

***Escherichia coli* and *Staphylococcus aureus* most common source of infection**

G. Bachir raho and B. Abouni

Laboratory of Molecular Microbiology, Health and proteomics, University of Sidi Bel abbes, Algeria

Escherichia coli and *Staphylococcus aureus* are a serious cause of a variety of community- and hospital-acquired infections. *E. coli* is one of the most common nosocomial pathogens that cause urinary tract infections (UTIs) and enterocolitis. *S. aureus* is also an etiological infection agent responsible for significant levels of morbidity and mortality. According to Broad Institute. (2010), *Escherichia coli* accounts for 17.3% of clinical infections requiring hospitalization and is the second most common source of infection behind *Staphylococcus aureus* (18.8%). In recent years, the emergence of resistant *Staphylococcus aureus* and resistant *Escherichia coli* strains to many antibiotics has been observed worldwide. These have become a major concern in global public health invigorating the need for new antimicrobial compounds. This review described these two bacteria, their taxonomies, morphology and biochemical characteristics, habitat and growth characteristics, the caused infections, their treatment and resistances to antibiotics.

Keywords: *Escherichia coli* and *Staphylococcus aureus*; infection; characteristics

1. Introduction

Infectious diseases are the leading cause of global morbidity and mortality [1]. In 1990, infections cause 16 million deaths, and in 2010, the number of deaths had fallen to 15 million [2]. The spread of infectious diseases results as much from changes in human behavior--including lifestyles and land use patterns, increased trade and travel, and inappropriate use of antibiotic drugs--as from mutations in pathogens [3]. *Staphylococcus aureus* and *Escherichia coli* are a major cause of various humans and animals infections. The first causes skin and soft tissues infections, surgical site infections, and bone and joint infections. *Staphylococcus aureus* is a common cause of hospital-acquired bacteraemia and it is associated with hospital-acquired respiratory tract infections [4]. *E. coli* is the most common cause of urinary tract infections (UTIs) in humans [5], and is a leading cause of enteric infections and systemic infections [6]. The systemic infections include bacteremia, nosocomial pneumonia, cholecystitis, cholangitis, peritonitis, cellulitis, osteomyelitis, and infectious arthritis. *E. coli* is also leading cause of neonatal meningitis [7]. A wide range of antimicrobial agents effectively inhibit the growth of *E. coli*. The β -lactams, fluoroquinolones, aminoglycosides and trimethoprim-sulfamethoxazole are often used to treat community and hospital infections due to *E. coli* [8], but antimicrobial resistant isolates, especially those that are fluoroquinolone resistant and those producing extended-spectrum β -lactamases have increased significantly during the 2000's and in certain areas many nosocomial and community-acquired *E. coli* are now resistant the several important antimicrobial classes [8].

Penicillinase-resistant penicillins (flucloxacillin, dicloxacillin) remain the antibiotics of choice for the management of serious methicillin-susceptible *S. aureus* (MSSA) infections, but first generation cephalosporins (cefazolin, cephalothin and cephalexin), clindamycin, lincomycin and erythromycin have important therapeutic roles in less serious MSSA infections such as skin and soft tissue infections or in patients with penicillin hypersensitivity. All serious MRSA infections should be treated with parenteral vancomycin or, if the patient is vancomycin allergic, teicoplanin [9].

Antibiotic resistant staphylococci are major public health concern since the bacteria can be easily circulated in the environment. Infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) have increased worldwide during the past twenty years [10, 11]. Some reports of *S. aureus* isolates with intermediate or complete resistance to vancomycin portend a chemotherapeutic era in which effective bactericidal antibiotics against this organism may no longer be readily available [12, 13]. Multiple drug-resistant *S. aureus* have been frequently recovered from foodstuffs [4], water and biofilm formation [14] nasal mucosa of humans [15], clinical cases [16] and livestock [17].

This paper aims to review the taxonomies, morphology and biochemical characteristics, habitat and growth characteristics, the caused infections, the treatment and resistances to antibiotics of these two bacteria.

