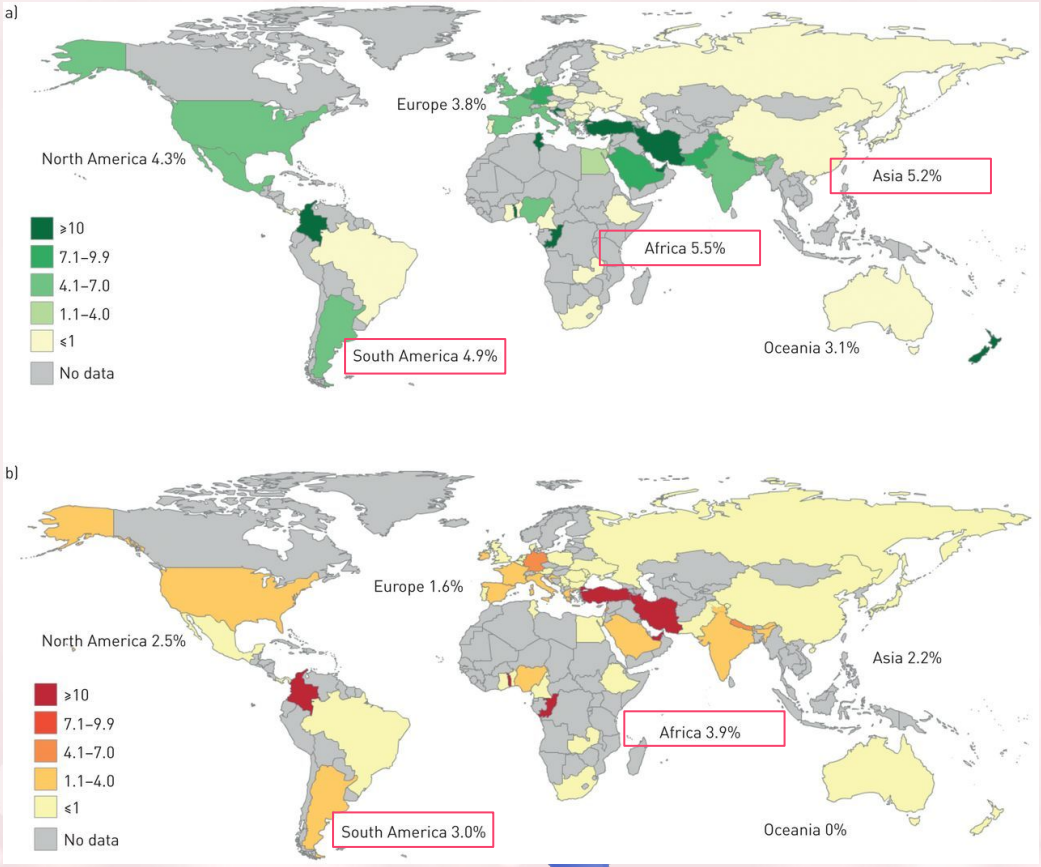
Part of our commensal microbiota

X

BLEVES et al., 2010
WINSTANLEY et al., 2016

Epidemiology

Prevalence of a) *Pseudomonas aeruginosa*-community-acquired pneumonia (CAP) and b) antibiotic-resistant *P. aeruginosa*-CAP by continent



RESTREPO et al, 2018

Virulence

Motility and attachment

Flagellum and the type IV pili

Biofilm formation

Exopolysaccharides (EPSs), alginate, Pel and Psl, and extracellular DNA

Extracellular invasive enzymes and toxins

Extracellular proteases, phospholipases, enzymes and toxins that induce cytotoxicity

