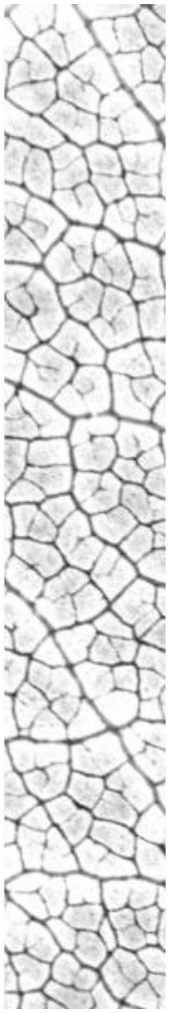

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Review on bacterial etiology of neonatal infections

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Abstract
Neonatal infection is a term used to describe any microbial infection being documented in the first month of life. Neonatal infections and sepsis are the major problem in preterm neonates who have an increased incidence of infection. The incidence is significantly higher in neonates of low weight, e.g., less than 1000g compared with neonates of 1000-2000g. The incidence of neonatal bacterial infection depends on geographic area and may vary from country to country as well as within the same country. According to the reported incidences, bacteria causing neonatal infections may widely differ among different countries according to the environmental factors, so, the pathogens most often implicated in neonatal infections in developing countries differ from those seen in developed countries. Overall, in most developing countries, Gram-negative bacteria remain the major cause of infection and are mainly represented by *Klebsiella spp*., *Escherichia coli*, *Pseudomonas spp., Enterobacter spp.* and *Salmonella spp.,* Gram positive organisms, represented by *S. aureus*, coagulase negative streptococci (CoNS), *S. pneumoniae* and *S. pyogenes* were also isolated from neonatal infections, whilst, Group-B Streptococci are generally rare.

Keywords: neonates, bacteria, infections, intensive care unit

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INTRODUCTION

In spite of the considerable measures in hygiene strategies, using of new and effective antibacterial agents and advanced techniques for diagnosis, neonatal infection remains the main cause of neonatal death due to the vulnerability of neonates for infection because their humoral and cellular defense mechanisms are inadequately developed, in addition, the signs and symptoms of infections may be difficult to distinguish (Shahsanam, et al. 2008). Most studies have been reported that, neonatal infections and sepsis are the major problems in preterm neonates who have an increased incidence of infection. Incidence of neonatal infection is significantly higher in neonates of less than 1000gm. in comparison with a birth weight of 1000-2000g (Klinger, et al. 2000).

Neonatal mortality is neonate death occurring within 28 days postpartum, which is often attributed to infections and inadequate access to basic medical care, during pregnancy and after delivery (Norton, 2005). World Health Organization (WHO) reported that, the deaths of neonates are estimated as high as four million yearly, all around the world, 35% of those are caused by bacterial infections during the neonatal period, which represents, about 2 deaths per minute. High rate of those deaths incidences were reported in the developing countries where mortality rate of neonates by sepsis be recorded as high as 85%. On the other hand, the neonate's mortality in developed countries due to sepsis was estimated around 20% for three consecutive decades (WHO, 2001). These neonatal deaths can be ascribed mainly to bacterial infections, asphyxia during delivery and complication of premature and low birth weight. It seems that bacteria mainly implicate in neonatal deaths, since they possess different virulence factors, these include interaction of maternal-fetal colonization, trans-placental immunity, in addition in addition to physical and cellular defense mechanisms of the neonate (Jumah and Hassan, 2007).

The neonatal bacterial infection may vary around the world, from country to country and even from region to region among the same country according to geographic, environmental and socio-economic factors. However, neonatal mortality is estimated about 34 per 1000 live births in Asia, 42 per1000 live births in Africa and 17 per 1000 live births in Latin America and the Caribbean (Vergnano, et al. 2005) compared with relatively, low death ratio, being reported in the USA and Australia which is about 6–9 per 1000 live birth while in Europe, it is 0.3-3 per 1000 live births (Heath, et al. 2003). In Iraq, United Nations (UN) estimated the

