4

Current Understanding of Streptococcal Urinary Tract Infection

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1. Introduction

Group B streptococcus (GBS), also known as *Streptococcus agalactiae* is a Gram-positive, β-hemolytic, chain-forming bacterium and a commensal within the genital tract flora in approximately 25% of healthy adult women (Campbell et al., 2000). The organism is a leading cause of serious infection in newborns, pregnant women, and older persons with chronic medical illness (Baker et al., Edwards&Baker, 2005). In neonates GBS infection most commonly causes pneumonia, meningitis, and sepsis. In addition to maternal cervicovaginal colonization and neonatal infection that can result from vertical transmission of GBS from mothers to their infants, the bacterium can also cause urinary tract infection (UTI). The spectrum of GBS UTI includes asymptomatic bacteriuria (ABU), cystitis, pyelonephritis, urethritis, and urosepsis (Bronsema et al., 1993, Edwards&Baker, 2005, Farley et al., 1993, Lefevre et al., 1991, McKenna et al., 2003, Munoz et al., 1992, Ulett et al., 2009). GBS ABU is particularly common among pregnant women, although those most at risk for cystitis due to GBS appear to be elderly individuals (Edwards&Baker, 2005, Falagas et al., 2006, Muller et al., 2006). In addition to acute and asymptomatic UTI other invasive diseases caused by GBS infection include skin infections, bacteraemia, pneumonia, arthritis, and endocarditis (Liston et al., 1979, Patil&Martin, 2010, Tissi et al., 1997, Trivalle et al., 1998). Thus, GBS is considered unique in terms of its ability to cause a spectrum of diseases in newborns and adult humans and its ability to colonize the genital tract of healthy women in a commensal-type manner. In contrast to GBS disease conditions resulting from neonatal infection, the clinical and microbiological features of GBS UTI and asymptomatic genital tract colonization are not well characterized. Moreover, the risk factors for the various diseases caused by GBS including UTI and the pathogenesis of the different diseases caused as a result of GBS infection are not well defined.

Recent advances in the awareness, diagnosis and treatment of GBS infections, particularly in relation to vertical transmission and neonatal infection, have significantly reduced mortality in the newborn population. Establishment of preventative and treatment guidelines by the Centres for Disease Control (CDC) beginning in the 1990s has resulted in a reduction in mortality rates due to acute GBS infection in newborns from approximately 30-50% to 4–5% (Dermer et al., 2004). Guidelines for the prevention of GBS infections in newborns first published in 1992 and revised in 1997 include surveillance programs and administration of antibiotics during labour (intrapartum antibiotic chemoprophylaxis) (1992, 1997). Since the mid-1990s, most pregnant women in the United States have been screened for infection by

GBS and the success of intrapartum antibiotic chemoprophylaxis for the prevention of vertical transmission of GBS has been noted (Verani et al., 2010). However, preventive strategies to identify at-risk individuals are controversial and the rates of GBS-related stillbirths, prematurity, and late onset disease (LOD) have not decreased (Gibbs et al., 2004). The incidence of morbidities in newborn survivors of acute GBS infection ranges from 20–60% and includes neurological sequelae (Gibbs et al., 2004, Lukacs et al., 2004). The manner in which specific preventative strategies are implemented may also affect disease prevalence due to GBS in some areas (Krasnianin et al., 2009, Rausch et al., 2009). Thus, infections due to GBS and the ensuing diseases that result remain a significant cause of morbidity and mortality in newborns as well as healthy adults (Berner, 2004, van der Poll&Opal, 2008).

In addition to representing a major infection risk for neonates and pregnant women GBS is also a prominent pathogen of the elderly, immunocompromised, and individuals with diabetes and malignancies. These populations are particularly at risk for invasive GBS infection (Edwards&Baker, 2005, Farley, 2001). The manifestations of GBS infection in these populations are highly varied; however, some of the most common clinical presentations include skin and soft tissue infections, bacteraemia, pneumonia, arthritis, UTI, and endocarditis (Baker, 1997, Farley, 2001, Lee et al., 2007, Trivalle et al., 1998). The case fatality rate for GBS infection in elderly adults was estimated to be approximately 15% in the United States between 2001 and 2005 (Edwards&Baker, 2005, Farley, 2001). Importantly, there is no vaccine currently available to prevent GBS disease in neonates or adults despite a substantial research effort in identifying potential immunogens as vaccine candidates in immunization strategies (Doro et al., 2009).

The recent emergence of GBS strains that are resistant to multiple antibiotics represents a significant concern in the treatment of these infections in adults and children (Andrews et al., 2000, Bland et al., 2001, Dahesh et al., 2008, Heelan et al., 2004, Kimura et al., 2008, Nagano et al., 2008, Simoes et al., 2004). Penicillin-derived antibiotics remain the drugs of choice for treatment of GBS infections in infants and adults (Sendi et al., 2008, Verani&Schrag, 2010). These antibiotics inhibit cell wall synthesis during active growth of the bacteria. Vancomycin, cefezolin, clindamycin and telavancin are also used for the treatment of GBS infections. Trends of increasing antibiotic resistance (Edwards, 2006) may reflect clonal dissemination and horizontal transfer of resistance genes, which occurs among some GBS isolates (Puopolo et al., 2007). In addition, the identification of GBS strains resistant to penicillin, clindamycin and erythromycin represents a significant concern for the treatment of infections (Andrews et al., 2000, Bland et al., 2001, Dahesh et al., 2008, Heelan et al., 2004, Kimura et al., 2008, Nagano et al., 2008, Simoes et al., 2004). A large number of microbiological studies on GBS infection over the past two decades have underscored the importance of GBS as a major public health concern and a need for improvements in preventative and therapeutic strategies. An improved understanding of the mechanisms of GBS disease pathogenesis is vital for such strategies.