Toxic secondary metabolites

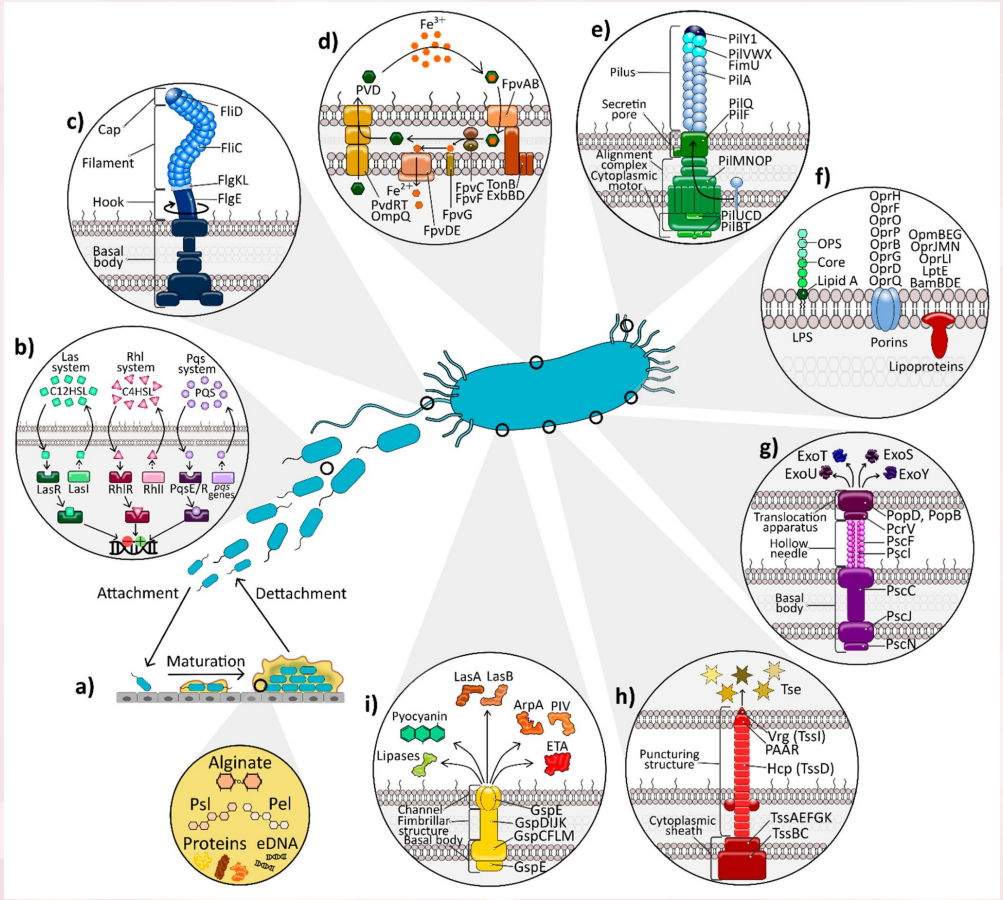
Phenazines and hydrogen cyanide

Iron Acquisition Systems and Factors Controlling Iron Homeostasis

Pyoverdin Ie and pyochelin siderophores and the HasAp hemophore

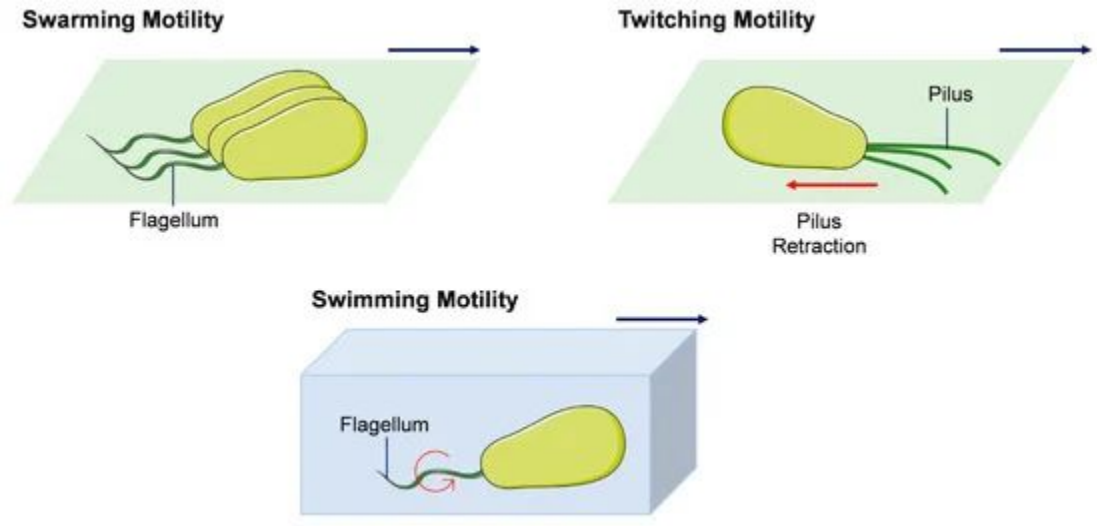
SÁNCHEZ-JIMÉNEZ et al., 2023

Virulence



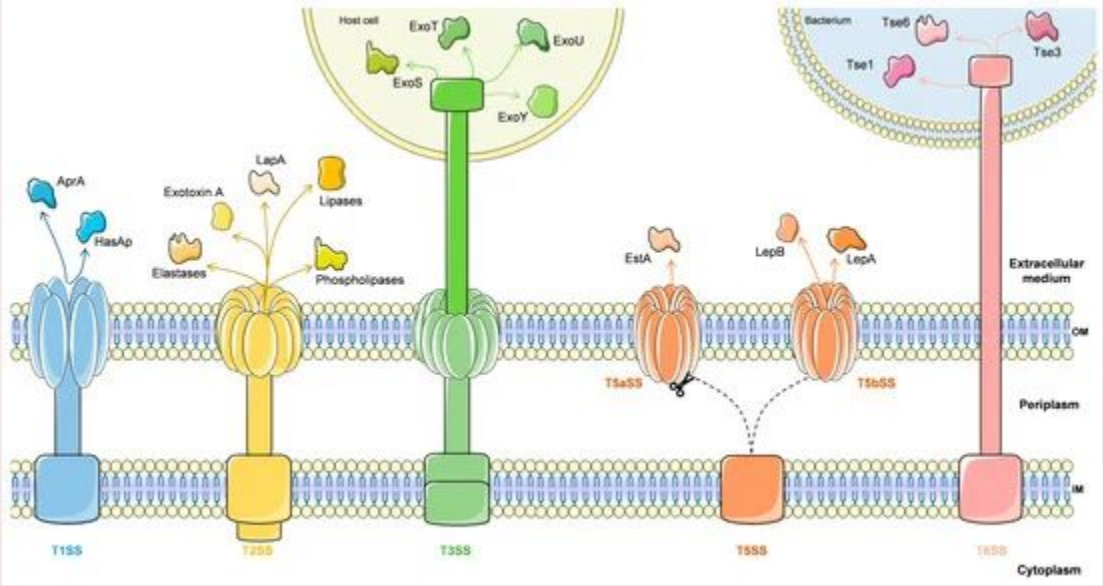
JURADO-MARTIN et al., 2021.

Virulence



SOUZA et al., 2021

Virulence



SOUZA et al., 2021

Pathogenesis

Bacteremia

In immunocompromised hosts

Infections

Acute (planktonic) or chronic (biofilm)

Versatile genome

High rate of pathogenicity

Major cause of infections

Ventilator-associated pneumonia, urinary tract, bloodstream, and chronic infections

