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Chapter

Cell Surface and Cytosolic Proteins of Group B Streptococcus Adding New Dimensions in Its Colonization and Pathogenesis

Manju Ohri Pai, Venkatesh Srinivasa Pai, Pratima Gupta and Anuradha Chakraborti

Abstract

Streptococcus agalactiae or Group B streptococcus (GBS) is an opportunistic human pathogen known for their invasive diseases caused in newborns, pregnant women, and nonpregnant adults. This pathogen even being an asymptomatic colonizer of adult humans, still they result in a broad range of disease manifestations starting from mild skin diseases to pneumonia, meningitis, and septicemia. Of the 10 GBS capsular types, the majority of invasive neonatal diseases are associated with the serotype III. GBS is a pathogen that has developed some strategies to resist host immune defenses. The formidable array of GBS virulence factors makes this bacterium at the forefront of neonatal pathogens. The involvement of bacterial components in the host-pathogen interaction of GBS pathogenesis and its related diseases is thought to be due to a variety of virulence factors expressed by *Streptococcus agalactiae*. Pathogenic factors of streptococcus promote infections by their coordinated activity. These factors/determinants initially get a stimulus by the communication between specific ligands and their respective receptors in a host-pathogen interaction. These in turn activate adhesion and invasion mechanisms by mediating the attachment of pathogen via cell wall associated/secretory proteins, e.g., adhesins followed by their entry into the host cell eventually deciding their fate to live by activation of mechanisms like phagocytosis. These mediators/determinants also modulate the immune responses by the host toward the pathogen. A number of new GBS surface-exposed or secreted proteins have been identified (GBS immunogenic bacterial adhesion protein, leucine-rich repeat of GBS, serine-rich repeat proteins), the three-dimensional structures of known streptococcal proteins (αC protein, C5a peptidase) have been solved, and an understanding of the pathogenetic role of "old" and new determinants has been better defined in recent years. Recently, a 39kDa Invasion Inhibitory Factor (IIF) was isolated from GBS playing an important role in its invasion. A homogeneous non-toxic 39 kDa factor from the cytosol of GBS showing a homology with xenobiotic response element type transcriptional regulator protein adds another quill to the GBS protein panama, thus indicating that such protein molecules can be efficiently explored as suitable vaccine candidates. These observations add a novel aspect to bacterial pathogenesis where bacteria's own intracellular protein component can act as a potential therapeutic candidate by decreasing the severity of disease thus promoting its invasion inhibition.

Keywords: group B streptococcus (GBS), *Streptococcus agalactiae*, pathogenesis, cytosolic proteins, invasion

1. Introduction

Fry, in 1938 was the first to report Lancefield Group B β-hemolytic streptococci in three patients with puerperal sepsis [1]. After that, many sporadic cases were reported from different parts of the world in next 30 years but still this organism remained unexplored and unnoticed for most of the clinicians [2–4]. Then after reports of emerging GBS infections in neonates was followed up by increasing reports of infections in neonates followed by reports from pregnant women with localized uterine infection or chorioamnionitis commonly associated with bacteremia. The prognosis was found good with antimicrobial therapy. In other adults, the underlying infection often leads to fatality [5]. Till the 1990s, the scenario of GBS infection was the same, then after there was a substantial decline in reports of GBS infections. Current nomenclature designates polysaccharide antigens as type antigens with antigenically distinct types, Serotype Ia through IX, now are characterized. Complete genome sequence of type III and V (most common and virulent serotypes) opened new avenues for identification of novel potential vaccine targets [6, 7]. Early concepts suggested a thick, rigid peptidoglycan layer external to the cytoplasmic membrane surrounded by concentric layers of cell wall antigens. In accordance with the Lancefield's classification, there are different Group specific carbohydrates. These group specific carbohydrates were initially thought to be covered by a type-specific capsular polysaccharide (CPS), which was further deciphered by a study model showing evidences where group B carbohydrate and the CPS are linked independently to cell wall peptidoglycan [8]. Immunoelectron techniques using reference strains with homologous type-specific antisera reveals abundant CPS on Lancefield prototype strains Ia, II, III, IV, V, and VI, whereas less dense capsules are found on type Ib [9–11]. Studies also reveal that the expression of these capsular structures can be regulated by altering the cell growth. In addition, the ultrastructural studies using immunogold labeling and transmission electron microscopy shows that C protein also has a surface location along with GBS pilus-like structures that extend from the bacterial surface [12, 13].