1.1 Host range and GBS serotypes

GBS was once seen only as a veterinary pathogen. The organism was originally isolated from cattle in the 1930s and prior to the 1980s was regarded as a prominent cause of bovine mastitis in dairy cows. Indeed, the species name, agalactiae, translates to "no milk" and reflects this history. Subsequently, epidemiology and prevalence studies indicated that GBS was associated with disease in neonates and the bacterium was increasingly recognized beginning in 1977 as a major cause of postpartum infection in human newborns (Ferrieri et

al., 1977). GBS is now universally accepted as among the most common causes of neonatal sepsis and meningitis. Research in the mid-1980s demonstrated that GBS was carried in the genital tract and the gastrointestinal flora in up to 30% of healthy adult women, which reflected intermittent, transient, or persistent colonization (Boyer et al., 1983, Dillon et al., 1982). Over the last fifteen years studies have demonstrated that GBS is a significant cause of serious disease in non-pregnant adults including elderly people and immunocompromised individuals. Emerging trends in GBS disease incidence and prevalence strongly suggest that changes in the recognition and treatment of GBS infections are impacting the types of individuals affected by the bacterium and invasive disease in adults is now more common than in neonates (Baker, 2000. , Falagas et al., 2006, Muller et al., 2006).

There are ten different capsular serotypes of GBS, namely Ia, Ib, and II-IX. These are based on the structure of the surface polysaccharide capsule of the bacterium. Nontypeable GBS also exist and are associated with some infections in humans including UTI (Baker&Barrett, 1974, McKenna et al., 2003, Persson et al., 1985). Capsular serotyping of GBS can be performed by latex agglutination using commercial antisera (Slotved et al., 2003), which differentiates the major Lancefield groups (Facklam, 2002) based on serotype-specific antibody-based binding. Molecular serotyping (MS) methods have gained popularity and can provide additional insight into serotype traits that are not able to be derived from antisera-based approaches, possibly as a result of limited antigen expression in some strains (Ferrieri et al., 2004, Kong et al., 2002, Manning et al., 2008, Ramaswamy et al., 2006, Wen et al., 2006). MS identification of all ten serotypes is possible (MS Ia, Ib, and II-IX) with the use of a multiplex PCR and reverse line blot hybridization assay targeting a GBS species-specific gene (*cfb*) and serotype-specific sequences in various other capsular loci genes (Kong et al., 2005). Among the ten different types, the serotypes most frequently associated with serious disease are serotypes Ia, II, III, and V (Edwards&Baker, 2005). There is some evidence to suggest that switching can occur between capsular types in GBS (Martins et al., 2010).

1.2 GBS disease spectrum and Co-morbidities

GBS is a frequent cause of puerperal infections including pneumonia, sepsis, meningitis, amnionitis and endometritis. These infections are common in newborns, pregnant women, and adults with underlying medical conditions (Nizet et al., 2000, Pass et al., 1982). Diabetes mellitus and malignancy are among the most common underlying conditions associated with these GBS infections (Huang et al., 2006). Other co-morbidities that have been associated with GBS disease in adults include cardiovascular abnormalities, genitourinary disorders, neurologic deficits, cirrhosis, steroid use, AIDS, renal dysfunction, and peripheral vascular disease. Relapse of GBS disease in affected individuals is not uncommon, with approximately 5% of non-pregnant adults experiencing a second episode of GBS disease after resolution of the primary infection (Sendi et al., 2008). The pathogenic basis of this recurrence is unknown but it is nonetheless an important consideration clinically.

The nature of GBS as a frequent constituent of the resident vaginal bacterial microflora in healthy adult women means that the bacterium is regarded as a normal commensal under these circumstances. Colonized women often carry GBS for long periods of time and usually do not show clinical symptoms as a result of persistent genital tract infection. On the other hand, conditions during pregnancy may lead to increased GBS multiplication in the urogenital tract and GBS can grow to high numbers in human amniotic fluid. This may lead to serious consequences for both the colonized mother and the infant. Between 15%-45% of pregnant women harbour GBS in the gastrointestinal and or genitourinary tracts (Schuchat,

1998); neonates acquire the bacteria at birth from their asymptomatically colonized mothers in approximately 1% of all live births (Baker, 2000. , Nandyal, 2008, Schuchat, 1998). The neonatal lung can receive a substantial inoculum from infected amniotic fluid at birth (Nizet et al., 2000). In addition, GBS may be acquired by the growing fetus prior to birth *in utero*, which can trigger adverse pregnancy outcomes. Thus, GBS continues to be an important perinatal pathogen but causes a wide spectrum of diseases that is associated with various co-morbidities.

1.3 Detection and identification of GBS

The majority of GBS infections can be diagnosed through routine laboratory testing of clinical samples such as blood, cerebrospinal fluid, or aspirates from sites of local suppuration. In the majority of cases isolates are rapidly identified by typical colony morphology on agar medium such as tryptic soy agar-5% sheep blood, and are tested for catalase, which streptococci do not express. Isolates are grouped into the Lancefield B group (Facklam, 2002) using commercial typing antisera for latex agglutination assays. GBS antigens can occasionally be detected in blood, cerebrospinal fluid, and urine but are not routinely tested for in any diagnostic assays. A Gram stain of a clinical specimen can be useful in the detection of infection but is not specific and therefore not definitive for identification. Polymerase chain reaction and optical immunoassay may, on the other hand, provide rapid and specific results for the detection of GBS infection; however, optimization and validation of these assays to ensure sensitivity and specificity has limited their widespread application in the clinical laboratory (Daniels et al., 2009, Schwope et al., 2010).