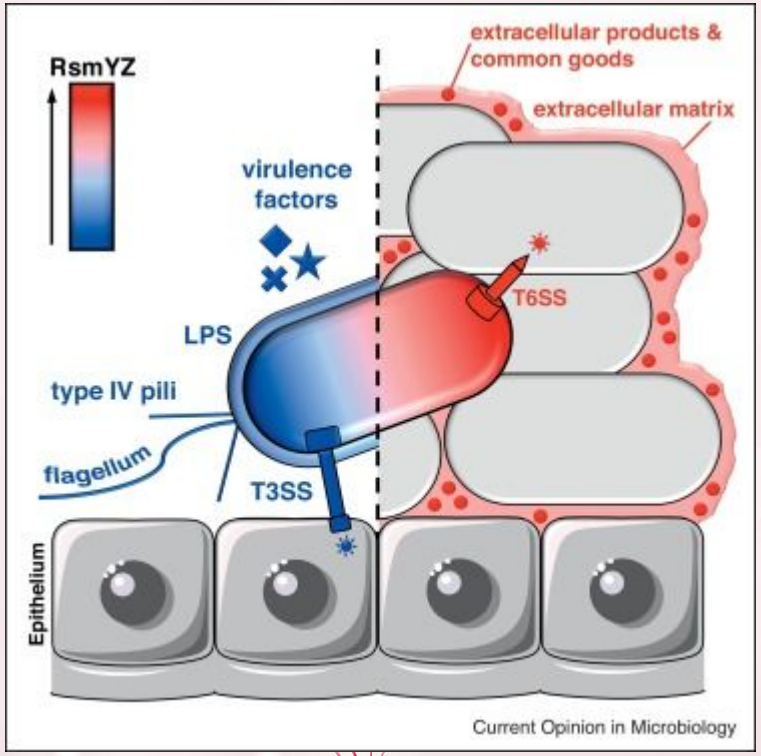
Multidrug resistance

Natural or rapidly developed during treatments

VALENTINI et al., 2018

SOUZA et al., 2021

Pathogenesis



(VALENTINI et al., 2018)

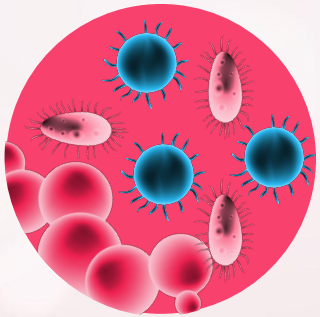
Diagnosis

Sputum collection

Pulmonary infections

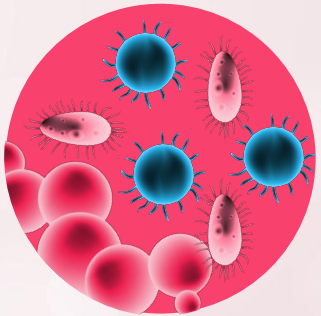
Bacterial culture

Blood, skin lesions, urine secretion from the drain, cerebrospinal or eye fluid



Radioimmunoassay

Urinary tract infections



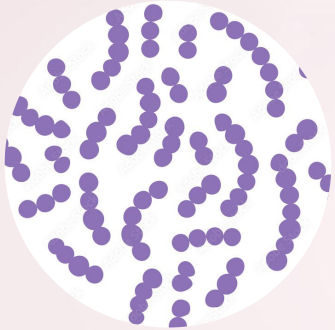
Treatment

Antibiotic therapies

β-lactam-β-lactamase inhibitors
Ceftolozane-tazobactam and ceftazidime-avibactam
Carbapenems
Polymyxins

Non-antibiotic therapies

Inhibition of quorum sensing and bacterial lectins, use of iron chelation, phage therapy, vaccine strategy, nanoparticles, antimicrobial peptides and electrochemical scaffolds

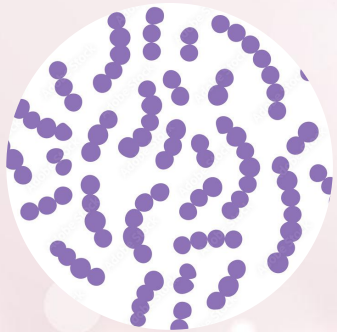


Streptococcus pneumoniae

Characteristics

The symptoms of pneumonia are: chills, fevers, chest pain, shortness of breath, severe cough, stiff neck, headache, earache, mental confusion and pain when looking at bright lights.

