Chapter 1
General Introduction
Introduction to Pathogens

Figure 1.1: Scientific classification
1.1. **Staphylococcus species**

The Staphylococcus genus includes at least 40 species. Of these, nine have two subspecies and one has three subspecies (LG Harris *et al.*, 2002).

1.1.1. **Staphylococcus aureus**

With its capacity of swiftly developing antibiotic resistance, Staphylococcus is one of the most notorious facultative anaerobic pathogen causing community acquired and nosocomial infections (LG Harris, 2002).

One of elementary property of *Staphylococcus aureus* is to asymptomatically colonize in humans both in nose and skin. Approximately 30% of humans are asymptomatic nasal carriers of *S. aureus* and it is exceedingly adaptive to changing environments during infections (LG Harris, 2002; Henry F Chambers, 2009). *S. aureus* is chief cause of bacteremia resulting into high mortality and morbidity when equated to similar infections by other pathogens. These are highly prevalent and trivial to treat presenting a major clinical challenge (Christoph K Naber, 2009). Toxic shock syndrome by release of superantigens into the blood stream, superficial skin lesions, localized abscesses in other sites, osteomyelitis, furunculosis and endocarditis are resultant of *S. aureus* infection. *S. aureus* is also related to food poisoning with enterotoxin released into foods (Baron S, 1996). Various culturing techniques, multiplex PCR test for presence of PVL, clumping factor, coagulase, hemolysins and thermostable deoxyribonuclease and Antimicrobial susceptibility testing are routinely deployed for diagnosis of *S. aureus* (Baron S, 1996; Dilip N, 2008; William J Mason, 2001). Methicillin-resistant *S. aureus* (MRSA) causes eruptions in hospitals and can be epidemic. Methicillin resistance is indicative of multiple resistances (Christoph K. Naber, 2009).

1.1.2. **Staphylococcus epidermidis**

Earlier termed as innoxiously harmless, *S. epidermidis* now garners attention as major pathogen for nosocomial infections in immunocompromized, immunosuppressed, chronic illness holders and extremely diseased patients (Maureen T McCann, 2008).

*Staphylococcus epidermidis* is non-hemolytic, facultative anaerobe colonized in human epithelium and mucous membranes (EBI, 2013). Its major patho-genetic factor
is the ability to form adherent biofilms capable to stick to polymeric substances. \textit{S. epidermidis} cause infection related to implanted medical devices (IMDs) (JKM Knobloc, 2001). Device related treatments are difficult to exterminate wherein bacteria under biofilm protection on surface of IMDs outlive treatments (Maureen T McCann, 2008). Infections with devastating consequences caused by \textit{S. epidermidis} include prosthetic valve endocarditis following prosthetic valve implantation (Verhoef J, 1983), keratitis due to contact lens use (Elder, M F, 1995), delayed onset post-operative endophthalmitis associated with intraocular lens implantation (Jansen B, 1991), bacteriuria following the use of urinary catheters (Warren JW, 2001), intravascular catheter-associated infection (Rupp ME, 2005) and prosthesis-related infection including the septic loosening of joint prostheses after total joint arthroplasty (Gallo J, 2003). A noteworthy proportion of \textit{S. epidermidis} infections may be attributable to transmission among patients and that certain strains can become endemic over long periods in this setting (P Villari, 2000).

1.1.3. \textit{Staphylococcus haemolyticus}
Second most frequent hospital-acquired infections are attributed to \textit{Staphylococcus haemolyticus} (EGA Fredheim, 2009). Earlier considered inferior to \textit{S. aureus} due to infrequent infection capacity, it now plays major role in nosocomial infections. Capacity of biofilm formation is determinant of these coagulase-negative staphylococci (CoNS) of causing prosthetic-device-related infections (Falcone M, 2007). The bacteria can be found on normal human skin flora and can be isolated from axillae, perineum, and inguinal areas of humans and are second most abundant CoNS found from blood stream (GDI de Silva, 2002). Its infections include infection of urinary tract, wounds, bone and joints (Tristan A, 2006), septicemia (Bruce A Gunn, 1988), peritonitis, endocardium or endocarditis (Keymer E, 1951) leading to heart failure or death (Falcone M, 2007). Though being less virulent then others Staphylococcus’s, it now poses high threats due to its capacity of acquire multi-antibiotic resistance (Vignaroli C, 2006).