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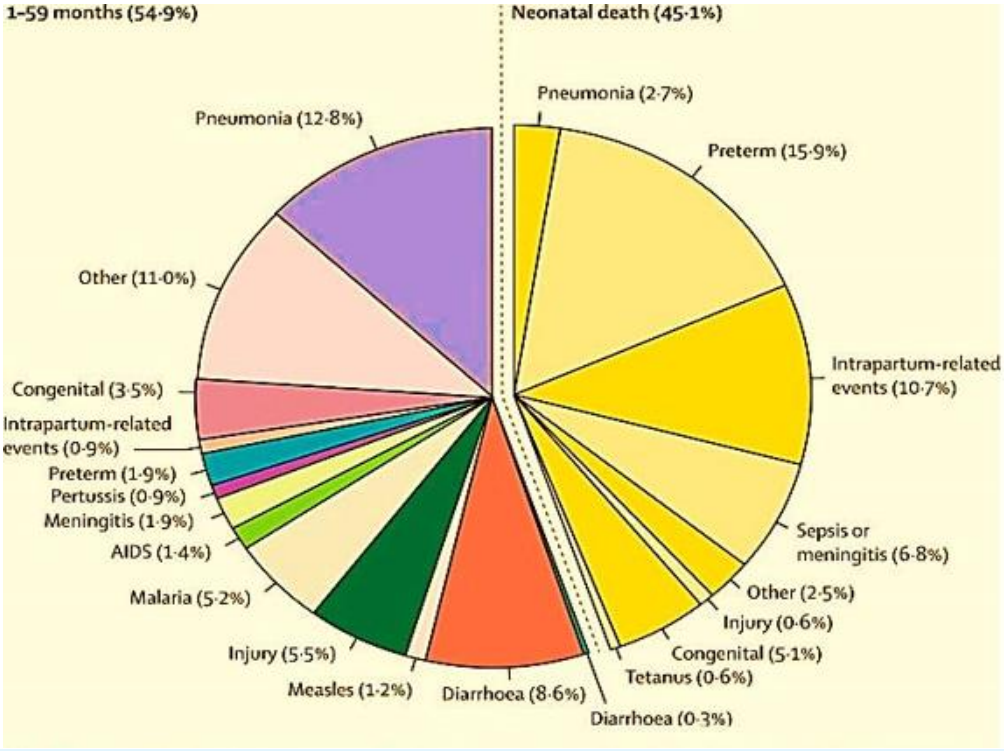

Fig. 1. Global causes of under-5 deaths in 2015 (Liu et al., 2016)

mortality rate about 33 per 1000 live births for period between 2005-2010 (UN, 2013), whilst, Central Intelligence Agency (CIA), world fact-book, estimated the mortality rate in Iraq, about 38.86 per 1000 live births till May 2013 (CIA 2013). **Fig. 1**, (Liu, et al. 2016) showed the neonatal infections transmit by many ways, depending on the routes of entry, they can be categorized into: Antenatal infections (Prenatal, Congenital infections (Intrapartum) and Postnatal infections (Nosocomial**).**

Antenatal infections transmit directly from the mother to an embryo during intrauterine period. Congenital infections transmit from the mother to an embryo or a fetus during the delivery, while, Postnatal infections transmit to the neonate after birth as nosocomial infection (Auriti, et al. 2003).

All available evidences indicate that, the etiologic agents of neonatal infections may widely differ among countries according to some factors, mostly the environmental, socio-economical and heal thing educations. Gram-negative bacteria have been reported to be, the predominant organism responsible for infections in most developing countries (Dawodu, et al. 2002), while, in developed countries, Gram positive bacteria have been the most frequent etiological agent. On the other hand, the bacterial profile was changing with the development of diagnosis and treatment strategies (Polin and Saiman, 2003). However, intrinsic and extrinsic factors are associated with neonates and increases the risk of infections.

Spreading of antibiotics resistant organisms in hospitals is a significant problem. Which may due to the wide availability of over the counter antibiotics and the inappropriate use of broad spectrum antibiotics in the community (Motara, et al. 2005). The spectrum of organisms that cause neonatal infections changes overtime and varies from region to region and from hospital to hospital even in the same country/city.

THE BACTERIAL ETIOLOGY OF NEONATAL INFECTIONS

As it is known that microorganisms causing neonatal infections may either, bacteria, fungi or viruses. The distribution of these causes may depend of seasonal, environmental and hygienic factors. During the 1950s, *Staph. aureus* was reported to be the common causative agent of nosocomial infection in hospitalized neonates, while, during the 1960s, Gram-negative bacilli, represented by *E. coli, Klebsiella spp.* and *Pseudomonas aeruginosa,* were reported as the most common pathogens causing neonatal infection (Sundaram, et al. 2009). Later, during 1970s, Staphylococcus spp., e.g. both, coagulase positive Staph. aureus, including MRSA and coagulase negative staphylococci (CoNS), e.g. *Staph. epidermidis* became the common causes of infections in the Neonatal Intensive Care Unit (NICU). However, gram-positive cocci and even gram positive bacilli continue to be the predominant organisms causing high ratio of neonatal infections in comparison with that infections caused by

Gram-negative bacilli which were estimated as 20-30% of neonatal nosocomial infections (Polin and Saiman, 2003). Although, gram positive bacilli, *Bacillus cereus* is an uncommon but it is live threating pathogen causing blood stream infections, respiratory system infection and central nervous system infection of preterm neonates or low-birthweight neonates with prolonged mechanical ventilation and intravascular catheter.