Gram-positive



Opportunistic pathogen

Asymptomatically colonizes in the nasopharynx, forming biofilms

Antibiotic resistance

Leading cause of community-acquired pneumonia, meningitis, and otitis media

Wu et al., 2004

Epidemiology

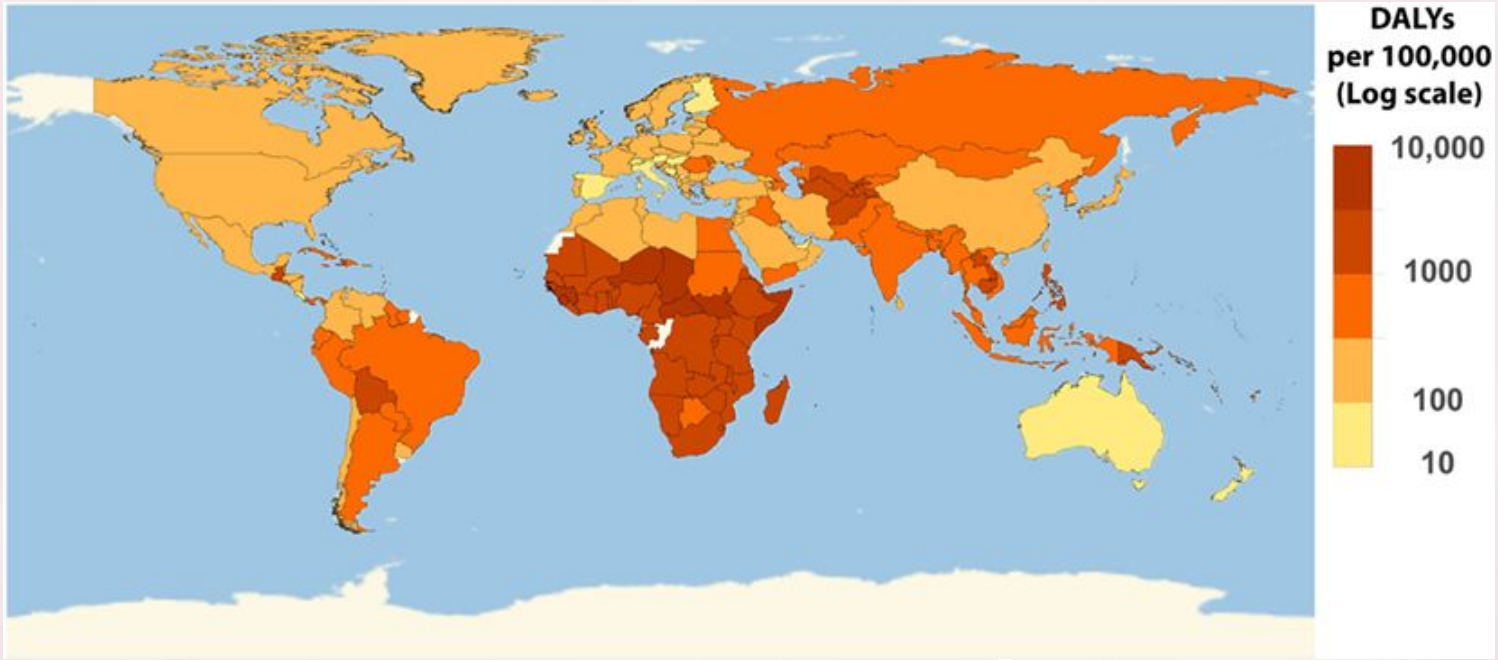


Figure 6: Global distribution of pneumococcal pneumonia

BROOKS e MIAS, 2018

Virulence

01 Capsule

Prevent the bacteria from being phagocytosed by limiting complement activation on its surface, masking of surface antigens and affecting the ability of the bacterium to adhere to and invade the host cell