1.1.4. \textit{Staphylococcus saprophyticus}
As a causative pathogen for uncomplicated urinary tract infection, \textit{Staphylococcus saprophyticus} is second to \textit{E. coli} specifically for infection in young sexually active females (Mark E Rupp, 1992; Wallmark G, 1978). Its role in causing UTI in men is
Chapter 1 | Introduction

not well defined, although data are emerging (Motwani Bharat, 2004). The bacteria may also reside in the urinary tract and bladder of sexually active females and causes UTI said as Honeymooners UTI because of its links to intercourse (Rupp ME, 1992). While *Staphylococcus aureus* and *Staphylococcus epidermidis* are often involved in nosocomial infections, *S. saprophyticus* is not involved in catheters (Makoto Kuroda, 2005). Complications of *S. saprophyticus* infection such as recurrent infection, acute pyelonephritis, nephrolithiasis, septicemia, and endocarditis have been documented but are all rare (Choi SH, 2006; Raz R, 2005). The urine sediment of a patient with UTI caused by *S. saprophyticus* has a characteristic appearance microscopically. Chemical screening methods for bacteriuria do not always succeed in diagnosing UTI caused by *S. saprophyticus* (Hovelius B, 1984). Unlike most other CoNS, *S. saprophyticus* rarely resistant to most antibiotics active against gram-positive organisms (Masato Higashide, 2008).

1.2. Streptococcus species

1.2.1. *Streptococcus pneumoniae*

“The captain of all the men of death” -Sir William Osler (Watson DA, 1993).

Though above statement was given by Sir William Osler a century ago, *Streptococcus pneumoniae* still stands at the captains’ position causing Community Acquired Pneumonia (CAP) world-wide (Reed AC Siemieniuk, 2011; Herrera-Lara S, 2013). Pneumococcus haunts human upper respiratory tract including the healthy hosts commonly as a commensal co-inhabiting with other pathogens (Watson DA, 1993). It’s a commensal which can cause endogenous infection in respiratory tract and elsewhere (Heritage, E.G.V, 1998). Other Pneumococcal infections include otitis media, meningitis and bacteremia (NYC Health, 2002; Patterson MJ, 1996). Elucidation of inflammation and inflammatory responses are major characteristics of ailments displayed by *S. Pneumoniae* including otitis media that is inflammation of middle ear (Roberts DB, 1980); meningitis is inflammation of protective membranes covering the brain and spinal cord (Van de Beek, 2004); Bacteraemia is invasion of blood stream by viable bacteria associated with systemic inflammatory response (Forner L, 2006). Culture technique (Incompetent), PCR assays and Urine Antigen detection form main laboratory diagnosis techniques for *S. pneumoniae* whose reliability is yet questionable! (Chiara Azzari, 2011; John G. Bartlett, 2011)
Responsible for 1.2 million infant deaths worldwide excluding the huge number of deaths of targets in immunocompromized states like HIV and elderly people it wins a second position after *H. Influenza*. Epidemic spread of pneumococci is resultant from its efficient transmission through infested respiratory secretions (Watson DA, 1993).

1.2.2. *Streptococcus pyogenes*

Harbouring on flesh! Yes it is *Streptococcus pyogenes*.