2. GBS disease outcomes

GBS is also known to be a leading cause of pneumonia and sepsis in newborns which can lead to fatal complications. As a resident of the maternal genital tract, during delivery, it may become a major cause of colonization and infection in the newborns. The neonate gets exposed to this organism through the birth canal through an ascending route in-utero via the intact or ruptured membranes, thus leading to neonatal infections. A vertical transmission of 29–85% with a mean rate of approximately 50% was reported among newborns born to women from whom GBS was isolated either from their vagina or rectum or both during delivery. In contrast, only 5% of neonates are reported to be asymptomatically colonized at one or more sites during their first 48 h of life from mothers who are culture negative for GBS [14]. The risk of a neonate acquiring colonization by the vertical route correlates directly with the density of colonization (inoculum size). Majorly the transmission route is fecal oral. The GBS colonization acquired vertically or horizontally in neonates or young infants usually persists for weeks or months.

The mode of transmission likely is fecal-oral. Whether acquired by vertical or horizontal mode, colonization of mucous membrane sites in neonates and young infants usually persists for weeks or months [15].

It has also emerged as the third most common cause of infantile pyogenic meningitis [1, 2]. Exposure of pregnant females to this organism in developed and developing countries seem to be similar however, it is confusing to see an apparent lower incidence of GBS in less developed or developing countries. The data shows that in developed countries, neonatal GBS disease occurs 0.4–1.4 per 1000 live births with a fatality of up to 60%. Studies conducted in different centers during the 1990's in developing nations fail to identify this pathogen [16]. Recent studies in Malawi, however had mixed results showing GBS as an important cause of neonatal sepsis [17] while very few studies are from India, showing 6.2% Early onset disease (EOD) burden and Nigeria still fail to report any disease burden [18–20] Several reasons are hypothesized that why the disease burden may be low in certain developing countries. First, there may be low maternal GBS colonization, which could then lead to low neonatal disease burden. Secondly, poor or less awareness among the pregnant mothers for GBS testing during their course of pregnancy. Few studies conducted in developing countries have reported quantitative maternal genital colonization, and those that have, reported a low prevalence of maternal GBS colonization [21]. In 2002, the implementation of guidelines to prevent early onset neonatal sepsis and screening at 35–37 week of gestation of pregnant women tremendously decreased the incidence of GBS infections [22]. Maternal postpartum sepsis and infective endocarditis are also important complications associated with GBS infections [5, 23, 24]. In the recent years, osteomyelitis and septic arthritis often involving the knee, hip, or shoulder joints are also part of the GBS disease spectrum specially seen in adults [25].

2.1 Host-bacterial interactions in pathogenesis

Pathogenesis of any organism is a multistep, sequential invasion in the host cells mediated by specific molecules (may it be proteins, lipids or carbohydrate-protein complexes), which bring about the pathogen-host cell interaction by standard receptor-ligand interactions. Group B Streptococcus pathogenesis is also thought to be a multistep process [26]. In the ocean of many other pathogenic bacteria, GBS encodes a number of virulence factors for its pathogenesis. The colonization and breaching of mucosal surfaces by GBS thus allows its entry to normally sterile sites like blood stream, CNS and fetal membranes [27, 28]. The main virulence factor of GBS is thought to be pore forming toxins (Beta hemolysins/cytolysins and CAMP factor) and sialic acid rich CPS. Their virulence potential is because of its antiphagocytic properties [29]. Till date, nine serotypes (I to IX) on the basis of the capsular polysaccharide have been reported. The CPS also has a pivotal role in preventing complement activation, therefore does not influence adherence of GBS to epithelial cells but does reduce internalization [30]. Previous reports have shown that Serotype III accounts for approximately 50% of all neonatal infections as well as approximately 90% of cases of neonatal meningitis in US [31, 32]. Our earlier study has also shown that Type III isolates are more predominant as compared to other serotypes both in their invasiveness and biofilm formation [33]. Despite the advancement of the understanding about various virulence factors, their understanding on the regulation and use of these virulence tools has not yet been much explored. Thus, intensive investigations are done to elucidate the pathogenesis of GBS infection in neonates. The exclusive clinical features of GBS infection pose several questions that provide an agenda for hypothesis development (a hypothetical model) and experimental testing (**Figure 1**):

1. How does the organism colonize pregnant women and gain access to the infant before or during delivery?

2. How do these bugs gain entry to the bloodstream and cross the blood–brain barrier?

3. How does GBS evade host innate immune defenses?

4. What factors of GBS induce sepsis?

5. Is there any role of intracellular factors of GBS in its pathogenesis?

6. How does the regulation of virulence factors occur during infection?

Some advancement in knowledge of pathogenesis has been achieved through development of cell culture systems and animal models. Many cell surface proteins, and other moieties including lipid moieties have been studied for their role in host-pathogen interactions. However, not much about the cytosolic proteins of GBS is known. The group B streptococcal virulence factors defined to date, with proposed role in pathogenesis, are shown in **Table 1** and discussed briefly below.

