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The Superbug Gonococcus

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Abstract

Human ancestors harbored many of the bacteria (fungi, viruses, & parasites) on their body and also within the body. These bacteria were friendly and thankful to the host. These bacteria got good shelter and nutrition from the host. Bacteria were helping our ancestors, to understand normal and friendly bacteria. Training our immune system to recognize harmful bacteria and destroy them. These bacteria were fighting with harmful bacteria for the space and nutrition. These bacteria are called commensals. If the body's immune system comes down, these commensals may utilize the opportunity and may become pathogenic (opportunistic). To name few commensal organisms on human body are 1) *Staphylococcus epidermidis* in skin, 2) *Cutibacterium acnes* in hair follicles, 3) *Streptococcus mutans* and *Streptococcus salivarius* in oral cavity, 4) *Escherichia coli* in GI tract, 5) *Lactobacillus crispatum* and *Lactobacillus iners* in vagina along with commensal *Neisseria* species (*N lactamica*, and *N mucosa*)[1]. *Neisseria gonorrhoeae* (Ng) species modified itself so well; initially it was a humble pathogen, susceptible to sulfonamides. Over the years, slowly it developed tricks to evade the immune attack, and developed resistance to all the antibiotics which were used to treat it. Today WHO and all researchers call such organisms **"Superbug"**[2].

Keywords: Gonococcus, Protein 1, Protein 2, Protein 3, Pili, OMV (Outer Membrane Vesicles)

1 Introduction

Taxonomic position of Neisseria gonorrhoeae[3, 4]:

1. Kingdom: Bacteria
2. Phylum: Proteobacteria (Pseudomonadota)
3. Class: Beta proteobacteria
4. Order: Neisseria
5. Family: Neisseriaceae
6. Genus: *Neisseria*
7. Species: *Neisseria gonorrhoeae*

1879 – German Physician Albert Neisser discovered "*Neisseria gonorrhoeae*" and clarified that it causes discharging urethritis (STD).

2 Morphology of *Neisseria gonorrhoeae*[5-7]

Neisseria gonorrhoeae is Gram –ve diplococci. The bacteria divides in one plane, the daughter cells do not get separated fully, hence all the time appear as two bacteria together (diplococci). The adjacent faces are flat OR slightly concave, and the outer surface is rounded (convex shape), hence appears kidney-bean shape (coffee-bean shape). Size of

gonococci is 0.6 to 1.0 micron. Organism is non-motile, non-spore forming, and has no cystic stage. When exposed to penicillin like antibiotics, which target cell wall, the organism intelligently gets transformed into “L-forms”. L-forms are altered gonococci, with deficient cell wall and resistant to antibiotics.

Gonococci have pili (fimbria), hands of the organism to attach to the mucosal cells. For growth it requires carbon dioxide, and enriched media like chocolate agar. Organism is highly sensitive to cool temperatures, dryness and fatty acids, with a pH 7.2-7.6.

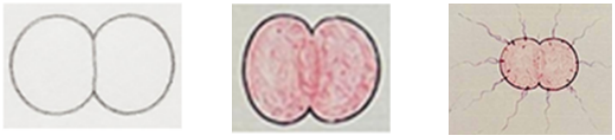

Fig. 1 (Courtesy: Dr Callista Juneja, Dr Geetanjali GD)

1930 – Humble *Neisseria gonorrhoeae* is susceptible to sulfonamide.

As the years passed by, the once humble gonococci realized the Charles Darwin theory “Struggle for existence, and survival of fittest”.

Hence gonococcus to survive in the human host modified its surface molecules, pili proteins, reviewed plasmid and chromosome functions, and today has learnt how to evade an immune attack and antibiotics killing, appreciated from research scholars as “Superbug”.

3 Ultrastructure of *Neisseria gonorrhoeae* (Weapons of the organism)

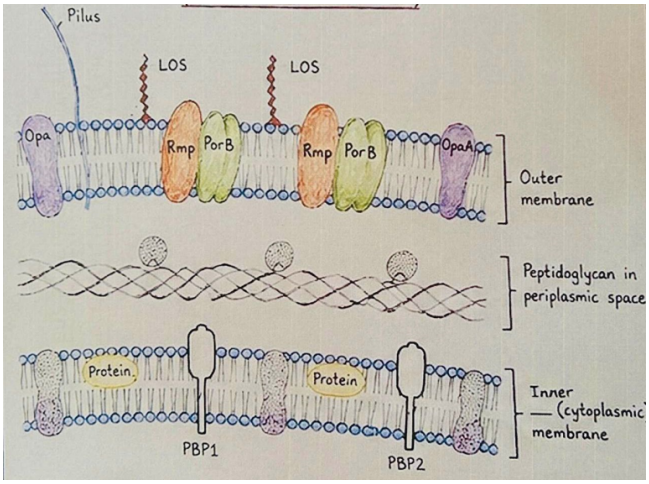

Fig. 2: Schematic structure of the cell wall in gonococcus, Concept in Nm: Thulin Hedberg S, Courtesy: Dr Callista Juneja, Dr Geetanjali GD)

1. Capsule is thin, fragile made of polyphosphate (pseudo capsule), helps the organism to evade immune attack, along with other structures.