According to the reported incidences, bacteria causing neonatal infections may widely differ among different countries according to the environmental factors, so, the pathogens most often implicated in neonatal infections in developing countries differ from those seen in developed countries. Overall, in most developing countries, Gram-negative bacteria remain the major cause of infection and are mainly represented by *Klebsiella spp*., *E. coli*, *Pseudomonas spp., Enterobacter spp.* and *Salmonella spp.* (Tallur, et al. 2000)) and the Gram positive organisms, *S. aureus*, CoNS, *S*treptococcus *pneumoniae* and *Streptococcus pyogenes* are most commonly isolated from neonatal infections. In addition, *Enterococcus spp*. and *Listeria spp*., whilst, GBS is generally rare (Dawodu, et al. 2002).

In developed countries, GBS has been reported as the most frequent etiological agent of neonatal infections, being responsible for high morbidity and mortality rates (Hyde, et al. 2002). CoNS are the common cause of nosocomial and bloodstream infections in NICU followed by *S. aureus* and *E. coli*. In conclusion, in developing countries, neonatal infections have a higher fatality rate, particularly when Gram negative bacteria are involved (Isaacs 2003). This may due to fecal contamination and these bacteria are highly adaptive pathogens (Livermore and Woodford 2006). The worldwide increasing in number of neonatal infections caused by gram negative bacteria being accompanied by rising rates of antibiotics resistance which is a serious global public health concern due to the challenge of increasingly limiting of treatment options (Sievert, et al. 2013). Das *et al.* (Das, et al. 2011) emphasized that, the prevalence of Gram negative bacilli colonization of the neonatal gut which definitely.

ETIOLOGIC OF GRAM NEGATIVE BACTERIA OF NEONATAL INFECTIONS

A variation was observed in the rate of isolation of Gram negative bacteria as etiologic agent of neonatal infections, which, might be attributed to some factors represented by; hospital policy in measures of such cases, drug using, climatic and hygienic factors may also affect the variability of results among different areas (Memmel, et al. 2004). It is not known whether these differences reflect true differences in pathogens across the world, reflect an epidemiological transition in some countries linked to the fact that most infected neonates in developing countries die at home before reaching the health facilities and they do not appear in the statistics (Baqir 2012).

Al-Musawy (Al- Musawy 2003) reported that*, K. pneumoniae* have highest rate of isolation from neonates in Baghdad, while Baqir (Baqir 2012), in Babylon found that, the predominant isolates was *Enterobacter aerogenes*, while the findings of Movahedian *et al.* (Movahedian, et al. 2006) indicated that *P. aeruginosa* was the commonest cause of neonatal infection. The high frequency for isolation of *P. aeruginosa* may be related with this bacterium as a significant pathogen associated with both nosocomial and community-acquired infection. It is regarded as endemic organism causing serious nosocomial infections including meningitis, endocarditis, otitis media, chronic pulmonary colonization, pneumonia, conjunctivitis, UTI and osteomyelitis (Mesaros, et al. 2007). Sievert *et al*, (Sievert, et al. 2013) described *P. aeruginosa* as a problematic and virulent pathogen that can be a cause of common infections in humans such as nosocomial pneumonia, UTI and bloodstream infections. It is the most common gram negative organism causing ventilator associated pneumonia and the second most common cause of catheter-associated UTI. On the other hand, Blanc *et al.* (Blanc, et al. 2007) emphasized that hospital environment can represent an important source of *P. aeruginosa***.** Its ability to survive in the moist environment and resistance to many antibiotics make *P. aeruginosa* a common pathogen in NICU (Pourshafie, et al. 2007) causing high mortality rates (Foca, et al. 2000). *P. aeruginosa* determines many kind of infections e.g., bacteremia, sepsis, UTI, dermatitis, respiratory system infections, soft tissue infections, bones and joints infections, gastrointestinal infections and a variety of systemic infections, particularly in immunosuppressed patients such as premature and low birth weight neonates. however, *P. aeruginosa* seem to be the commonest cause of neonatal infections (Movahedian, et al. 2006). Consequently, *P. aeruginosa* is regarded as a leading gram-negative pathogen that causes nosocomial infections because it is distributed in wide variety of environments depending on its capacity to adapt easily to the changes in the environment, its minimal nutritional requirements to grow and its ability to tolerate a range of physical conditions, including temperature, even though the optimum temperature for its growth is 37°C. It is capable of growing at temperatures as high as 42°C. Additionally, it can thrive in diluted sterilizers, disinfectants and catheters, and rapidly develops resistance to antibiotics.