2. *Escherichia coli*

Escherichia coli, originally called "Bacterium coli commune," was first isolated from the feces of a child in 1885 by the Austrian pediatrician Theodor Escherich [18]. This bacterium had been named Bacterium coli commune by the discoverer; in 1911 the name was changed to *Escherichia coli* in honor of its discoverer [19]. In the

1940s, Kauffmann proposed a scheme to differentiate *E. coli* on the basis of lipopolysaccharide O, flagellar H, and polysaccharide K antigens [20].

2.1 Taxonomy

E. coli belongs to the family *Enterobacteriaceae*. It is one of the six species of the genus *Escherichia* (others include *E. hermannii*, *E. fergusonii*, *E. vulneris*, *E. blattae*, *E. albertii*) [19].

2.2 Morphology and Biochemical characteristics

Escherichia coli is a Gram negative, non-spore-forming, straight rod (1.1–1.5 μm - 2.0–6.0 μm) arranged in pairs or singly; is motile by means of peritrichous flagella or may be non-motile; and may have capsules or microcapsules [21].

Escherichia coli is a facultatively anaerobic, chemo-organotrophic microorganism. It is oxidase negative, catalase positive, fermentative (glucose, lactose, D-mannitol, D-sorbitol, arabinose, maltose), reduces nitrate, and is β -galactosidase positive. Approximately 95 % of *E. coli* strains are indole and methyl red positive, but are Voges-Proskauer and citrate negative [22].

2.3 Habitat and Growth Characteristics

Although most strains of *E. coli* have been described as harmless commensal organism, they can be a versatile pathogens in immunocompromised patients [23]. The organism is an inhabitant of the human digestive tract and can also be found in other warm blooded animals. *E. coli* has been used as an indicator of fecal contamination in food and water due to its common occurrence in feces and its survival in water [23, 24].

The limits of temperature for growth of *E. coli* are 7–46°C, and the optimum growth temperature is approximately 37°C [25]. *E. coli* generally grows within the pH range of 4.4–9.0, at an aw of at least 0.95, and at NaCl levels of less than 8.5 % [25]. *E. coli* can be recovered easily from clinical specimens on general or selective media at 37°C under aerobic conditions. *E. coli* in stool are most often recovered on MacConkey or eosin methylene-blue agar, which selectively grow members of the *Enterobacteriaceae* and permit differentiation of enteric organisms on the basis of morphology [26].

2.4 Serological characterisation of *E. coli*

Serotyping and serogrouping of *E. coli* is useful for subdividing the species into serovars. Serological typing in *E. coli* involves serological identification of three surface antigens: O (somatic lipopolysaccharide), K (capsular) and H (flagellar).

Although the numbers of the different *E. coli* O, K, and H antigens reported in the literature vary, Ørskov and Ørskov (1992) state that there are 173 O antigens (Scheutz et al (2004) report 174), 80 K antigens and 56 H antigens. Mol & Oudega (1996) have suggested that the fimbrial (F) surface antigens should be a fourth component of serological testing.

Determining the serogroup (O antigen) and serotype (O and H, and often K antigens) is an important means of defining the various pathogenic strains of *E. coli*, since certain serotypes are associated with the various categories of diarrheagenic *E. coli*. For example, *E. coli* serotype O157:H7 is an enterohemorrhagic *E. coli*, and *E. coli* serogroup O124 is an enteroinvasive strain. *E. coli* serotyping is important technique for making the proper diagnosis and for performing foodborne outbreak and epidemiological investigations. However, novel *E. coli* serotypes frequently emerge as intestinal pathogens and, when recognized, are included in a specific category of diarrheagenic *E. coli*. Thus serotyping alone cannot be relied on for categorizing a strain of *E. coli*, and the identification of specific virulence characteristics/genes must also be performed [30].