The process of human infection by group B Streptococcus (GBS) is complex and multifactorial. Adhesion and invasion of streptococci into the host cell involves a number of pathogen-host cell interactions (**Figure 2**). Their entry and survival inside the respiratory epithelial cells may represent a mechanism by which these bacteria gain access into the blood circulation [35–37]. Two main cell types, respiratory epithelial cells and resident alveolar macrophages, are encountered by GBS infecting the lung [38–40]. The former is the sentinel barrier for the streptococcal transcytosis into deeper tissues and thereafter into the bloodstream. Streptococcal surface-associated proteins are critically important in the host- pathogen relationship as they can provide initial contact of the bacteria with its intended host before internalization [41]. An immunologic response is generated once GBS penetrates into lung tissue or bloodstream of newborn infant. This is followed by invitation to

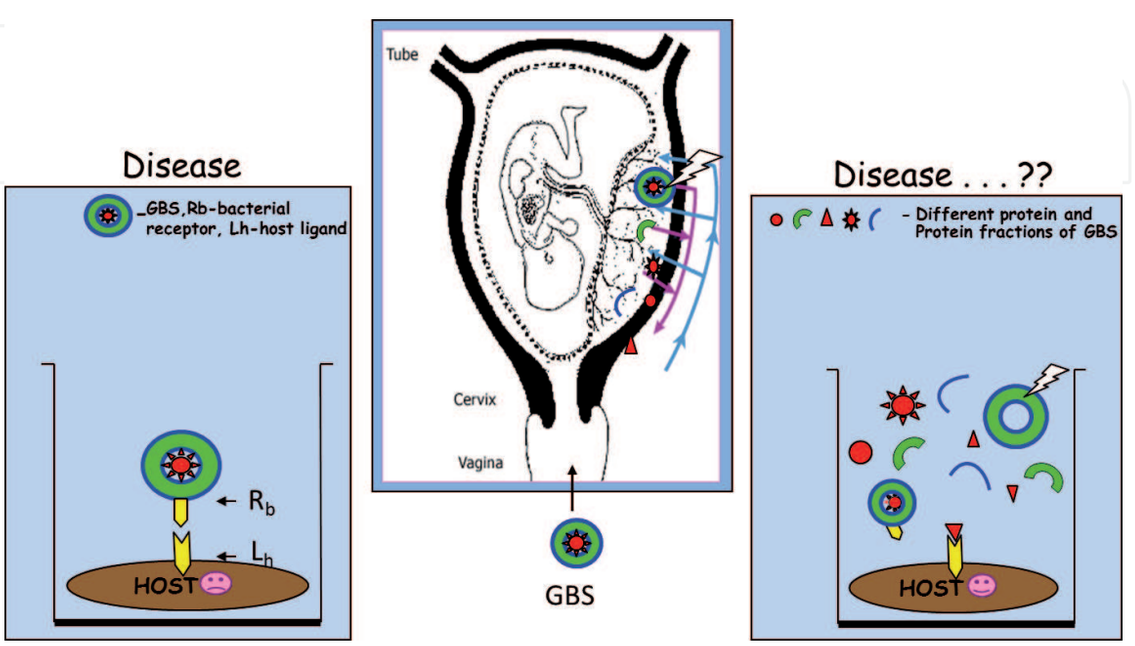

Figure 1.
Hypothetical model of host-pathogen interaction of GBS.

Virulence factor	Role in pathogenesis
Host cell adherence and invasion	
C surface protein	Adherence and invasion of epithelial cells
Lipoteichoic acid	Attachment of epithelial cells
Fibrinogen receptor, FbsA	Attachment of epithelial cells
C5a peptidase	Adherence and invasion of epithelial cells
Surface protein Lmb	Attachment of epithelial cells
Spb1 surface protein	Invasion of epithelial barriers
iagA gene	Promotes blood brain barrier invasion
Host tissue insult	
Beta-hemolysin/cytolysin	Damage and spread through tissues
Hyaluronate lyase	Promotes spread through host tissues
CAMP factor	Direct tissue injury
Molecules in immune evasion	
Exopolysaccharide capsule	Blocks opsonophagocytic clearance
C5a peptidase, ScpP	Inhibits neutrophil recruitment
CAMP factor	Impairment of antibody function
Serine Protease, CspA	Blocks opsonophagocytosis
Fibrinogen receptor, FbsA	Blocks opsonophagocytosis
C Protein	Blocks opsonophagocytosis
Beta-Hemolysin/cytolysin	Impairment of phagocyte killing
Superoxide dismutase	Impairment of oxidative burst killing
Carotenoid pigment	Impairment of oxidative burst killing
Dlt operon genes	Interferes with antimicrobial peptides
Penicillin binding protein Ia	Interferes with antimicrobial peptides
Molecules as inflammatory mediators	
Cell wall LTA	Cytokine activation
Cell wall peptidoglycan	Cytokine activation
Beta Hemolysin/cytolysin	Triggers iNOS and Cytokine release

Table 1.
GBS virulence factors and their role in pathogenesis.