1.4 GBS virulence factors and host cell responses

A number of GBS virulence factors that contribute to disease and infection in the host have been discovered. The role of these GBS virulence factors in UTI remains unexplored. A number of exotoxigenic virulence factors are produced by GBS, including hyaluronate lyase, Christine Atkins Munch Peterson (CAMP) factor, superoxide dismutase, proteases, nucleases, platelet-activating factor, collagenase/oligopeptidase, protein c, RIB, R protein, and C5a peptidase (Lindahl et al., 2005, Liu&Nizet, 2004, Nizet et al., 2000). The functions and structures of several of these virulence factors are reviewed elsewhere (Liu&Nizet, 2004). One of the major GBS virulence factor is the sialic acid-rich capsular polysaccharide, which has been extensively studied as a virulence factor for many years (Slotved et al., 2007). Capsular polysaccharide is anti-phagocytic and influences the pathogenicity of GBS by mediating evasion of phagocytes (Adderson et al., 2000). GBS lipotechoic acid (LTA) is another key virulence factor that contributes to successful infection in the host. GBS LTA is cytotoxic to human monocytes and induces inflammation including the production of pro-inflammatory cytokines such as TNF-α (Berner, 2002). Cytotoxicity including the ability to induce programmed cell death (PCD) in host cells may contribute to disease by promoting adhesion, invasion, and host immune-evasion (Nizet et al., 2000). β-hemolysin is produced in varying amounts by virtually all clinical isolates of GBS and has several known roles in virulence including cytotoxicity (Liu&Nizet, 2004, Nizet et al., 2000). β-hemolysin is expressed on the surface of GBS and is responsible for the characteristic β-hemolytic activity on blood agar (Nizet, 2002, Nizet et al., 2000). β-hemolysin has a role in early but not late PCD and its expression is abolished by glucose (Fettucciari et al., 2000, Ulett et al., 2003).
Several virulence factors of GBS including LTA, β-hemolysin, C5a peptidase and the R protein/antigen are involved in recognition by host cells and inducing or evading immune

responses (Cheng et al., 2001, Fasola et al., 1996, Henneke et al., 2005, Liu et al., 2004). The proficiency of GBS recognition by macrophages is considered a crucial component of early immune responses against the bacteria (Chattopadhyay et al., 2011, Franke-Ullmann et al., 1996, Jonsson et al., 1985, Sherman et al., 1992, Sibille&Reynolds, 1990). However, GBS are able to persist inside macrophages for an extended period of time after nonopsonic phagocytosis and eventually trigger death of the host cell (Cornacchione et al., 1998, Fettucciari et al., 2000, Ulett et al., 2003, Valenti-Weigand et al., 1996). Intracellular persistence and manipulation of death pathways in macrophages may represent a virulence mechanism whereby GBS contributes to the characteristically poor inflammatory response in the neonatal lung. GBS-induced cell death is also a prominent feature of hepatocytes in a rabbit model of GBS sepsis (Ring et al., 2002) and in neurons of the dentate gyrus in GBS meningitis (Bogdan et al., 1997).

2. Bacterial UTI: general aspects

Ten to forty percent of adult women will contract at least one UTI in their lifetime, and approximately 3% will experience more than one infection per year (Andriole&Patterson, 1991, Patton et al., 1991, Foxman, 2002). UTI are the second most common infectious diseases in humans after respiratory tract infections, and contribute to approximately 60 million hospital visits per year. The costs to health care systems have been estimated at over $2 billion annually (Andriole&Patterson, 1991, Barnett&Stephens, 1997, Hooton&Stamm, 1997, Patton et al., 1991). Chronic UTI are difficult to prevent and treat, and infections are often recurrent. Over 80% of UTI are caused by uropathogenic *Escherichia coli* (UPEC) (Ronald, 2002). Approximately 2% of UTI are caused by GBS. Among an estimated 40% of all adult women who will experience a UTI episode in their lifetime almost 1% will suffer UTI caused by GBS (Foxman, 2002). The urinary tract is a distinct mucosal surface of the body and bacterial colonization of the uroepithelium is unique compared to other mucosal surfaces. Colonizing bacteria must overcome the normal flushing actions of urine flow and the physical barrier of the uroepithelial lining. This lining embodies a tightly interlaced latticework of proteins called uroplakins (Apodaca, 2004). These are closely associated with a collection of lipids, sphingolipids, and cholesterol referred to as lipid rafts that cumulatively constitute a surface that is highly impregnable to urine, solutes, and potential pathogens such as UPEC and GBS (Apodaca, 2004).

2.1 Prevalence of GBS in the urinary tract

The spectrum of UTI caused by GBS includes ABU, cystitis, pyenorephritis, urethritus, and urosepsis (Bronsema et al., 1993, Farley et al., 1993, Lefevre et al., 1991, McKenna et al., 2003, Munoz et al., 1992). In many cases, GBS colonization of the urinary tract in women probably occurs by an ascending route from the vagina, where GBS can persist asymptomatically. GBS is cultured from approximately 2% of all UTI cases (de Mouy et al., 2007, Munoz et al., 1992, Persson et al., 1988). In the most recent single-centre analysis of adult patients in the United States GBS was cultured from urine during routine assessment for UTI in 2% of patients; most of these represented ABU (Ulett et al., 2009). This is consistent with findings in other studies (Aungst et al., 2004, Le et al., 2004). However, several studies have reported high rates of GBS UTI in non-pregnant adults (Edwards&Baker, 2005, Falagas et al., 2006, Muller et al., 2006, Toumi et al., 2006). In one study, GBS was cultured from 39% of all cases of symptomatic UTI among nursing home residents >70 years of age (Trivalle et al., 1998).

Other studies have reported that GBS UTI may account for up to one-third of all invasive infections due to GBS in elderly adults (Falagas et al., 2006, Hernaiz et al., 2004, Lefebvre et al., 2007, Munoz et al., 1992) and up to 7% of late-onset disease in neonates (Yagupsky et al., 1991). Urinary tract abnormalities, chronic renal failure (Munoz et al., 1992), diabetes mellitus (Ronald, 2003), corticosteroid use (Falagas et al., 2006), and prior UTI (Ulett et al., 2009) are among risk factors for GBS UTI.