2.5 Pathogenic *Escherichia coli*

Escherichia coli are normal inhabitants of the human gastrointestinal tract and are among the bacterial species most frequently isolated from stool cultures. When *E. coli* strains acquire certain genetic material, they can become pathogenic [31]. Virulent strains of *E. coli* can cause gastroenteritis, urinary tract infections, and neonatal meningitis. In rare cases, virulent strains are also responsible for haemolytic-uremic syndrome (HUS), peritonitis, mastitis, septicemia and Gram-negative pneumonia [32].

2.5.1 Gastrointestinal infection

The commonest site of human infections due to *E. coli* is the gastro-intestinal tract, on account of the ease of access of pathogens ingested with food and drink. The incidence of such infections depends on a variety of factors, including personal and food hygiene, and environmental temperature [33]. *E. coli* strains that cause diarrheal illness are categorized into specific groups based on virulence properties, mechanism of pathogenicity,

clinical syndromes and distinct O: H serotypes [34]. Five classes or virotypes of *E. coli* are recognized as causative agents of these diarrheal diseases amongst which include enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), enteropathogenic *E. coli* (EPEC), enteroaggregative *E. coli* (EAaggEC) and enterohemorrhagic *E. coli* (EHEC) (Table 1) [35]. Each class falls within a serological subgroup and manifests distinct features in pathogenesis.

Table 1 *E. coli* classes (virotypes) that are related to diarrheal diseases [41].

Name	Hosts	Description
Enterotoxigenic <i>E. coli</i> (ETEC)	Humans, pigs, sheep, goats, cattle, dogs, and horses	<ul style="list-style-type: none"> • Non-invasive strains. • Cause diarrhea in children, as well as traveler's diarrhea. • Produces a heat-stable (ST) enterotoxin • 200 million cases of diarrhea and 380,000 deaths each year.
Enteropathogenic <i>E. coli</i> (EPEC)	Humans, rabbits, dogs, cats and horses	<ul style="list-style-type: none"> • Has an array of virulence factors similar to Shigella toxin • Moderately invasive and elicit an inflammatory immune response.
Enteroinvasive <i>E. coli</i> (EIEC)	found only in humans	<ul style="list-style-type: none"> • Causes a syndrome that is identical to Shigellosis, with profuse diarrhea and high fever.
Enterohemorrhagic <i>E. coli</i> (EHEC)	Humans, cattle, and goats	<ul style="list-style-type: none"> • The most famous member of this virotype is strain O157:H7, which causes bloody diarrhea and no fever. • Can cause hemolytic-uremic syndrome and sudden kidney failure. • Moderately invasive and possesses a phage-encoded Shiga toxin that can elicit an intense inflammatory response.
Enteroaggregative <i>E. coli</i> (EAEC)	found only in humans	<ul style="list-style-type: none"> • EAEC bind to the intestinal mucosa to cause watery diarrhea without fever. EAEC are non-invasive. • They produce a hemolysin and an ST enterotoxin similar to that of ETEC.

2.5.2 Urinary Tract Infections

Uropathogenic *E. coli* cause 90% of the urinary tract infections (UTI) in anatomically-normal, unobstructed urinary tracts. The bacteria colonize from the feces or perineal region and ascend the urinary tract through the bladder. With the aid of specific adhesins they are able to colonize the bladder [36]. Bladder infections are 14-times more common in females than males by virtue of the shortened urethra. The typical patient with uncomplicated cystitis is a sexually-active female who was first colonized in the intestine with an uropathogenic *E. coli* strain. The organisms are propelled into the bladder from the periurethral region during sexual intercourse [37].

Different virulence factors of *E. coli* which are thought to have a role in the pathogenesis of Urinary Tract Infections, some of them are O Antigens, K Antigens, Serum resistance, Adhesins, Colicins, Invasins etc [36].