K. pneumoniae ranks the second stage after *P. aeruginosa* as a cause of neonatal infections. Das *et al.* (Das, et al. 2011) stated that *K. pneumoniae* plays a major pathogen in neonatal sepsis and nosocomial infections, while AL-Faleh (Al-Faleh 2010) stated that the incidences of *K. pneumoniae* accounted for 25% and

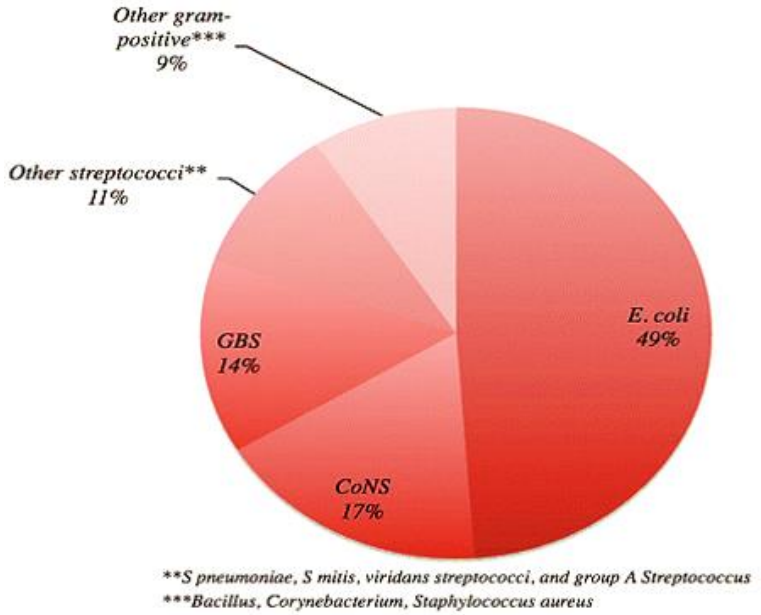

Fig. 2. *E. coli* is the most common cause of EOS in very low birth weight infants in the United States (Falciglia et al., 2012)

38% respectively. The possible explanation for high rate of isolation perhaps because *K. pneumoniae* represents a member of coliform bacteria and intended to be an indicator of fecal contamination (Das, et al. 2011). Although it is found as normal flora of the mouth, skin, and intestines, *K. pneumoniae* can cause destructive changes to human lungs if aspirated and it was well-established pathogens in NICU (Rayan and Ray 2004). It can cause upper respiratory tract infection, pneumonia, UTI, surgical wounds infection, diarrhea, conjunctivitis, osteomyelitis, meningitis, bacteremia and sepsis. Furthermore, *K. pneumoniae* was the most common cause of outbreaks in the NICU during the 1970s (Polin and Saiman, 2003). In recent years, *K. pneumoniae* has become important pathogen in nosocomial infections. Once *K. pneumoniae* infects the bloodstream, it can spread to every organ in the body. In addition, invasive devices, e.g. respiratory support equipment, urinary catheters and the increase use of antibiotics put neonates at increased serious risk to it (Groopman 2008).

Das *et al.* (Das, et al. 2011) pointed out, the high percentage of this bacterium was revealed in oral cavity may be because of prolonged use of a feeding tube affect the colonization of the gut and by vomiting.

E. coli is one of the main causes of neonatal infections, neonatal meningitis Urinary Tract Infection (UTI), gastroenteritis, pneumonia, peritonitis, and sepsis. Virulent strains of *E. coli* has been the subject of a bacterial outbreak that began in Germany in 2011 and other European countries and even North American regions (Mellmann, et al. 2011). It was reported by Das *et al.* (Das, et al. 2011) that, the percentages of *E. coli* isolation from neonate infections were 11% and 12.5% respectively. Friedman *et al.* (Friedman, et al. 2000) found that *E. coli* presented as high as 83% of late onset sepsis, while Stoll *et al.* (Stoll, et al. 2011) pointed out that it represented the causative agent of 29% neonatal sepsis and 44% neonatal CSF infection. Hilbert (Hilbert 2011) stated that *E. coli* accounted for 80% of Community Acquired-UTI and causing between 33% to 50% of all nosocomial UTI infection especially in patients undergoing long term catheterization. Stoll *et al.* (Stoll, et al. 2011), reported, that *E coli* is the most common cause of EOS in VLBW infants in the United States. **Fig. 2**.

The high incidence of *E. coli* in neonatal infections can be attributed to some reasons, e.g., *E. coli* is a fecal coliform bacteria and its presence is an indicative index as fecal contamination. Therefore, increased levels of fecal coliforms provide a warning of failure in hygiene conditions (Todar 2004), As it is known that *E. coli* is the typical inhabitant of the intestinal flora and a commensal of the vaginal flora, so, neonatal colonization with this bacterium often results from maternal transmission during delivery (Watt, et al. 2003). In addition, the increase in the intrapartum antibiotic exposure may alter the normal maternal microbiologic flora which result in colonization of neonatal skin and gastrointestinal tract with resistant and potentially pathogenic bacteria, thus several some studies reported that, the emergence of *E. coli* over GBS as the predominant organism responsible for neonatal infections (Bizzarro, et al. 2008).