*Streptococcus pyogenes* claims ample lives attaining a title of “one of the most frequent human pathogen” consequential for elevated mortality and morbidity specifically after 1980 (Stevens DL, 1999). Infecting 7 million people around the world it alone claims above 5 lakh lives (Carapetis JR, 2005). *S. pyogenes* colonizes throat and skin primarily causing decrepitude impetigo and pharyngitis thus diverting human defences (Anna Henningham, 2012; Olsen RJ, 2010). Necrotizing fasciitis, bacteraemia, myositis and streptococcal toxic shock syndrome (STSS) are among its devastating disorders. Patients may also develop immune-mediated post-streptococcal sequelae, such as acute rheumatic fever and acute glomerulonephritis, following acute infections (Friedman J, 1984; Weiss KA, 1997). Indigenous and poor communities are high time targets of this organism. Spreading from person-to-person *S. pyogenes* has high transmissibility in closed communities (Weiss KA, 1997). Immunohistochemical analysis and PCR can be used for diagnosis of GAS infections in formalin-fixed, paraffin-embedded samples (Anna Henningham, 2012; A. Mazon, 2003; Jeannette G, 2006).

1.2.3. *Streptococcus agalactiae*

Has ability to subvert host immune responses to superficial infections and deploying itself for invasive disease in body aiding to late diagnosis. *Streptococcus agalactiae* is highly opportunistic pathogen (Rajagopal L, 2009).

*Streptococcus agalactiae* is major etiologic agent of septicaemia and meningitis in pregnant women and neonates. While its significance was earlier denied in non-pregnant adults, now it is proved that GBS infections are a growing problem in elderly, immunocompromized adults and people with chronic diseases and other underlying medical conditions (Monica M. Farley, 1993; R Chaiwarith, 2011).
Presence of *S. agalactiae* in respiratory tract post neonatal period is rare case (Eickel V, 2009). Skin, soft-tissue, and osteoarticular infections, pneumonia, and urosepsis are common presentations (Monica M. Farley, 2001). Diabetes, neurological impairment, and cirrhosis elevate GBS risks (Po-Yen Huang, 2006). The methods for Group B streptococci identification include the hydrolysis of sodium hippurate, the CAMP reaction, pigment production, and antibiotic disk susceptibility. Also, immunological tests, such as Lancefield's classical precipitin test, immunofluorescence staining, counter immunoelectrophoresis, and coagglutination are available (Smith JP, 1979).

1.3. *Klebsiella* Species

1.3.1. *Klebsiella pneumoniae*

*Klebsiella pneumoniae* is a well-known opportunistic (C De Champs, 2004); human nosocomial (as most of hospital acquired) gram-negative bacterium extensively recognized for its ability to cause community-acquired pneumonia, urinary tract infections and intraabdominal infections (John L Carpenter, 1990; Wen-Chien Ko, 2002). It is a frequent causing primary pneumonia and bactermia. In humans, *K. pneumoniae* is a pulmonary pathogen inhabiting as a saprophyte in the nasopharynx and in the intestinal tract (Davis TJ, 1974). It has the ability to colonize in wide range of species and hence has elevated transfer rate via oro-faecal route or direct contact from humans to animals and vice versa (Janda JM, 2006). Risk factors for such pneumonia caused by *K. pneumonia* are immunosuppressed states and alcoholism (Korvick JA, 2004). Clinical observations of pneumoniae caused by Klebsiella species are toxic presentation with sudden onset, high fever, and hemoptysis. Chest radiographic abnormalities such as bulging interlobar fissure and cavitary abscesses are prominent (Wen-Chien Ko, 2002). Klebsiella infection can be diagnosed by biochemical tests and culture techniques in animals exhibiting medical signs (Podschun R, 1998).