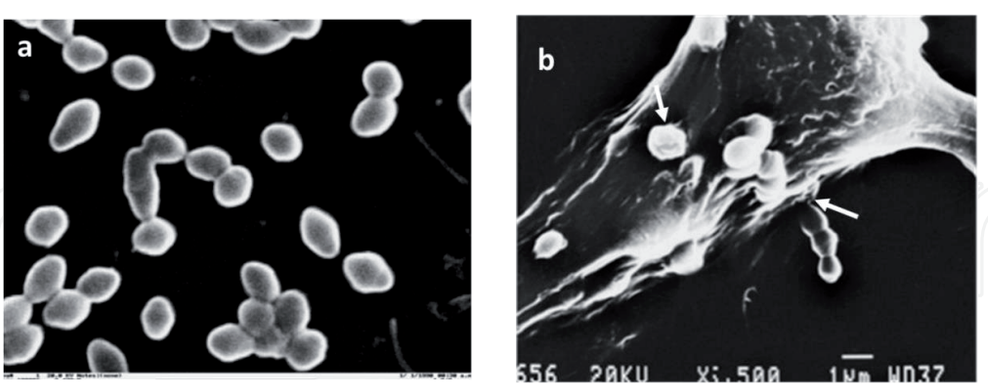

Figure 2.
Scanning electron micrograph (SEM) of (a) GBS, (b) GBS adhering to and invading into A549 cells (courtesy: Ohri et al. [34]).

host phagocytic cells like neutrophils and macrophages leading to bacterial uptake and opsonization by specific antibodies in the presence of complement [42–44]. Primarily sialic acid derivatives i.e. sialylated Group B Streptococcal polysaccharide capsule are the one to confront for opsonization mediated phagocytic killing followed by the other serotype specific epitopes of GBS capsular polysaccharide (CPS). It is also suggested that GBS may be chiefly a taxing human pathogen because its sialylated capsule has undergone selection to resemble host 'self' thus avoiding immune recognition. Surface proteins of GBS have high efficiency to avoid

opsonophagocytosis along with CPS. C protein or its components resist phagocytic killing and inhibits its interaction with complement or IgG [45]. A cell surface protease CspA, targets host fibrinogen producing adherent fibrin like cleavage products that coat the bacterial surface and interfere with opsonophagocytic clearance [46].

With a big pool of virulence factors encrypted by GBS, it has been confirmed to adhere to a variety of eukaryotic cellular structures. ECM proteins including laminin, fibronectin, fibrinogen, cytokeratin and plasminogen facilitates interaction with host-cell surface integrins thus promoting the entry of GBS into the varied host cells [41]. The initial step of adherence is thought to be mediated by a number of bacterial moieties such as laminin binding proteins, C5a peptidase, glyceraldehyde phosphate dehydrogenase, α-enolase and lipoteichoic acid [47]. In addition to adherence facilitating moieties, alpha C protein and invasion associated gene (iagA) are important molecules in the process of GBS invasion in host cells. Genome-wide phage display technique revealed a fibronectin-binding property associated with the surface-anchored group B streptococcal C5a peptidase, ScpB [48]. This dual functionality of ScpB was confirmed by decreased fibronectin binding of isogenic ScpB mutants and the direct interaction of recombinant ScpB with solid-phase fibronectin [48, 49]. Similar targeted mutagenesis studies showed that adherence of GBS to laminin involves a protein adhesin called Lmb [50], repetitive motifs within the surface-anchored protein FbsA mediates attachment to fibrinogen [51], and binding to human keratin 4 is carried out by the serine rich repeat domain protein Srr-1 [52]. Recently, GBS were revealed to express filamentous cell surface appendages known as pili [36]. Pili mediate GBS resistance to AMP's (antimicrobial peptides) and also aid in its attachment to the host cells. Two genetic loci have been found on GBS genome, which are responsible for pilus like structures. Among eight sequenced GBS genomes, not all genomes contain both loci [53]. One of these islands includes genes encoding PilB, an LP(x)TG motif–containing protein that polymerizes to form a pilus backbone and is the major structural component of GBS pili, along with accessory pilus proteins PilA and PilC [53, 54]. Isogenic GBS mutants lacking PilA or PilC showed decreased adherence to epithelial cells, but not mutants lacking the PilB backbone. In addition, the crystal structure of PilC reveals a specific IgG-like fold domain (N2) required for epithelial cell binding [54]. Upon bacterial binding to the host cell receptors, recruitment of host-cell actin to the site of bacterial entry has been observed [55, 56]. However, there are some studies which have shown that certain bacterial surface proteins like type III CPS and the N-terminal region of the alpha C protein partially mask the specific components of GBS that are critical for adherence/invasion of eukaryotic cells [29, 57, 58]. Thus decreasing the adherence and invasion efficiency of GBS to host cells. Similarly, Burnham et al., showed prior treatment of the epithelial cells by exogenous addition of phosphoglycerate kinase (PGK, a cell surface and a cytosolic protein of GBS) inhibited GBS internalization [40]. PGK as a major outer surface protein of GBS which showed a similar inhibitory effect using saccharomyces derived PGK in Type V GBS invasion. PGK from other sources like *Candida albicans* and *Schistosoma mansoni* has also been used to study host-pathogen interactions specifically invasion and adherence mechanisms [58–60]. Boone et al. [57] showed GBS-PGK released from the bacterial cell binds to plasminogen and actin. These secreted proteins demonstrate an interaction between the bacterial protein and their host cell receptors [61]. However, as reported by Hulse et al. [62] Type III capsular polysaccharide is also reported to attenuate invasion if pre-incubated with the host cells. A similar study was performed with Lactoferrin, an antimicrobial peptide, showing its invasion inhibitory activity on a broad range of organisms including streptococcus [61]. There are many other studies which report that cell surface molecules can also be used to inhibit adherence and invasion in bacteria. A recent published study