2.2 GBS ABU and UTI in pregnancy

While the overall prevalence of GBS UTI remains unclear, GBS bacteriuria during pregnancy occurs at rates of between 1 and 3.5% (Baker, 1997, McKenna et al., 2003, Whitney et al., 2004). Approximately 2-7% of pregnant women exhibit ABU caused by GBS and GBS ABU during pregnancy is considered a surrogate marker for heavy maternal genital tract colonization (Liston et al., 1979, McKenna et al., 2003, Moller et al., 1984, Persson et al., 1986a, Wood&Dillon, 1981) and is indicated for intrapartum antibiotic chemoprophylaxis (McKenna et al., 2003, Schrag et al., 2002). In addition, up to 7% of pregnancies may be complicated by GBS UTI, and GBS reportedly accounts for approximately 10% of all cases of pyelonephritis during pregnancy (Muller et al., 2006, Persson et al., 1986a, Persson et al., 1986b). GBS UTI may also contribute to chorioamnionitis (Anderson et al., 2007), premature onset of labour (Moller et al., 1984), and an increased risk of vertical transmission of GBS (Persson et al., 1985, Wood&Dillon, 1981). Stemming from this, maternal GBS ABU (including pure and predominant growth of GBS in the urine) has been associated with vertical transmission and an increased risk for early-onset disease (EOD) in newborn infants (Heath et al., 2009, Liston et al., 1979, Moller et al., 1984, Persson et al., 1986a, Persson et al., 1985, Wood&Dillon, 1981). One study found an elevated risk for EOD among infants born to women with low colony-count GBS ABU compared with mothers who did not have GBS ABU (Weng et al., 2010). However, studies have also demonstrated that some women with GBS ABU during the first trimester of pregnancy may not exhibit vaginal-rectal colonization at 35-37 weeks gestation (McKenna et al., 2003) or at the time of delivery (Edwards et al., 2002). Thus, while maternal ABU does not necessarily lead to vertical transmission, ABU at any point during pregnancy may be a risk factor for neonatal EOD and has therefore been an indication for intrapartum antibiotic chemoprophylaxis since 1996 (Schrag et al., 2002, Yancey et al., 1996). ABU may also be an indicator of potential preterm labour (Schrag et al., 2002, Yancey et al., 1996). The American College of Obstetricians and Gynecologists (ACOG) and CDC guidelines recommend the evaluation of pregnant women at 35-37 weeks gestation and antibiotic therapy for women with positive cultures for GBS ABU. The 1996 ACOG and CDC guidelines do not specify a colony-count threshold for defining GBS ABU. However, the 2002 and more recent guidelines recommend reporting of GBS at any concentration in urine (Lin&Fajardo, 2008). Finally, although pregnant women may receive antibiotics to treat GBS ABU this therapy may not eliminate GBS from the genitourinary tract, and recolonization after a course of antibiotics can occur (Baecher&Grobman, 2008, Gardner et al., 1979, Hall et al., 1976).

Most data on the risk for EOD among infants born to women with GBS ABU are derived from studies using thresholds $>10^5$ cfu/ml despite lower counts of 10^3 cfu/ml having been associated with acute GBS UTI (Persson et al., 1986b, Persson et al., 1985, Ulett et al., 2009, Wood&Dillon, 1981). Although low concentrations (10^3-10^4 cfu/ml) of GBS in urine can be associated with colonization (Centelles-Serrano et al., 2009) limited data support the risk for EOD among infants born to women with low colony-count GBS ABU (Persson et al., 1986a).

The recommendation to report any colony count of GBS in urine represents increased workload for clinical laboratories, which generally do not report bacterial growth in urine of other pathogens at concentrations $<10^4$ cfu/ml (McCarter et al., 2009) and rarely know whether urine samples are from pregnant women. In the context of universal late antenatal GBS screening, it is unclear how much EOD is prevented by screening for low colony-count GBS ABU and whether identification of low colony-count bacteriuria is cost-effective.

2.3 Diagnosis of GBS UTI

Diagnostic strategies for UTI vary substantially between clinicians (Hay&Fahey, 2002, Kaufmann&Modest, 2002, Libbus, 2002); however, patients with a combination of symptoms have a high probability of UTI (Bent et al., 2002, Nicolle, 2008). Pyuria concurrently with bacteriuria constitutes diagnostic criteria in some settings (Shaikh et al., 2007), although what constitutes clinically significant bacteriuria is not strictly defined; colony counts $>10^3$ cfu/ml of a uropathogen is however, now widely accepted diagnostic criteria for cystitis (Nicolle, 2008, Rubin et al., 1992). Clinically, UTI due to GBS may be indistinguishable from UTI caused by other uropathogens (Muller et al., 2006). A recent study of multiple uropathogens highlighted unique frequencies of host characteristics in UTI groups defined by the causal organism (Tabibian et al., 2008). This suggests that the clinical and microbiological features of UTI may differ depending on the infecting pathogen and the most ideal diagnostic approaches may depend on the causal organism. In one study the investigators regarded single-organism GBS bacteriuria and at least one UTI symptom as being a probable case of UTI and used urinary leukocyte esterase with pyuria as confirmatory for diagnosis (Ulett et al., 2009). Here, a provisional diagnosis was defined by the presence of single-organism GBS bacteriuria ($>10^4$ cfu/ml) with at least one symptom that included dysuria, increased urinary frequency and/or urgency, fever of >38°C, flank pain, and/or lumbar tenderness. In cases where urinalysis (UA) was performed, UTI was confirmed on the basis of positive urinary leukocyte esterase and significant pyuria ($\geq 10^7$ white blood cells/high-power field; non-spun). These are the generally accepted criteria for the diagnosis of UTI (Hay&Fahey, 2002, Kaufmann&Modest, 2002, Libbus, 2002) although inclusion of bacteriuria counts of $>10^3$ cfu/ml may provide additional clinical relevance. In this study group, patients were grouped into probable GBS UTI where UA was not performed and confirmed cases where (positive) UA data were available. Individuals defined as having GBS isolated from urine incidentally were selected on the basis of low-grade GBS bacteriuria ($<10^4$ cfu/ml) in the absence of symptoms. In this study, multiple patients were identified who had symptoms of UTI and positive UA findings but had GBS bacteriuria counts between 10^3-10^5 cfu/ml, which is consistent with reports that up to 30% of women with cystitis present with bacteriuria of $<10^5$ cfu/ml. Thus, the level of bacteriuria in GBS UTI may not correlate well with acute disease. The serotypes of GBS associated with UTI have not been well defined; however it appears that most serotypes can cause acute UTI. MS and antisera-based serotyping was used in one study to identify the serotypes associated with UTI (Ulett et al., 2009), and demonstrated a predominance of serotypes Ia, II, III, and V in patients with acute UTI. Other studies demonstrated that nontypeable GBS also cause acute UTI (McKenna et al., 2003, Persson et al., 1985).