2.5.3 Neonatal meningitis

In industrialized countries the incidence of neonatal bacterial meningitis is between 0.2 and 0.4 per 1000 live births, with an estimated mortality rate of 15 to 30 % which rises to nearly 40 % in premature infants. *E. coli* is currently the second cause of neonatal meningitis, behind group B streptococci [38]. Greater than 80% of the *E. coli* strains involved express K1 capsule. It is generally thought that the newborn acquires the K1 strain from its mother during passage through the birth canal. The strain then progressively invades the bloodstream and subsequently crosses endothelial surfaces into the brain. The K1 capsule is a critical determinant in invasion across the blood-brain barrier [39].

The K-1 antigen is considered the major determinant of virulence among strains of *E. coli* that cause neonatal meningitis. K-1 is a homopolymer of sialic acid. It inhibits phagocytosis, and responses from the host's immunological mechanisms. K-1 may not be the only determinant of virulence as siderophore production and endotoxin are also likely to be involved [40].

2.6 *Escherichia coli* and Antibiotic Resistance

2.6.1 β -lactam antibiotics

β -lactams antibiotics are the oldest and most broadly used class of antibiotics. They exert a bactericidal effect by inhibiting bacterial cell wall synthesis and are administered both orally and parenterally to treat a wide variety of bacterial infections. These antibiotics fall into three major structural categories—penicillins, cephalosporins and carbapenems. Resistance to these agents is mediated by β -lactamases which degrade them, and these enzymes play an important role in antibiotic-refractory Urinary Tract Infections [42]. The first β -lactamase enzyme was identified in *Bacillus (Escherichia) coli* before the clinical use of penicillin. In a sentinel paper published nearly 70 years ago, E. P. Abraham & E. Chain described the *B. coli* “penicillinase” [43]. TEM-1 (the most commonly encountered β -lactamase in gram-negative bacteria) enzyme was first recorded in *Escherichia coli* in 1965 and has since spread to 20–60% of isolates of *Enterobacteriaceae* [44]. Up to 90% of ampicillin resistance in *E. coli* is due to the production of TEM-1 [45]. The recent emergence of Extended Spectrum β -Lactamase -producing *E. coli* and *K. pneumoniae* has led to therapeutic failures and death when treating septicaemia with standard agents, like cefotaxime [46, 47]. The cephalosporins are the largest and most diverse family of beta-lactam antibiotics [48, 49]. They are divided into first, second, third, fourth and fifth generation drugs. The first agent cephalothin (cefalotin) was launched by Eli Lilly in 1964 [50]. An increase in the prevalence of β -lactam resistance, especially concerning the third-generation cephalosporins (3GCs), has been observed recently, according to the annual report of the European Antimicrobial Resistance Surveillance System. Three kinds of β -lactamase are commonly responsible for 3GC resistance: extended-spectrum β -lactamases (ESBLs), OXA-type penicillinases (or oxacillinases) and AmpC cephalosporinases (chromosomal or plasmid-mediated). Among ESBLs, the CTX-M β -lactamases have now become most prevalent [51].

2.6.2 Sulfonamides

Sulfonamides have been widely used to treat bacterial and protozoal infections ever since their clinical introduction in 1935. To overcome the rapid emergence of resistance, sulfonamides have generally been combined since the 1970s with diaminopyrimidines. The combination trimethoprim-sulfamethoxazole (Co-trimoxazole) was widely used, becoming in particular a mainstay of treatment for urinary tract infections [52, 53]. In 1995, the licensed indications for co-trimoxazole were restricted in favor of the use of trimethoprim alone, primarily owing to concern about the rare side effects of sulfonamides. Despite the massive reduction in the rate of sulfonamide use that accompanied the switch in prescribing from co-trimoxazole to trimethoprim, resistance to sulfonamides has persisted at high rates among clinical isolates of *Escherichia coli* [52]. Resistance to sulfonamides in *Escherichia coli* can result from mutations in the chromosomal DHPS gene (*folP*) or more frequently from the acquisition of an alternative DHPS gene (*sul*), whose product has a lower affinity for sulfonamides [53]. Three acquired genes imparting sulfonamide resistance have been described in *E. coli*; of these, only two (*sul1* and *sul2*) are prevalent in human isolates [52].