from our lab has reported the role of a cytosolic protein in inhibition of invasion of GBS into eukaryotic epithelial cells [34]. A 39 kDa invasion inhibitory factor (IIF) isolated from cytosol of GBS showed almost 70–80% reduction in invasion as compared to the crude cytosolic fractions indicating an anti-internalization mechanism. N-terminal sequence showed its homology with a xenobiotic response element(XRE) type transcriptional regulator protein. This family of transcription factors controls various metabolic functions in the bacteria, thus emphasizing on its probable role in pathogenesis as well [63]. Studies like these raise a question as to how an organism can itself contain or manufacture such a factor which can inhibit its own mechanism of pathogenesis thus indicating that bacteria's own components can also play an important role in its adherence and invasion process.

As most pregnant women have low concentrations of type-specific IgG in their sera, immunization of women during adolescence, before pregnancy, or in late pregnancy (i.e., early third trimester) would be the best approach for immunoprophylaxis [64]. In view of the substantial disease burden in nonpregnant adults, targeted adult immunization (e.g., diabetics or adults "65 years old) also is an attractive prevention strategy. GBS serotypes Ia, III, and V are reported to be most invasive forms to cause disease in infants and adults followed by serotypes Ib and II that account for 75–85% of infections [65–68]. The production of a trivalent or a pentavalent conjugate vaccine is technically achievable. The cost of developing suitable vaccines, although substantial, is considerably less than the death, disability, and treatment associated with these infections [69, 70]. In 2014, World Health Organization convened the first meeting for consultation on GBS vaccine development, focusing on the GBS maternal immunization program, which was aimed at reducing infections in neonates and young infants worldwide [70].

3. Conclusion

Despite the availability of the genome sequence of GBS, advances have been made in deciphering the various facets of molecular mechanisms involved in disease pathogenesis. This has taken our knowledge a step forward in knowing the pivotal role of certain molecular targets which can be explored as target vaccine candidates. Though, GBS being a commensal and an adaptable organism which adjusts its niche according to the environment, it fine tunes its gene expression for its pathogenesis paradigms. Thus, it becomes more imperative to understand how this pathogen responds to its external environment to appropriately express this large repertoire of factors for colonization or invasion of the host tissue targets, which is still under infancy. As it is commonly said 'Prevention is better than Cure', thus to prevent GBS disease the physicians, public health officials, parents, and patients must join hands and campaign for pregnant women, neonates and young infants, and at-risk adults.

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Conflict of interest

There are no conflicts of interest.

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References

[1] Fry RM. Fatal infections by haemolytic streptococcus group B. Lancet. 1938;**1**:199-201

[2] Franciosi RA, Knostman JD, Zimmerman RA. Group B streptococcal neonatal and infant infections. The Journal of Pediatrics. 1973;**82**:707-718

[3] Baker CJ, Barrett FF. Transmission of group B streptococci among parturient women and their neonates. The Journal of Pediatrics. 1973;**83**:919-925

[4] Howard JB, McCracken GM Jr. The spectrum of group B streptococcal infections in infancy. American Journal of Diseases of Children. 1974;**128**:815-818

[5] Farley MM, Harvey RC, Studell T, Smith JD, Schuchat A, Wenger JD, et al. A population based assessment of invasive disease due to group B streptococcus in non-pregnant adults. The New England Journal of Medicine. 1993;**328**:1087-1811

[6] Tettelin H, Masignani V, Cieslewicz MJ, et al. Complete genome sequence and comparative genomic analysis of an emerging human pathogen, serotype V Streptococcus agalactiae. Proceedings of the National Academy of Sciences of the United States of America. 2002;**99**(19):12391-12396