Enterobacter aerogenes is one of the important causes of neonatal infections but not the main cause. Sundaram *et al.* (Sundaram, et al. 2009) concluded that, the frequency of *E. aerogenes* isolation in India was under changing. During a period from (1998), it represented the most common organism causing 35% of neonatal sepsis, while a significant reduction in this

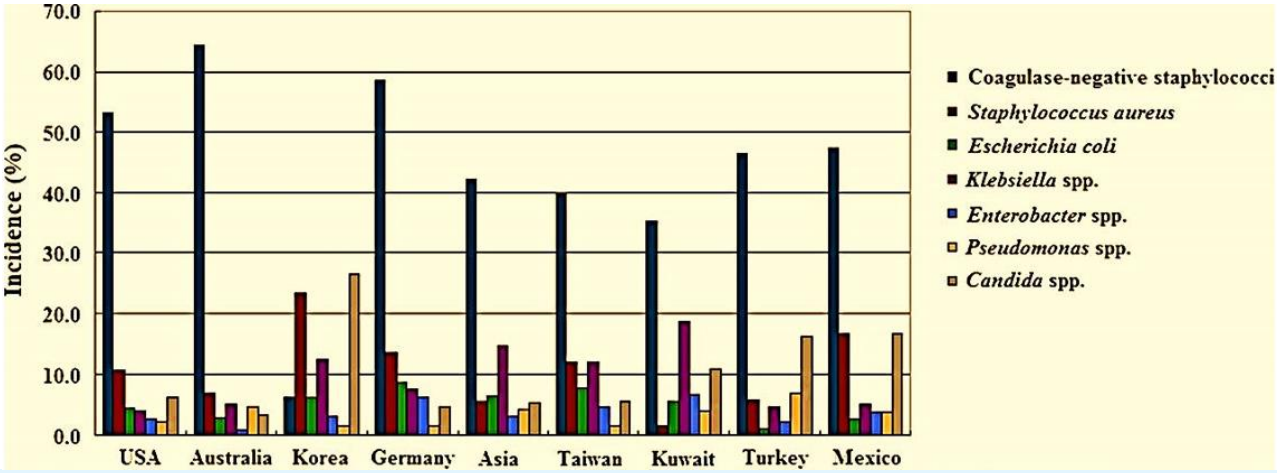

Fig. 3. Major causative pathogens of neonatal late-onset sepsis and their incidence by geographical areas (Dong and Speer, 2014)

incidence revealed after (2001) due to this bacterium dropped significantly with the emergence of Gram positive cocci especially CONS and *S. aureus*.

The sources of infection in *Enterobacter spp.* outbreaks varied from milk powder, thermometers, transducer head used in Intensive Care Unit, colonized patients, and water which was used to bathe the neonate (Dijk 2002). In Fiji, Narayan *et al.* (Narayan, et al. 2009) reported investigation of an outbreak of *E. aerogenes* infection in NICU where *E. aerogenes* was transmitted through direct injection of contaminated normal saline into the bloodstream of neonates, which was shared among the case patients.

ETIOLOGIC GRAM POSITIVE BACTERIA OF NEONATAL INFECTIONS

It must always take into account that CoNS are considered as non-pathogenic until their implication as nosocomial agents with emergence of multi-drug resistance which are responsible for high mortality rates worldwide (Beekmann, et al. 2003). The results being obtained by Al-Faleh (Al-Faleh 2010) reported that CoNS were the most common late-onset pathogens accounting for around 80% of all Gram positive infections in Al-Riyadh, Saudi Arabia. The emergence of high percentage isolation of CoNS suggests that may result from repeated handling of the neonates by personal and family with poor hygiene or it may be an over diagnosed entity as it is difficult to clearly definite from possible infections and probable contaminants even with the availability of guidelines (Al-Faleh 2010). Some other studies have reported lower incidences, in the United States, CoNS represented 32.5% of Gram positive pathogens in late onset infections (Cohen, et al. 2009), while in India, Trotman and Bell (Trotman and Bell 2006) recorded that CoNS causes 4% of Very Low Birth Weight (VLBW) neonate infections.

The emergence of CoNS populations with heterogeneous resistance to Oxacillin causes a great difficulty to detect them in clinical routine laboratories (Antunes, et al. 2007). Hospital acquired infections is regarding as a risk factor for neonates due to relative immaturity of their immune system, along with dependence on technology, particularly the use of indwelling catheters, and prolonged hospital stays (Nash, et al. 2013).

The pattern of isolation of CoNS isolated from neonatal infections is in different according to some factors. The reported incidences of *S. epidermidis* by Giusti *et al.* (Giusti, et al. 1999) and Antunes *et al.* (Antunes, et al. 2007) were 74% and 52% respectively, while it was higher than Baqir (Baqir 2012) who stated that, the frequency was 14%. *S. epidermidis* is a particular concern for patient with catheters or other surgical implants because it forms a virulence factor that occurs most commonly on intravenous catheters and on medical prostheses. Coagulase negative staphylococci (CoNS) have emerged as the predominant pathogens of LOS, accounting for 53.2%–67.9% of LOS in industrialized and 35.5%–47.4% in some developing regions (Boghossian, et al. 2013), as indicated in **Fig. 3**.