2.4 How does GBS colonize the urogenital tract?

GBS infection often begins with binding to epithelial cells at mucosal surfaces, such as those lining the respiratory or urogenital tracts. GBS are able bind to human vaginal epithelial cells under low pH conditions, which are characteristic of vaginal mucosa. These

interactions occur via low avidity interactions of cell-wall-associated LTA and via higher-affinity interactions mediated by hydrophobic GBS surface proteins (Tamura et al., 1994). Many of these host-cell interactions involve attachment of GBS to extracellular matrix molecules such as fibronectin, fibrinogen and laminin, which in turn bind host-cell-surface proteins such as integrins (Maisey et al., 2008). For example, ScpB, which is a GBS cell-surface protein previously characterised for its ability to cleave the complement-derived chemoattractant C5a (Beckmann et al., 2002), can bind fibronectin (Cheng et al., 2002). ScpB can bind to integrins, which may promote both binding to host cells and complement proteolysis (Brown et al., 2005). Naturally occurring ScpB variants with a deletion that destroys peptidase function retain the capacity to bind fibronectin (Cleary et al., 2004, Tamura et al., 2006). GBS attachment to fibrinogen is mediated by the surface-anchored protein FbsA (Schubert et al., 2004), and adherence to laminin involves the adhesin Lmb (Spellerberg et al., 1999). The serine-rich repeat domain protein Srr-1 binds human keratin 4 (Samen et al., 2007) and the GBS surface protein LrrG, containing the leucine-rich-repeat motif found in many invasins, binds to epithelial cells, suggesting that it serves as an adhesin during GBS infection (Seepersaud et al., 2005). In each of these examples, these binding interactions probably promote GBS adherence to epithelial cells.

GBS were also recently shown to express pili (Lauer et al., 2005), which typically facilitate Gram-negative bacterial attachment to host cells (Sauer et al., 2000). Among eight sequenced GBS genomes, two genetic loci encoding pili were identified, the second existing in one of two variants, although not all genomes contain both loci (Rosini et al., 2006). GBS pilus island 2′ includes the genes encoding PilB, an LP(x)TG-motif-containing protein that polymerises to form a pilus backbone, and accessory pilus proteins PilA and PilC (Dramsi et al., 2006, Maisey et al., 2007). Epithelial cell adherence is reduced in isogenic GBS mutants lacking PilA or PilC, but not those lacking PilB (Dramsi et al., 2006). The role of GBS pili in binding in the urogenital tract is unknown.

2.5 Modeling GBS UTI from clinical studies

Uropathogenic GBS (UPGBS) have been shown to bind to both murine and human bladder uroepithelium in in vivo (Figure 1) and in vitro (Figure 2) studies. These models were developed to study the pathogen-host interaction underlying GBS UTI. UPGBS bind more efficiently to bladder epithelial mucosa when compared with non-UPGBS (Ulett et al., 2010).

Binding models of GBS UTI to study host cell interactions in vivo and in vitro have been derived from clinical studies conducted in the past five years. The largest of these clinical studies of GBS UTI to date was performed in the United States using a cohort of 387 patients with positive GBS cultures in urine. This study investigated the traits of UPGBS that cause acute UTI and ABU using detailed analysis of patients groups alongside serotyping comparisons, and risk factor analysis. The study also investigated the demographic data alongside standard diagnostic microbiological measures for the defined patient groups, which are summarized in Table 1. In this study, a total of 62 patients of the 387 patients with positive GBS urine culture had single-organism bacteriuria $>10^4$ cfu/ml concurrent with at least one UTI symptom and were defined as having probable GBS UTI. The most prevalent serotypes of GBS causing UTI in this study according to MS were serotypes V, Ia, and III, as shown in Table 2. Together, these serotypes accounted for 76% of GBS UTI cases. Serotype III GBS was the only serotype that was more frequently isolated from UTI case patients than from controls. Thus, in this study GBS UTI occurred mostly as uncomplicated cystitis in middle-aged women (>50 yrs) in the absence of chronic underlying disease but was associated with a prior history of UTI.