[7] Glaser P, Rusniok C, Buchrieser C, Chevalier F, Frangeul L, Msadek T, et al. Genome sequence of Streptococcus agalactiae, a pathogen causing invasive neonatal disease. Molecular Microbiology. 2002;**45**:1499-1513

[8] Deng L, Kasper DL, Krick TP, Wessels MR. Characterization of the linkage between the type III capsular polysaccharide and the bacterial cell wall of group B streptococcus. The Journal of Biological Chemistry. 2000;**275**:7497-7504

[9] Kasper DL, Baker CJ. Electron microscopic definition of surface antigens of group B streptococcus. The Journal of Infectious Diseases. 1979;**139**:147-151

[10] Christina VH, Laura P, Luciana T, Simona R, Giovanna A, Laura N, et al. Immunochemistry of capsular type polysaccharide and virulence properties of type VI *Streptococcus agalactiae* (group B streptococci). Infection and Immunity. 1993;**61**:1272-1280

[11] Rýc M et al. Immuno-electronmicroscopic demonstration of capsules on group-B streptococci of new serotypes and type candidates. Journal of Medical Microbiology. 1988;**25**:147-149

[12] Paoletti LC, Ross RA, Johnson KD. Cell growth rate regulates expression of group B streptococcus type III capsular polysaccharide. Infection and Immunity. 1996;**64**(4):1220-1226

[13] Lauer P, Rinaudo CD, Soriani M, Margarit I, Maoine D. RosiniR et al, genome analysis reveals pili in group B streptococcus. Science. 2005;**309**:105

[14] Schrag SJ, Zywicki S, Farley MM, Reingold AL, Harrison LH, Lefkowitz LB, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. The New England Journal of Medicine. 2000;**342**:15-20

[15] Ancona RJ, Ferrieri P, Williams PP. Maternal factors that enhance the acquisition of group B streptococci by newborn infants. Journal of Medical Microbiology. 1980;**13**:273-280

[16] Le Doare K, Heath PT. An overview of global GBS epidemiology. Vaccine. 2013;**31**(Suppl 4):D7-D12

[17] WHO. World Health Organization Young Infants Study Group. Conclusions

from the WHO multicenter study of serious infections in young infants. Pediatric Infectious Disease Journal 1999b;**18**(Suppl.):S32-S34

[18] Gray KJ, Bennett SL, French N, Phiri AJ, Graham SM. Invasive group B streptococcal infection in infants, Malawi. Emerging Infectious Diseases. 2007;**13**(2):223-229

[19] Delair S, Mukhtar M, Olateju E, et al. Isolates from bacteremic neonates in central Nigeria - a pilot study. In: World Society of Pediatric Infectious Diseases Conference; Cape Town, South Africa; 2013

[20] Sridhar S, Grace R, Nithya PJ, Balaji V, Niranjan T, Manish K, et al. Group B streptococcal infection in a tertiary hospital in India--1998-2010. The Pediatric Infectious Disease Journal. 2014;**33**(10):1091-1092

[21] Viswanathan R, Singh AK, Basu S, et al. Multi-drug resistant gram negative bacilli causing early neonatal sepsis in India. Archives of Disease in Childhood. Fetal and Neonatal Edition. 2012;**97**(3):F182-F187

[22] Stoll BJ, Schuchat A. Maternal carriage of group B streptococci in developing countries. The Pediatric Infectious Disease Journal. 1998;**17**(6):499-503

[23] CDC. Prevention of perinatal group B streptococcal disease: Revised guidelines from CDC. MMWR August 16, 2002/51(RR11); 1-22

[24] Schuchat A. Epidemiology of group B streptococcal disease in United States: Shifting paradigms. Clinical Microbiology Reviews. 1998;**11**:497-513

[25] Schuchat A, Wenger JD. Epidemiology of group B streptococcal disease: Risk factors, prevention strategies and vaccine development. Epidemiologic Reviews. 1994;**16**:372-402

[26] Farley MM. Group B streptococcal disease in non-pregnant adults. Clinical Infectious Diseases. 2001;**33**:556-561

[27] Tamura GS, Kuypers JM, Smith S, Raff H, Rubens CE. Adherence of group B Sterptococci to cultured epithelial cells: Role of environmental factors and bacterial surface components. Infection and Immunity. 1994;**62**:2450-2458

[28] Doran KS, Chang CW, Jennifer VM, Eckmann BL, Nizet V. Group B streptococcal beta-hemolysin/cytolysin promotes invasion of human lung epithelial cells and the release of IL-8. The Journal of Infectious Diseases. 2002;**185**:196-203

[29] Bolduc GR, Baron MJ, Gravecamp C, Lachenauer CS, Madoff LC. The alpha C protein mediates internalization of group B streptococcus with human cervical epithelial cells. Cellular Microbiology. 2002;**4**:751-758