2.6.3 Trimethoprim

Trimethoprim (TMP) was first used for the treatment of infections in humans in 1962 [54]. Six year later, Trimethoprim resistance was described [55] and in 1971 1% of *E. coli* isolates from urinary specimens were reported resistant [56]. Since then there has been a constant increase in TMP resistance worldwide and in some regions only a minor part of the *E. coli* population is still susceptible to TMP [57].

2.6.4 Quinolones

Fluoroquinolones are broad-spectrum antimicrobial agents that are highly effective for the treatment of a variety of infections in humans and animals [58]. The first quinolone was nalidixic acid in 1962 followed by the fluoroquinolones (FQX) with ofloxacin (1985), ciprofloxacin (1986) (second-generation), levofloxacin (1993) and moxifloxacin (1999) which is described in some publications as a third generation [59, 60]. Fluoroquinolones are indicated for the management of acute uncomplicated UTIs as well as complicated UTIs and pyelonephritis for adults, but uropathogen resistance to them is increasing. In Spain, fluoroquinolone resistance had become such a problem that, by the mid-1990s, they were not first choice in the treatment of *E. coli* urinary tract infections [61]. In Beijing during 1997-1999, approximately 60% of *E. coli* strains isolated from hospital-acquired infections and approximately 50% of community-isolated *E. coli* strains were resistant to ciprofloxacin [62]. Resistance to ciprofloxacin and levofloxacin in *E. coli* reached 21.6% and 20.4%, respectively, of isolates tested in 2005. In the North American Urinary Tract Infection Collaboration Alliance surveillance study, 5.5% and 5.1% of urinary *E. coli* isolates from outpatients in the United States and Canada were resistant to ciprofloxacin and levofloxacin, respectively [63]. In *Escherichia coli*, mutational alterations in the Fluoroquinolones target enzymes, namely, DNA topoisomerase II (DNA gyrase) and topoisomerase IV, are recognized to be the major mechanisms through which resistance develops [64].

2.6.5 Pivmecillinam

Pivmecillinam is a β -lactam antimicrobial that has been used for the treatment of acute uncomplicated urinary infection for more than 20 years [65]. Use of pivmecillinam may spare the use of other agents, such as cotrimoxazole and quinolone antimicrobial agents, where there are concerns about resistance emerging in community *E. coli* and it may be desirable to preserve these other agents for treatment of infections other than acute cystitis [66].

3. *Staphylococcus aureus*

3.1 Brief history

In 1880, both Sir Alexander Ogston & Louis Pasteur provided the first description of “micrococci” isolated from furuncles and abscesses [67]. The name *Staphylococcus* (staphyle, bunch of grapes) was introduced by Ogston (1883) for the group micrococci causing inflammation and suppuration. He was the first to differentiate two kinds of pyogenic cocci: one arranged in groups or masses was called “*Staphylococcus*” and another arranged in chains was named “Billroth’s *Streptococcus*.” [39]. In 1884, Rosenbach described the two pigmented colony types of staphylococci and proposed the appropriate nomenclature: *Staphylococcus aureus* (yellow) and *Staphylococcus albus* (white) [68].

3.2 Taxonomy

The name *Staphylococcus aureus* comes from the Greek words “staphyle,” meaning a bunch of grapes, “coccus,” which means round-shaped, and “aureus,” for golden, because most colonies have a characteristic orange-yellow coloring on the traditionally used agar plates [69, 70].

Historically, based on morphologic similarities, the genera *Staphylococcus*, *Micrococcus*, *Planococcus* and *Stomatococcus* were placed together in the family *Micrococcaceae*. More recently, however, based on DNA/rRNA analysis and guanine–cytosine (GC) content, the genus *Staphylococcus* has been classified together with the genera *Bacillus*, *Brochothrix*, *Gemella*, *Listeria* and *Planococcus*, in the family *Bacillaceae* of the broad *Bacillus Lactobacillus Streptococcus* cluster of Gram-positive bacteria with a low GC-content [71, 72, 73].