02 Biofilm

Protection, adherence and survival on surfaces

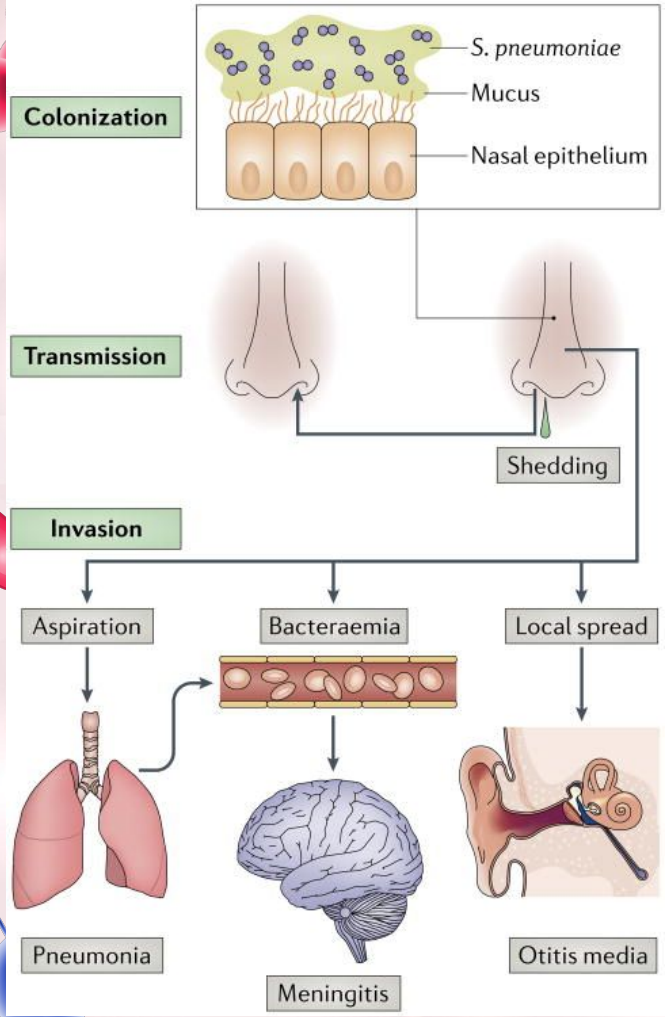
03 Enzymes

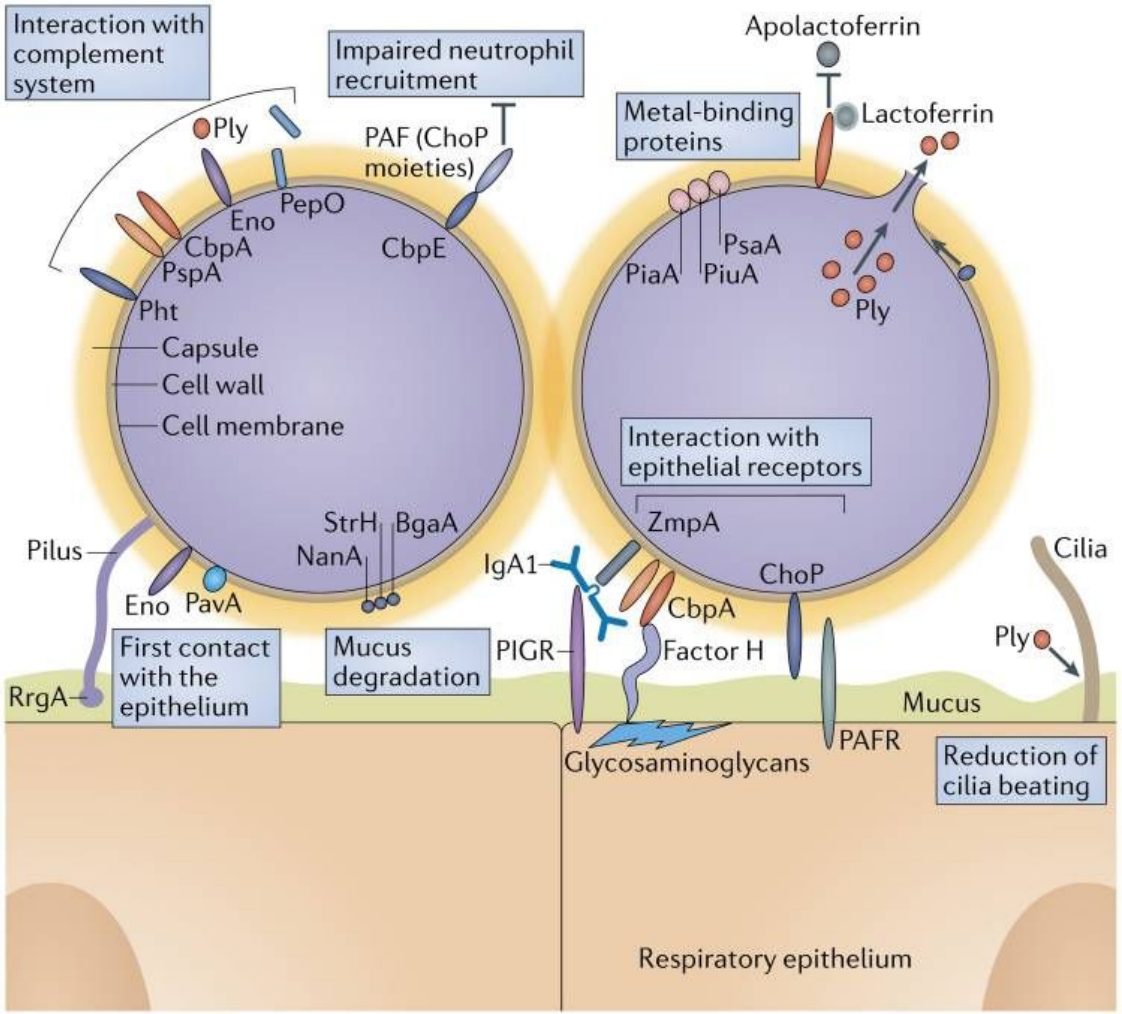
Extracellular enzymes such as protease IgA1, hyaluronidase Hyl and enzymes that inhibit complement activation

04 Toxins

Pneumolysin, pore-forming cytotoxin

ENGHOLM et al., 2017
PARVEEN et al., 2024





WEISER et al., 2018

Vaccine

There are 90 serotypes of S. pneumonia and three vaccines recommended for protection against pneumococcal disease: 2 conjugate and 1 polysaccharide

PCV15 (Vaxneuvance®)

S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F

PCV20 (Prevnar20®)

S. pneumoniae serotypes (1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F)

Pneumococcal polysaccharide vaccine or PPSV23 (Pneumovax 23®)

PPSV23 contains polysaccharide antigen from 23 types of pneumococcal bacteria

CDC, 2024

Diagnosis, drugs resistance and treatment