Zaidi and coworkers (Zaidi, et al. 2009) studied the etiology of EOS in newborns in developing countries, Latin America, the Caribbean Asia, and Africa, then, they stated that *S. aureus* is the most common gram-positive pathogen causing neonatal infection in these areas, **Fig. 4**.

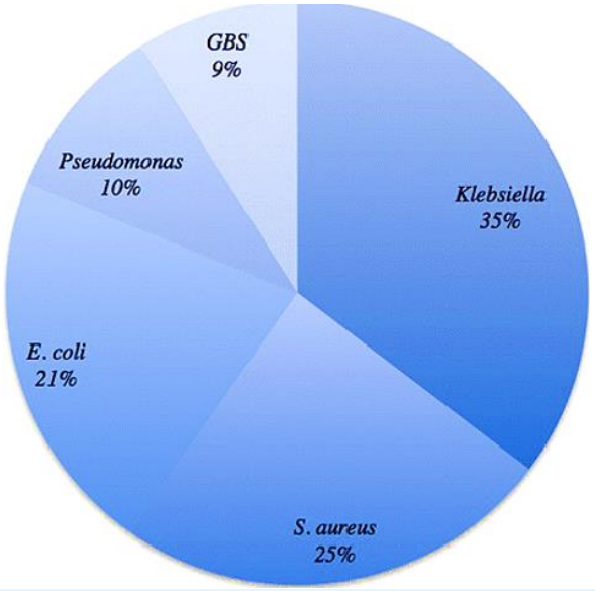

Fig. 4. *S. aureus* was the most common gram-positive pathogen in Early Onset Sepsis (EOS) in developing nations (Falciglia et al., 2012)

S. aureus has long been recognized as one of the most common etiologic agent of neonatal infections, Sundaram *et al.* (Sundaram, et al. 2009) noticed that this bacterium became the dominant organism causing Late Onset Sepsis (LOS) after 2001, primarily due to an increase in LOS exclusively in Low Birth Weight (LBW) and VLBW neonates and the resultant longer hospitalization with using of invasive devices and catheters which make neonate more vulnerable to the infection. Naher and coworkers (Naher, et al. 2013) showed that *S. aureus* accounted for (33%) of bacteria isolated from blood stream of neonates. whereas, Al-Faleh (Al-Faleh 2010) reported it accounted for only 6.12%. The high isolation rate of *S. aureus* can be ascribed to its ability colonize surfaces particularly, skin and mucus surface. However, the presence of *S. aureus* in a sample and its isolation rate depends on several factors, e.g., virulence of isolates of isolate, health status of patients, environmental conditions and laboratory techniques (Abdallah, et al. 2007). As compared to other bacteria, *S. aureus* is more resistant to the action of disinfectants, tolerant to desiccation and they keep viable for long time in the environment after having been discharged from patients, furthermore, it is resistant to many antibiotics particularly Methicillin (Methicillin Resistant *S. aureus*, MRSA). It withstands temperature and salty environment as high as 60°C for 30 minutes and 15% NaCl, respectively (Dancer 2008). Furthermore, its adaptive power to antibiotics and to competition with other bacteria enabled *S. aureus* to be one of the most potent pathogens (Deurenberg, et al. 2004), consequently, it can cause a range of infectious diseases from mild cases, such as skin and soft tissue infections to severe, life-threatening infections e.g. pneumonia, meningitis, osteomyelitis, endocarditis, toxic shock syndrome (TSS), bacteremia, and sepsis. Infections may spread through many ways, contact with pus from an infected wound, skin-to-skin contact, and contact with objects such as towels, sheets and clothes. Deeply penetrating *S. aureus* infections can be severe (Fang and Hedin 2003).

According to the results recorded by some studies, *Enterococcus faecalis* is also implicated in neonatal infections. *Enterococcus spp.* is an important pathogen in neonatal meningitis and sepsis, since it accounted for 10% from CSF samples and 5% from blood samples (Garges, et al. 2006). On the other hand, *E. faecalis* was the causative agent of the bloodstream infections at (NICU) of a cardiology hospital in Brazil (Strabelli, et al. 2006). Outbreaks and endemic *E. faecalis* infections particularly in NICU indicated for person to person transmission because of immunosuppression resulted by underlying syndroms and therapeutic policy, e.g., central venous catheterization (Samuelsson, et al. 2003). As it is known, that *E. faecalis* is one of the normal flora in gastrointestinal and genitourinary tract, even though, it plays an important role in nosocomial infection causing high, relatively, high rate mortality. It has been described as the second-most commonly isolated agent of nosocomial infections in United States during the period of 1986-1989 (Fernandes, et al. 2000). The widespread of *E. faecalis* as a nosocomial pathogen can be explained by its possession of various survival and virulence factors. Survival factors include;