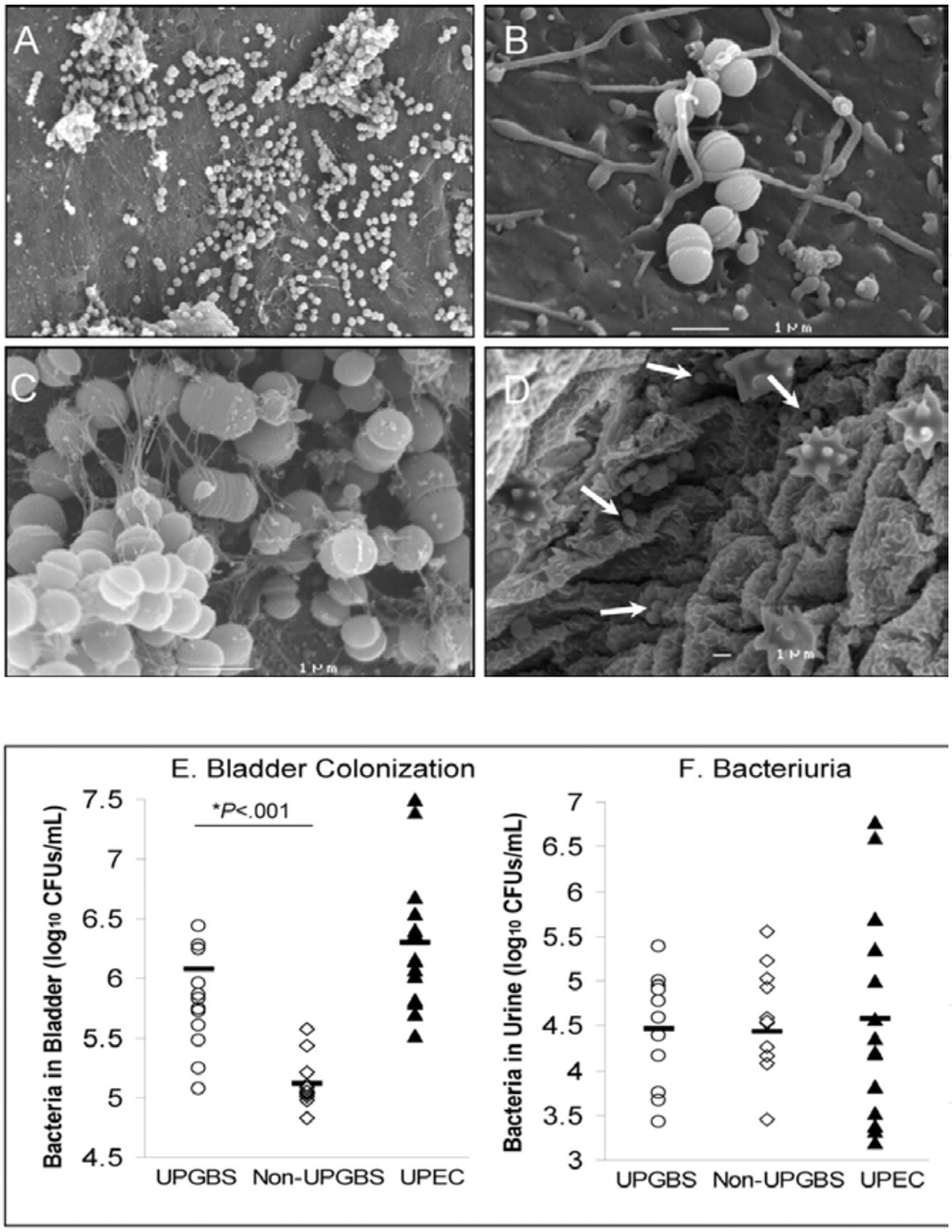

Fig. 1. UPGBS bound to bladder uroepithelium in a murine model of GBS cystitis (A–C, flattened bladder; D, native conformation). The arrows in panel *D* show bound UPGBS between folds of bladder uroepithelium. Panel E illustrates better bind of UPGBS to bladder mucosa compared with non-UPGBS although binding is not as efficient as uropathogenic *Escherichia coli* (UPEC) and levels of bacteriuria are simiular (F). Reproduced, along with Figure 2, with permission from (Ulett et al., 2010) courtesy of Oxford Journals.