- Pneumonia is usually diagnosed on the basis of symptoms and there is no investigation into the causative agent
- There is an increase in resistance to the most commonly prescribed antibiotics, such as pelicillin and macrolide.
- Common resistance mechanisms are mutation of the antibiotic target, target modification and efflux transporters.
- However, antibiotics are still the main form of treatment.

LI et al., 2023

Streptococcus pyogenes

Introduction

- *Streptococcus pyogenes* is a significant human-specific bacterial pathogen;
- Causes a broad spectrum of diseases from mild infections (pharyngitis) to life-threatening conditions (necrotizing fasciitis, toxic shock syndrome);
- Inadequate treatment can lead to severe complications such as rheumatic fever and post-streptococcal glomerulonephritis.

Main Characteristics

01 Morphology

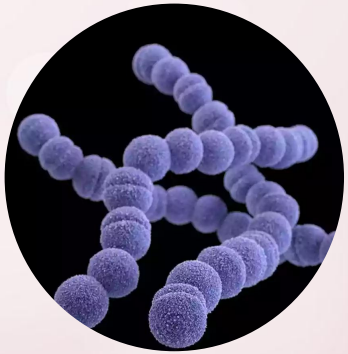
Gram-positive, catalase-negative, β-hemolytic cocci that form chains or pairs.