ability for competition with other bacteria, tolerance of nutritional conditions, survive in extreme environmental conditions, e.g., high alkaline pH (9.6), high salt concentrations, bile salts, detergents, heavy metals, ethanol, azide, and desiccation (Gilmore 2002), survive over long periods on inanimate objects such as thermometers and stethoscopes, and it grows in a wide range of temperature (Tendolkar, et al. 2003). On other hand, this bacterium possesses a group of virulence factors, since it is able to suppress lymphocytes' action (Lee, et al. 2004), formation of biofilm and possession of lytic enzymes, cytolysin, aggregative substance, pheromones, and lipoteichoic acid (Rocas, et al. 2004). Furthermore, ability of *E. faecalis* to resist potent antibiotics, e.g., vancomycin (VREF) contributes in its pathogenicity (Rayan and Ray 2004). Consequently, *E. faecalis* can cause various infections, e.g. endocarditis, bacteremia, UTI, sepsis, pneumonia and meningitis (Hidron, et al. 2008). It colonizes the mouth and respiratory tract by its ability to adhere to oral cavity epithelia and it has been reported as the second leading cause of UTI in hospitalized neonates. It must always take into account that presence of central venous catheter causes direct contact between neonate's bloodstream and the environment (Strabelli, et al. 2006). In the assessment of the rate of isolation, it is important to take the time of onset of the infection into

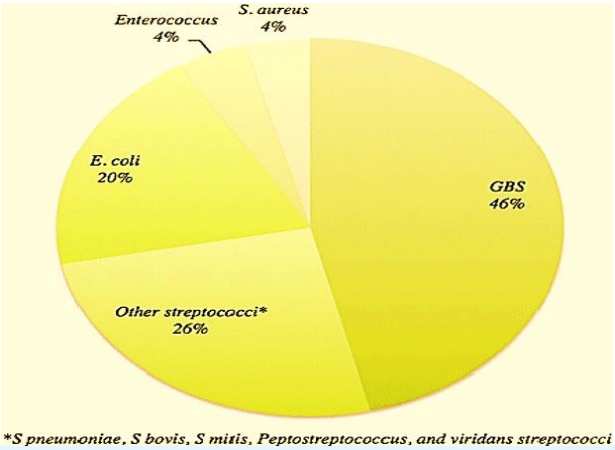

Fig. 5. GBS is the most common cause of Early Onset Sepsis (EOS) in term newborns in the United States (Falciglia et al., 2012)

consideration, this factor affects the rate of isolation of *E. faecalis* in neonates (Cohen, et al. 2009). Cohen-Wolkowiez *et al.* (Cohen, et al. 2009) reported that this bacterium accounted 4% for Early Onset Sepsis (EOS) and 17% for LOS. However, this organism was reported as a causative agent of amniotic fluid infection (Hitti, et al. 1997). Other bacteria, e.g. *Streptococcus agalactiae* (GBS) also implicates in neonatal infections. It is the most common cause of EOS in term newborns, as indicated in **Fig. 5**, (Stoll, et al. 2006).

Streptococcus agalactiae accounted for 60% in CSF samples and 70% in blood samples in neonates (Garges, et al. 2006), while, Cohen-Wolkowiez *et al.* (Cohen, et al. 2009) found that *Streptococcus agalactiae* accounted for 22.6% EOS. Other studies showed low frequency of isolation of *S. Sagalactiae*, e.g. 11% (Trotman and Bell 2006), 6.12% (Al-Faleh 2010) and 6% (Holst, et al. 2010). This variation in the rate of isolation of this bacterium may ascribe to the differences in maternal health, hygienic conditions during pregnancy and delivery, and to hospital policy between countries and between different regions in the same country (Black, et al. 2010).

Maternal colonization of the lower genital tract with GBS during pregnancy increases the risk of neonatal infection by vertical transmission (Ohlsson and Shah 2009), who stated that 20 to 30% healthy women can be colonized recto-vaginally with GBS, and 50 to 70% of neonates to these women will themselves become colonized. GBS is recognized as the most frequent cause of early onset neonatal infection (CDC 2002). GBS early onset infection which occurs with pneumonia and respiratory failure complicated by bloodstream infection and sepsis. It was concluded that GBS early onset neonatal infection caused because of the ascending infection through the placental membranes to initiate intrauterine infection, or because of the aspiration of infected vaginal fluids during the birth process (Doran and Nizet 2004).