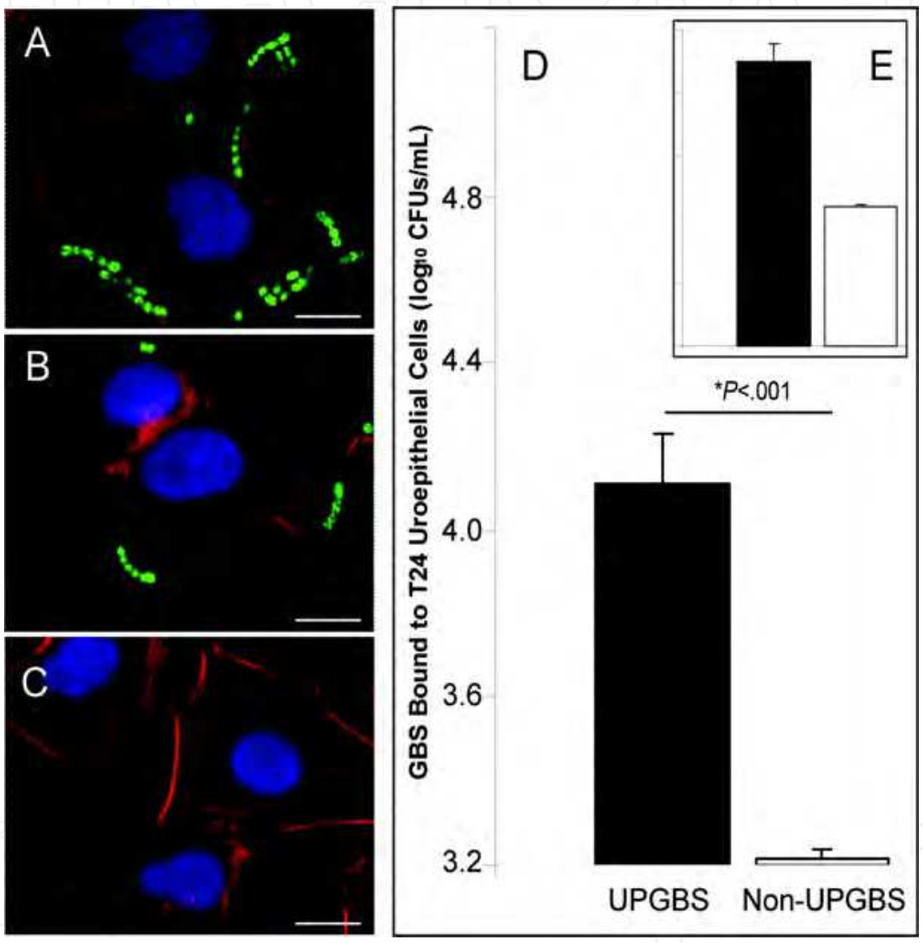

Fig. 2. UPGBS (green) bound to human bladder cells (blue, nuclei; red F-actin) at multiplicities of infection of 50 (A) and 5 (B). Uninfected cells in (*C*). Measures of binding of UPGBS and non-UPGBS to T24 (*D*) and 5637 (*E*) cells shows higher binding of UPGBS.

	Total Specimens (*n*=387)[a]	GBS UTI Cases[b]			Controls[d] (*n*=51)	*P* (All cases vs controls)
		UA +ve[c] (*n*=31)	UA ND[c] (*n*=31)	All (*n*=62)		
Age (mean years; range)	46; 18-95	54; 19-82	52; 19-93	53; 19-93	30; 18-64	< 0.001[g]
Female sex	322 (83)	25 (81)	27 (87)	52 (84)	46 (90)	0.002[h]
Symptoms						
- Dysuria	68 (17.6)	18 (58.1)	17 (54.8)	35 (56.5)	0 (0)	ND
- Frequency	57 (14.7)	11 (35.5)	12 (38.7)	23 (37.1)	0 (0)	ND
- Flank pain	35 (9.0)	7 (22.6)	7 (22.6)	14 (22.6)	0 (0)	ND
- Fever	15 (4.0)	4 (13.0)	2 (6.0)	6 (10.0)	0 (0)	ND
- C/W cystitis[e]	130 (33.6)	25 (80.6)	24 (77.4)	50 (81.0)	0 (0)	ND
- C/W pyleonphritis[f]	65 (16.8)	6 (19.4)	7 (22.6)	12 (19.0)	0 (0)	ND
Pregnant	99 (30.1)	1 (4)	5 (18.5)	6 (11.5)	35 (76)	
Possible Risk factors						
- Limited mobility	13 (3.4)	1 (3.2)	0 (0)	1 (1.6)	0 (0)	1.000
- Diabetes mellitus	91 (23.5)	5 (16.1)	4 (12.9)	9 (14.5)	9 (17.6)	0.651
- Chronic kidney disease	72 (18.6)	4 (12.9)	0 (0)	4 (6.5)	7 (13.7)	0.219
- Indwelling urinary catheter	4 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)	ND
- Altered mental status	14 (3.6)	3 (9.7)	2 (6.5)	5 (8.1)	0 (0)	0.063[i]
- Prior History of UTI	76 (19.6)	9 (29.0)	9 (29.0)	18 (29.0)	6 (11.8)	0.032[j]
Pure GBS isolated	207 (53.5)	31 (100)	31 (100)	62 (100)	15 (29.4)	ND
GBS count >10^7 cfu/L	319 (82.4)	31 (100)	31 (100)	62 (100)	0 (0)	ND
Mean GBS count (x 10^7/L)	4.7 ± 3.6	7.4 ± 3.5	6.1 ± 3.1	6.7 ± 3.4	0.5 ± 0.3	ND
UA done	210 (54.3)	31 (100)	0 (0)	31 (50)	9 (17.3)	ND
- Pyuria	114 (54.3)	31 (100)	ND	31 (100)	0 (0)	ND
- Leukocyte esterase	122 (58.1)	31 (100)	ND	31 (100)	0 (0)	ND
- Hematuria	74 (35.2)	21 (67.7)	ND	21 (67.7)	2 (22)	ND
- +ve and C/W UTI[d-f]	91 (43.3)	31 (100)	ND	31 (100)	0 (0)	ND

Table 1. Patients who had GBS isolated from urine during routine assessement for UTI at University of Alabama Hospital between August 2007-2008. NOTE. Data are no. (%) of patients, unless otherwise indicated; [a.] Consecutive urine specimens sent for culture, from which GBS was isolated; [b.] Patients with ≥1 symptom(s) of UTI and pure growth of GBS >10^7 cfu/L; [c.] UA: +ve (consistent with UTI) positive leukocyte esterase and pyuria; ND not done; [d.] Subjects without symptoms from whose urine GBS was isolated in counts <10^7/L; [e.] Symptoms consistent with (C/W) cystitis: dysuria and/or frequency; [f.] Symptoms C/W pyelonephritis: dysuria and/or frequency plus flank pain and/or fever >38°C; [g.] By Mann–Whitney U test; [h.] By Pearson χ^2 analysis. Gender comparisons performed using population data (equal group sizes) from the US Census Bureau for Birmingham (male-female ratio 85.7); [i.] By Fisher's exact test; [j.] By forward stepwise logistic regression subsequent to Pearson χ^2 analysis; Reproduced, with Table 2, with permission from (Ulett et al., 2009) courtesy of The American Society for Microbiology.