02 Growth Conditions

Facultative anaerobe, thrives in 5-10% CO_2.

03 Serotyping

Based on M protein – over 80 serotypes identified.



Jennifer Oosthuizen/CDC

Epidemiology

01 Global Burden

18.1 million cases of severe infections globally. 1.78 million new cases per year.

02 Geographical Variability

Prevalence of rheumatic fever higher in developing countries.

In developed countries, invasive infections like necrotizing fasciitis more common.

03 Transmission

Via respiratory droplets, direct contact with infected wounds, or contaminated surfaces.

Virulence

- **M Protein**: Primary virulence factor that helps evade phagocytosis.
- **Capsule**: Composed of hyaluronic acid, further protecting against immune responses.
- **Exotoxins**: Pyrogenic exotoxins cause symptoms like the rash of scarlet fever and toxic shock syndrome.
- Other factors: Streptokinase, streptolysins, and hyaluronidase contribute to tissue invasion and damage.

Pathogenesis

- **Infection Sites:** Pharynx, skin, muscle, fascia, genital mucosa.

- **Invasive Infections**:
  - Necrotizing fasciitis (flesh-eating disease)
  - Toxic Shock Syndrome (TSS)

- **Necrotizing fasciitis:**
  S. pyogenes invades deeper tissues, often through minor skin trauma. Enzymes facilitate rapid tissue destruction. As immune cells are destroyed, inflammation becomes overwhelming, leading to extensive tissue necrosis.

Pathogenesis

- **Toxic Shock Syndrome (TSS):**
  - The exotoxins act as superantigens activating a massive number of T-cells.
  - The excessive T-cell activation triggers a 'cytokine storm’
  - The cytokine storm causes hypotension, vascular permeability, and shock. Blood vessels become leaky, resulting in fluid loss and a drop in blood pressure, which can lead to multiorgan failure.

Diagnosis

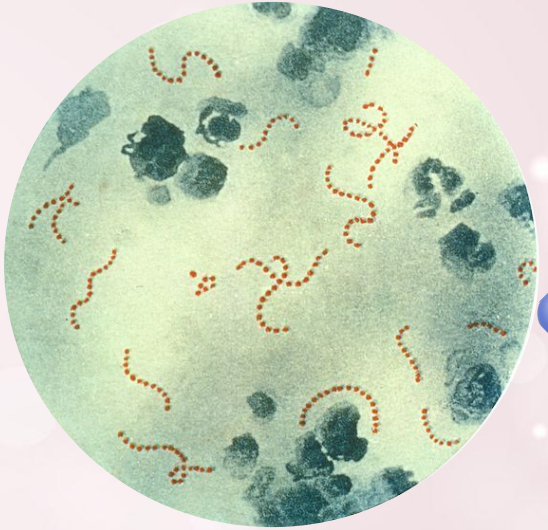
- **Streptococcal Pharyngitis:**
  - Rapid Antigen Detection Test (RADT).
  - Throat culture (gold standard).

- **Necrotizing Fasciitis & TSS:**
  - Blood cultures, imaging (CT, MRI).
  - Clinical signs of rapid tissue destruction and shock.

Treatment

- **Pharyngitis:**
  - Oral penicillin for 10 days or intramuscular benzathine penicillin.
  - Macrolides for patients allergic to penicillin.

- **Invasive Infections:**
  - Intravenous antibiotics (vancomycin or clindamycin).
  - Surgical debridement for necrotic tissue.
  - Supportive care for TSS (IV fluids, ventilatory support, dialysis if needed).



CDC, public domain

Resistance

- **Antibiotic Resistance:**
  - Resistance to macrolides has been observed in some strains.
  - Penicillin remains effective for most S. pyogenes infections.

- **Challenges:** Monitoring resistance trends and ensuring proper use of antibiotics to prevent treatment failure.

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THANKS!

Any questions?