2. Trilaminar cell wall consists of a) the outer membrane, b) middle peptidoglycan, and c) inner cytoplasmic membrane.

The outer membrane contains very important constituents (Weapons of organism), to attack host cells, evade immune system, and neutralize the antibiotics. They are a) Phospholipids, b) Lipopolysaccharides, c) Por B (porin or protein 1), d) Opa (opacity associated proteins or protein 2), e) Rmp (reduction modifiable protein or protein 3), f) Omp A (outer membrane protein A),

g) PBP1 & PBP 2 (Penicillin binding protein 1 & 2), h) Tbp 1 & Tbp 2, & Lbp (Transferrin binding protein 1 & 2, Lactoferrin binding protein), and i) Pili (Fimbria).

Phospholipids form the structural lipids of cell wall, protect from host immune system, lyse the phagolysosome membrane inside the neutrophils and protect the bacteria, and forms selective barrier[8, 9].

Lipopolysaccharides are a mixture of lipid A and oligosaccharide, a strong endotoxin. They stimulate innate immunity, triggers the release of cytokines TNFα, and IL-12. Bacteria often alter LOS, using host sugars (Sialic acid), mimic human glycosphingolipids. This helps the bacteria to evade immune recognition, resist complement mediated killing and helps to survive in blood stream. NG changes LOS structure, adapts itself to hide in recess of the host, turns on/off virulence factor, helps the bacteria to have phase variation and antigenic variation. Hence bacteria do not allow buildup of lasting immunity[10].

Por B was called earlier Protein I, and PorB1a. It helps the bacteria to have ion exchange, nutrient acquisition, suppresses host dendritic cells to stimulate proliferation of T cells. Por B plays active role in bacteria to invade host urogenital epithelium and suppress killing mechanism of macrophages and neutrophils[11].

Opa (opacity associated protein or protein 2) is an outer membrane protein, helps in firm adhesion to host epithelial cells, host cells swallow and allow it to invade tissues and cross mucosal barrier. Opa promotes aggregation of bacteria, soon they form micro colonies, on the host surface. Opa is immunogenic, frequently changes its molecules, hence confuse antibodies, and evade immune recognition[12].

Rmp (Reduction modifiable protein) gives stability to outer membrane. Rmp repeatedly stimulates host immune system to produce anti-Rmp antibodies. This anti-Rmp antibodies bind

to Rmp molecules, and do not allow the true bactericidal antibodies to attack Por B, and LOS. Thus, anti-Rmp antibodies can be called as "Blocking antibodies" to true antibodies[13].

Omp A (Outer membrane protein A) maintains structural integrity of outer membrane, help in invading host cells, and also survival of organism inside the neutrophils[14].

PBP1 & PBP 2 (Penicillin binding protein 1 & 2) are enzymes produced by gonococcus, target β-lactam antibiotics like penicillin and ceftriaxone. Gonococci developed resistance to antibiotics, because of these enzymes[15].

Tbp 1 & Tbp 2, & Lbp are Transferrin binding protein 1 & 2, and Lactoferrin binding proteins present on the surface of the gonococcus. Tbp 1 & Tbp 2 extract the iron from transferrin and Lbp extract iron from mucosal lactoferrin. Iron is essential for the growth of gonococci and also for the virulence of gonococci[16].

Pili (Fimbria) are hands of gonococcus, hair like structures, emerging out of the surface of gonococcus. Length is 0.6 nanometers. Kellogg studied morphology of fresh gonococcal colonies and old gonococcal colonies and grouped them into 5 subgroups. They are Type 1 & Type 2 (Virulent organisms, have pili), Type 3 & Type 4 (Non-virulent organisms, no pili, if iron is supplied, they can become pileated and virulent), Type 5 (not pileated, but can develop pili, in the absence of iron). Pili can extend and retract in length on epithelial surface, help the organism to crawl and move. Pili helps the organism to attach to epithelial surface and invade. Pili prevents killing by neutrophils, intracellularly. Pili are made up of 1000s of repeating subunits (monomers). Complete amino acid sequence of strain MS11, and R10 are studied. Variable region of pili changes the surface amino acids, confuse antibodies, and evade the immune attack[17, 18].

4 Resistance to antibiotics[19-21]

Gonococcus has the natural ability to take up DNA from other *Neisseria* species, other bacteria, dying cells, and host cells. Gonococcus process DNA, selectively picks up 10 base sequences (GCCGTCTGAA). Gonococcus utilizes this DNA either as food OR to repair the damaged chromosome and to revitalize the chromosome and plasmid. This revitalized chromosome and plasmid learn to develop resistance from the antibiotics used to treat.

In 1930, sulfonamide was used to treat gonorrhoeae, in 2 years it developed resistance. 1940, penicillin was used (resistance in 1980), 1960, spectinomycin and tetracycline were used (resistance in 1967), 1986 two drugs were used, ciprofloxacin and azithromycin (resistance in 1996), 2010 two drugs were used, ceftriaxone and azithromycin (resistance in 2011).

Newer antibiotics:

1. Zoliflodacin (spiropyrimidinetrione) and 2) Gepotidacin (triazaacenaphthylene) have completed trial III, to treat gonorrhoeae.

5 Conclusion

In the beginning the gonococcus was humble bacteria, susceptible to sulfonamide. Today the organism has learnt many survival tricks of changing surface molecules to evade the immune attack. It picks up the macromolecule DNA, incorporates into its own chromosome and plasmid, learned the tricks to resist the antibiotics used to treat. Today WHO and Researchers call it "The Superbug".

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