[30] Baker CJ, Edwards MS. In: Remington JS, Klein JO, editors. Group B Streptococcal Infections. Infectious Diseases of the Fetus and Newborn Infant. Philadelphia: W B Saunders; 1995. pp. 980-1054

[31] Harrison LH, Elliot JA, Dwyer DM, et al. Group B streptococcal serotype distribution of isolates from colonized pregnant women at time of delivery in United Arab Emirates. Pediatric Infectious Disease. 1998;**17**:499-503

[32] Kaur H, Kumar P, Ray P, Chakraborti A. Biofilm formation in clinical isolates of group B streptococci from North India. Microbial Pathogenesis. 2009;**46**:321-327

[33] Rubens CE, Raff HV, Jackson JC, Chi EY, Bielitzki JT, Hillier SL. Pathophysiology and histopathology of group B streptococcal sepsis in Macaca nemestrina primates induced after intra amniotic inoculation: Evidence for

bacterial cellular invasion. The Journal of Infectious Diseases. 1991;**164**:320-330

[34] Ohri M, Parashar S, Pai VS, Ghosh S, Chakraborti A. A cytosol derived factor of group B streptococcus prevent its invasion into human epithelial cells. World Journal of Microbiology and Biotechnology. 2018;**34**(45):1-14

[35] Rubens CE, Smith S, Hulse M, Chi EY, Belle GV. Respiratory epithelial cell invasion by group B streptococci. Infection and Immunity. 1992;**60**:5157-5163

[36] Weigand PV, Chattwal GS. Correlation of epithelial cell invasiveness of GBS with clinical source of isolation. Microbial Pathogenesis. 1995;**19**:83-91

[37] Alenghat E, Esterly JR. Alveolar macrophages in perinatal infants. Pediatrics. 1984;**74**:221-223

[38] Goldstein E, Lippert W, Warshauer D. Pulmonary alveolar macrophage: Defender against bacterial infection of the lung. The Journal of Clinical Investigation. 1974;**54**:519-528

[39] Sherman MP, Lehrer RI. Oxidative metabolism of neonatal and adult rabbit lung macrophages stimulated with opsonized group B streptococci. Infection and Immunity. 1992;**47**:26-30

[40] Burnham CAD, Shokoples SE, Tyrrell GJ. Phosphoglycerate kinase inhibits epithelial cell invasion by group B streptococci. Microbial Pathogenesis. 2005;**38**:189-200

[41] Shigeoka AO, Hall RT, Hemming VG, Allred CD, Hill HR. Role of antibody and complement in opsonization of group B streptococci. Infection and Immunity. 1978;**21**(1):34-40

[42] Anderson DC, Hughes BJ, Edwards MS, Buffone GJ, Baker CJ. Impaired chemotaxigenesis by type III group B streptococci in neonatal sera: Relationship to diminished concentration of specific anticapsular antibody and abnormalities of serum complement. Pediatric Research. 1983;**17**:496-502

[43] Edwards MS, Nicholson WA, Baker CJ, Casper DL. The role of specific antibody in alternative complement pathway-mediated opsonophagocytosis of type III, group B streptococcus. The Journal of Experimental Medicine. 1980;**151**:1275-1287

[44] Payne NR, Kim YK, Ferrieri P. Effect of differences in antibody and complement requirements on phagocytic uptake and intracellular killing of "c" protein-positive and -negative strains of type II group B streptococci. Infection and Immunity. 1987;**55**:1243-1251

[45] Harris TO, Shelver DW, Bohnsack JF, Rubens CE. A novel streptococcal surface protease promotes virulence, resistance to opsonophagocytosis, and cleavage of human fibrinogen. The Journal of Clinical Investigation. 2003;**111**:61-70

[46] Beckmann C, Waggoner JD, Harris TO, Tamura GS, Rubens CE. Identification of novel adhesins from group B streptococci by use of phage display reveals that C5a peptidase mediates fibronectin binding. Infection and Immunity. 2002;**70**:2869-2876

[47] Cheng Q, Stafslien D, Purushothaman SS, Cleary P. The group B streptococcal C5a peptidase is both a specific protease and an invasin. Infection and Immunity. 2002;**70**(5):2408-2413

[48] Spellerberg B, Rodzinski E, Martin S, Weber Hynemann J, Schnitzler N, et al. Lmb, a protein with similarities to the LraI adhesin family, mediates attachment of Streptococcus agalactiae to human laminin. Infection and Immunity. 1999;**67**:871-878

[49] Schubert A, Zakhikany K, Shreiner M, Frank R, Spellerberg B, Eikmann BJ, et al. A fibrinogen receptor from group B streptococcus interacts with fibrinogen by repetitive units with novel ligand binding sites. Molecular Microbiology. 2002;**46**:557-569