List. monocytogenes was also reported elsewhere to implicate in neonatal infection. In US, this bacterium isolated in a frequency of 1.6% of CSF samples and 0.5% blood samples be obtained from infected neonates (Garges, et al. 2006). In Iraq, it was isolated in a frequency of 3% from bacteremic neonates Naher *et al.* (Naher, et al. 2013). However, according to above results, it seems that Listeriosis is relatively not common, and it mainly occurs in neonates and immunocompromised persons. Pregnant women may acquire listeriosis by ingestion of *listeria* through contaminated food or drinks and can carry it asymptomatically in their vagina or genitourinary tract. Maternal infection with *L. monocytogenes* can result in some serious complications e.g., premature labor, chorio-amnionitis, spontaneous abortion, or stillbirth (Jackson, et al. 2010). Fetal Listeriosis can occur via descending trans-placental transmission, ascending transmission through ruptured amniotic membranes and vertical transmission can also occur via passage through an infected birth canal (Lamont, et al. 2011). Generally, there are two clinical presentations of neonatal listeriosis, these are either early onset or late onset listeriosis. The former case usually begins at a mean age of 1.5 days and mainly associated with sepsis or meningitis, accounting for 20-40% mortality rate, while late-onset neonatal listeriosis frequently begins at a mean age of 14 days and presents with purulent meningitis accounting for 0-20% mortality rate. Anyway, the mortality rate in older children has reported to be less than 10% (Gaschignard, et al. 2011). The incidence of neonatal listeriosis was decreased in the United States since the early 1990s (Bortolussi 2008).

Despite *Bacillus cereus* is a common cause of food poisoning, it is increasingly being acknowledged as an opportunistic pathogen can cause systemic infections with bacteremia, pneumonia, meningitis, sepsis and endocarditis as well as localized infections of the central nervous system, respiratory tract, eye, wounds and soft tissue (Lede, et al. 2011). The pathogenicity and virulence of *B. cereus* are related to production of several toxins and enzymes include necrotizing enterotoxin, emetic and diarrheal toxin, hemolysin and phospholipases. Furthermore, *B. cereus* can form biofilm which enables it to attach to the medical instruments and another surfaces (Auger, et al. 2009). Consequently, *B. cereus* is highly virulent pathogen in neonates causing severe illness. It causes systemic infections in immuno-compromised patients or those with indwelling foreign bodies such as catheters (Gaur and Shenep 2001). In a series by Gaur *et al.* (Gaur, et al. 2001), of 21 neonates with *B. cereus* infections, mortality was 80% for all VLBW neonates.

Invasion of the oral cavity of febrile or immunosuppressed neonates by *B. cereus* is prevalent, therefore, oral cavity may become colonized with *B. cereus* either through the inhalation of spores, feeding

bottle or by vegetative cells passing through in contaminated food (Bottone 2010).

The assessment of the origin of neonatal infections with *B. cereus* is often difficult because it is a ubiquitous in the air, water, soil, feces and other environments, furthermore, the lack of awareness of its hazardous toxicity in neonates may mistakenly be overlooked and considered as a contamination without clinically relevant (Deindl, et al.2007). As mentioned above, there are numerous environmental reservoirs for *B. cereus* in hospitals include air filtration and ventilation equipment, fiber-optic bronchoscopy equipment, (Kuroki, et al. 2009), gloves, hands of staff, intravenous catheters. Some epidemiological studies shed light on neonatal infections occurred in Europe caused by *B. cereus*. In Britain, Gray *et al.* (Gray, et al. 1999) stated that, the outbreak occurred in NICU caused by this bacterium, which was isolated from endotracheal secretions of intubated neonates, and contaminated equipment, e.g. ventilator was suspected to be the source of infection. A report from Netherlands by Van-Der-Zwet *et al.* (Van-Der-Zwet, et al. 2000) pointed out, that the respiratory tract of neonates was colonized with a single *B. cereus* strain which was detected on the hands of nursing staff and in mechanical ventilation equipment. (Hilbert 2011) reported that, intravenous catheters and ventriculoperitoneal can be as agents of transmission of neonatal meningitis caused by *B. cereus*. In U.S. Turabelidze *et al.* (Turabelidze, et al. 2013) investigated *B. cereus*–positive tracheal aspirates from neonates on ventilators in NICU. *B. cereus* isolates were characterized in 33.3% of neonatal different samples and 11% environmental samples.

All available evidences indicate that most neonatal infections with *B. cereus* occurred in NICU, may be because the advances in NICU throughout the past several years have improved survival of VLBW neonates, but due to their immature immune systems, prolonged hospitalization with long term mechanical ventilation and intravascular catheters made them more vulnerable to infections caused by environmental bacteria such as *B. cereus*. Nosocomial infections by *B. cereus* was considered a serious issue because of the hospital environment may contain its endospores which are highly resistant to harsh environmental conditions and common methods of decontamination, such as heating, desiccation, chemical exposure and radiation. Furthermore, alcohol-based hand washing solutions used in NICU are not sporicidal (Sankararaman and Velayuthan 2013).

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