1.4. *Shigella* Species

Shigellae are Gram-negative, nonmotile, facultatively anaerobic, non-spore-forming rods. They are differentiated from the closely related *Escherichia coli* on the basis of pathogenicity, physiology (failure to ferment lactose or decarboxylate lysine) and serology. (Thomas L. Hale, 1996) Shigella is causative genus of Shigellosis, is
divided into 4 species namely *S. flexneri, S. dysenteriae, S. boydii, and S. sonnei*. Each of these species are further classified into serotypes and serogroups respectively 15 (including subtypes), 13, 18, and 1 serotypes (Kaisar A Talukder, 2003). Symptoms of shigellosis include abdominal pain, tenesmus, watery diarrhea, and/or dysentery (multiple scanty, bloody, mucoid stools). Clinical manifestations may include abdominal tenderness, fever, vomiting, dehydration, and convulsions. Shigellosis can be correctly detected in most patients on the basis of fresh blood in the stool. Neutrophils in faecal smears are also a strongly indicative of infection. Nonetheless, watery, mucoid diarrhea may be the only indication of many *S. sonnei* infections, and any clinical diagnosis should be confirmed by cultivation of the etiologic agent from stools. (Thomas L. Hale, 1996) It is one of the most common causes of child morbidity and mortality in developing nations with crowding inhabiting conditions where transmission from person to person is common (Chien-Shun Chiou, 2001). Shigellosis causes 1.1 million deaths with 160 million cases worldwide per year in which 2/3 of patients are below the age of 5 (Kotloff, KL, 1999).

1.4.1. *Shigella boydii*
As shigellas are closely related to *E. coli* so they are generally considered as same species yet *Shigella boydii* being distinctly related to enteroinvasive *E. coli* makes it a genetically divergent and a step forward in evolution (Kotloff, KL, 1999). These species restricted to Indian sub-continent having 18 known serotypes; are named after the American bacteriologist Mark Frederick Boyd (Feng L, 2004). The number of *S. Boydii* serotypes in the Shigella scheme was 15 in 1958. Since then, a number of provisional serovars of *S. boydii* have been proposed from reference laboratories (Yang F, 2005; Ansaruzzaman M, 2005). *Shigella boydii* infection results into shigellosis whose intensity depends upon underlying condition of the patient (Yang F, 2005).

1.4.2. *Shigella dysenteriae*
*Shigella dysenteriae* has 12 serotypes attributed to it and its infection is a major concern for developing nations (Thomas L. Hale, 1996; Kaisar A Talukder, 2003). *S. dysenteriae* spreads by contaminated water and food causing the most severe dysentery because of its powerful and noxious Shiga toxin, exclusively produced by
this species (Kaisar A Talukder, 2003; Gross RJ, 1980). Shiga toxin is highly
destructive for eukaryotic cells and results into devastating circumstances (K Sandvig,
2004). The Shiga toxin of S. dysenteriae has enterotoxic activity and other serotypes
of shigellae produce Shiga-like toxins (O'Brien AD, 1979). Being a causative for
bacillary dysentery, Shigella dysenteriae is also associated with the development of
Hemolytic uremic syndrome, which comprises anemia, thrombocytopenia, and renal
failure (K Sandvig, 2004). At least three periods of epidemic outbreaks of dysentery
due to S. dysenteriae 1 have been recorded previously in the Indian subcontinent, in
dysenteriae infections are rare (Pan TM, 1997).

1.4.3. Shigella flexneri

Shigella flexneri is named after the American physician Simon Flexner, in addition to
the Japanese physician Kiyoshi Shiga, who sought the cause of dysentery. It is a
human intestinal pathogen, causing dysentery by conquering the epithelium of the
colon leading to acute inflammatory response. Flexneri causes worldwide, 1.5 million
deaths per year (EMBL-EBI, 2013; J Wei, 2003). This bacterium commonly inhabits
contaminated water or food is transmissible from person to person. On infection the
host develops severe abdominal cramps, fever and frequent passage of blood stool
(EMBL-EBI, 2013). Shigella flexneri 2a is the most prevalent of Shigella flexneri
species (Fan Yang, 2005).

1.4.4. Shigella sonnei

S. sonnei is the main serogroup found in industrialized countries, where it causes
approximately 70% of both endemic and travel related cases of shigellosis (Kathryn E
Holt, 2012). Now pathogen is making its way to developing nation, replacing the
more divergent S. flexneri due to areas undergoing economic development and
improvements in water quality (Kotloff L, 2002). Shigella sonnei is named for the
Danish bacteriologist Carl Olaf Sonne. Shigella sonnei remains the most frequently
isolated species from the children aged <5 (Mead PS, 1999).