[50] Samen U, Eikmanns BJ, Reinscheid DJ, Borges F. The surface protein Srr-1 of Streptococcus agalactiae binds human keratin 4 and promotes adherence to epithelial HEp-2 cells. Infection and Immunity. 2007;**75**(11):5405-5414

[51] Rosini R, Rinaudo DC, Soriani M, Lauer P, Mora M, Maione D, et al. Identification of novel genomic islands coding for antigenic pilus-like structures in *Streptococcus agalactiae*. Molecular Microbiology. 2006;**61**:126-141

[52] Maisey HC, Hensler M, Nizet V, Doran KS. Group B streptococcal pilus proteins contribute to adherence to and invasion of brain microvascular endothelial cells. Journal of Bacteriology. 2006;**189**(4):1464-1467

[53] Dramsi S et al. Assembly and role of pili in group B streptococci. Molecular Microbiology. 2006;**60**:1401-1413

[54] Krishnan V et al. An IgG-like domain in the minor pili GBS52 of Streptococcus agalactiae mediates lung epithelial cell adhesion. Structure. 2007;**15**:893-903

[55] Ozeri V, Rosenshine I, Ben-Ze'ev A, Bokoch GM, Jou T, Heinski E. De novo formation of focal complexes like structures in host cells by invading streptococci. Molecular Microbiology. 2001;**41**:561-573

[56] Tyrell GJ, Kennedy A, Shokoples SE, Sherburne RK. Binding and invasion of HeLa and MRC-5 cells by Streptococcus agalactiae. Microbiology. 2002;**148**:3921-3931

[57] Boone TJ, Burnham CAD, Tyrrell GJ. Binding of group B streptococcal phosphoglycerate kinase to plasminogen and actin. Microbial Pathogenesis. 2011;**51**:255-261

[58] Alloush HM, Lopze-Ribot JL, Masetn BJ, Chaffin WL. 3-phosphoglycerate kinase: A glycolytic enzyme protein present in cell wall of Candida albicans. Microbiology. 1997;**143**:321-330

[59] Keung WL, Salaby KA, Thankur A, Medhat AM, Karim AM, Overde PT. Cloning of the gene for phosphoglyceratekinase from Schistosoma mansoni and characterization of its gene products. Molecular and Biochemical Parasitology. 1995;**71**:221-231

[60] Lee KW, Thakur A, Karim AM, Lo Verde PT. Immune response to Schistosoma mansoni phosphoglycerate kinase during natural and experimental infection: Identification of a schistosome specific B cell epitope. Infection and Immunity. 1995;**63**:4307-4311

[61] Valenti P, Antonini G. Lactoferrin: An important host defence against microbial and viral attack. Cellular and Molecular Life Sciences. 2005;**62**:1-12

[62] Hulse ML, Smith S, Chi EY, Pham A, Rubens CE. Effect of type III Group B streptococcal capsular polysaccharide on invasion of respiratory epithelial cells. Infection and Immunity. 1993;**61**:4835-4841

[63] Vogel CF, Matsumura F. A new cross-talk between the aryl hydrocarbon receptor and RelB, a member of the NF-kappaB family. Biochemical Pharmacology. 2009;**77**(4):734-745

[64] Baker CJ, Noya FJD. Potential use of intravenous immune globulin for group B streptococcal infection. Reviews of Infectious Diseases. 1990;**12**:S476-S482

[65] Zaleznik DF et al. Invasive disease due to group B streptococcus in pregnant women and neonates from diverse population groups. Clinical Infectious Diseases. 2000;**30**:276-281

[66] Weisner AM, Johnson AP, Lamagni TL, Arnold E, Warner M, Heath PT, et al. Characterization of group B streptococci recovered from infants with invasive disease in England and Wales. Clinical Infectious Diseases. 2004;**38**:1203-1208

[67] Baker CJ, Rench MA, McInnes P. Immunization of pregnant women with group B streptococcal type III capsular polysaccharide-tetanus toxoid conjugate vaccine. Vaccine. 2003;**21**:3468-3472

[68] Mohle-Boetani JC et al. Comparison of prevention strategies for neonatal group B streptococcal infection: An economic analysis. JAMA. 1993;**270**:1442-1448

[69] Institute of Medicine (US) Committee to Study Priorities for Vaccine Development; In: Stratton KR, Durch JS, Lawrence RS, editors. Vaccines for the 21st Century: A Tool for Decisionmaking. Washington, DC, USA: National Academies Press; 2000. Appendix 25, Streptococcus, Group B

[70] Lin SM, Zhi Y, Ahn KB, Lim S, Seo HS. Status of group B streptococcal vaccine development. Clinical and Experimental Vaccine Research. 2018;7(1):76-81