GBS Serotype	All Specimens (*n*=387)[a]		GBS UTI Cases[b]						Controls[d] (*n*=51)	
			UA +ve[c] (*n*=31)		*UA ND*[c] (*n*=31)		*All* (*n*=62)			
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Ia	81	(21)	6	(19)	8	(26)	14	(23)	8	(16)
Ib	31	(8)	2	(7)	3	(10)	5	(8)	5	(10)
II	69	(18)	5	(16)	3	(10)	7	(11)	12	(24)
III	48	(12)[e]	8	(26)	5	(16)	13	(21)[e]	5	(10)
IV	24	(6)	2	(7)	1	(3)	3	(5)	5	(10)
V	125	(32)	8	(26)	12	(37)	20	(32)	10	(20)
VI	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
VII	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
VIII	2	(1)	0	(0)	0	(0)	0	(0)	1	(2)
NT[f]	7	(2)	0	(0)	0	(0)	0	(0)	5	(10)
IX	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)

Table 2. Molecular serotypes of GBS that cause UTI, from the largest study of 387 patients with positive urine cultures for GBS to date. NOTE. Data are no. (%) of GBS isolates, unless otherwise indicated; [a.] Consecutive urine specimens sent for culture, from which GBS was isolated; [b.] Patients with ≥1 symptom(s) of UTI and pure growth of GBS $>10^7$ cfu/L; [c.] UA: +ve (consistent with UTI) positive leukocyte esterase and pyuria; ND not done; [d.] Subjects without symptoms from whose urine GBS was isolated in counts $<10^7$/L; [e.] Difference between the prevalence of serotype III among all GBS UTI case patients and all other non-GBS UTI cases (*n*=325), significant by Pearson χ^2 analysis (P=0.026); [f.] Isolates were identified using antisera as: NT (3), II (2), IV (1) and V (1).

3. Conclusions

In summary, GBS is an important pathogen that causes serious infections in newborns, pregnant women, and elderly people with chronic illness. While early diagnosis and management of GBS among pregnant women can reduce the incidence of neonatal infection the prevalence of GBS disease in adult populations emphasizes the need for additional

preventative and therapeutic measures. Moreover, the emergence of antibiotic-resistant strains of GBS imposes a significant threat to the successful treatment of these infections. This is particularly relevant to GBS UTI, which is associated with relatively high rates of treatment failure and poor clinical outcomes (Munoz et al., 1992). Screening pregnant mothers for GBS ABU appears to be important in relation to the vertical transmission of GBS to infants however more research is needed to clarify this aspect of GBS UTI. An overarching and intriguing theme with GBS infection in humans is that GBS can efficiently colonize the genital tract of healthy adult women long-term without triggering apparent disease but, on the other hand, can also cause acute disease in some individuals. How this occurs is unknown.

Research efforts to understand GBS pathogenesis should focus on the different strains of GBS that cause distinct clinical conditions of UTI such as ABU and cystitis in order to analyse the virulence traits that are associated with these infections. How these infections progress to disease in some individuals is completely unknown but acute inflammation in GBS UTI appears to differ mechanistically compared to that which occurs in other Gram-negative UTI. Further longer-term surveillance studies of GBS UTI and ABU will help to better define the clinical features and serotypes associated with these infections. The question of how GBS might adapt to the niche environment of the urinary tract is another intriguing and unanswered question. A better understanding of the molecular mechanisms used by GBS to colonise uroepithelium and persist in the bladder will be an important area for future investigation. Broader utilization of appropriate in vivo and in vitro models beyond those already characterized will help to answer these questions. One area for investigation, for example, would be to use human urine as a growth medium to study fitness traits of UPGBS as has been performed for other uropathogens to discover key elements of UTI disease pathogenesis and how some successful uropathogens persist within the urinary tract in the absence of direct binding to cellular targets. Such studies will pave the way to develop new preventive and perhaps therapeutic strategies for GBS UTI. While many of the current strategies have focused on the development of vaccines for prevention of GBS disease (Maione et al., 2005) their potential for reducing GBS disease burden due to UTI is unknown. Identification of alternate drug targets would also be a goal of future research. Elucidation of the mechanisms that underlie GBS disease pathogenesis is pivotal for the identification of such alternate drug targets and also in the development of novel vaccines. A better understanding of how GBS regulates expression of its virulence survival factors is imperative. Finally, the underlying phenotypic basis for UPGBS could be gained by comparing GBS isolated from asymptomatic infection to cystitis strains by comparative genome sequencing approaches. Discoveries from such research may challenge the existing paradigms and reveal surprising insights into the versatile nature of this important human pathogen.

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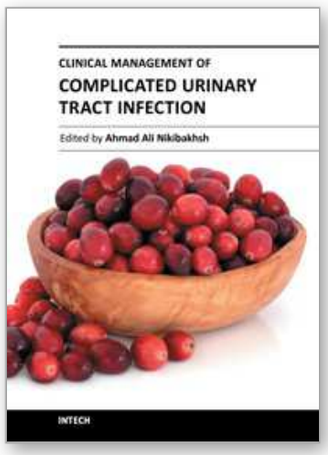

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Complicated urinary tract infections (cUTIs) are a major cause of hospital admissions and are associated with significant morbidity and health care costs. Knowledge of baseline risk of urinary tract infection can help clinicians make informed diagnostic and therapeutic decisions. Prevalence rates of UTI vary by age, gender, race, and other predisposing risk factors. In this regard, this book provides comprehensive information on etiology, epidemiology, immunology, pathology, pathogenic mechanisms, symptomatology, investigation and management of urinary tract infection. Chapters cover common problems in urinary tract infection and put emphasis on the importance of making a correct clinical decision and choosing the appropriate therapeutic approach. Topics are organized to address all of the major complicated conditions frequently seen in urinary tract infection. The authors have paid particular attention to urological problems like the outcome of patients with vesicoureteric reflux, the factors affecting renal scarring, obstructive uropathy, voiding dysfunction and catheter associated problems. This book will be indispensable for all professionals involved in the medical care of patients with urinary tract infection.

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