According to current knowledge, including the newly described species published in 2009-2010, the *Staphylococcus* genus groups together 45 species and 21 subspecies [74].

3.3 Morphology and Growth Characteristics

Staphylococcus aureus is Gram-positive coccus - shaped microorganism (with diameter of between 0.7 μm to 1.2 μm) that generally occurs in grape-like clusters, but can also be found in singles and pairs. Cells are non-motile, lack flagella and do not form spores, though they are able to survive in dormant state for years under unfavorable conditions. *Staphylococcus aureus* grows best under aerobic conditions but is able to employ a fermentative metabolism, making it a facultative anaerobe [75, 76, 77, 78].

The organism is able to utilize several different carbohydrates during respiration. However, under anaerobic conditions, *S. aureus* will typically ferment glucose resulting in the production of lactic acid [79], and ability to ferment mannitol [80].

Members of the species grow in the presence of salt, under high osmotic pressure, low moisture and at wide pH and temperature ranges [75, 77]. A unique characteristic of *S. aureus* is its ability to grow in salt concentrations as high as 15%. The optimum water activity for *S. aureus* is about 0.99 but it is also capable of growing at water activities as low as 0.83 [81] if other intrinsic and extrinsic factors are optimal for growth of this pathogen.

Staphylococcus aureus is capable of growing in temperatures ranging from 7 to 48.5°C with an optimum growth temperature of 30 to 37°C [82]. In addition to being able to grow in wide range of temperatures, *S. aureus* can also grow in a wide range of pH values ranging from 4.2 to 9.3 with an optimum pH of 7 to 7.5 [83]. As with all Gram-positive bacteria, the cell wall contains peptidoglycan; however, it is also contains ribitol-teichoic acid molecules that are specific to *S. aureus* and act as antigens [76]. In addition to the presence of ribitol-teichoic acid in the cell wall of *S. aureus*, some strains may also exhibit the protein A, that can comprise up to 7 % of the cell wall and may coat the outside of the cell [84]. Both ribitol-teichoic acid and protein A work to increase the virulence of the microorganism [76]. The cell wall of *S. aureus* is also very thick in comparison with other gram-positive bacteria. This increased thickness provides the organism with a very high internal pressure making it nearly impossible for many antimicrobial drugs to enter the cell [77]. *S. aureus* can easily distinguished from pathogenic streptococci by its production of catalase. However, it is relatively similar to the other less virulent staphylococci. Due to this similarity *S. aureus* must be distinguished via diagnostic tests. Most strains of *S. aureus* will exhibit β - hemolysis when grown on blood agar which can be a distinguishing characteristic. *S. aureus* is differentiated from other staphylococcal species on the basis of coagulase reaction (coagulase positive) [80]. Coagulase binds to prothrombin in the blood causing fibrin to be polymerized, resulting formation of a clot [76]. The coagulase produced by *S.aureus* is considered a determinant of the pathogenicity of the organism [85].

3.4 Natural habitat

Staphylococci are widely distributed in various environments. Natural populations are associated with the skin, skin glands, and mucous membranes of humans and many animals alike. They are sometimes found in the intestinal, genitourinary, and upper respiratory tracts of these hosts. They have also been isolated from animal products and other sources, such as soil, sand, seawater, fresh water, dust, and air [86]. *Staphylococcus aureus* generally have a benign or symbiotic relationship with their host; however they may develop the lifestyle of a pathogen if they gain entry into the host tissue through trauma of the cutaneous barrier, inoculation by needles or direct implantation of medical devices. Infected tissues of host support large populations of staphylococci and in some situations they persist for long periods. The presence of enterotoxigenic strains of *S. aureus* in various food products is regarded as a public health hazard because of the ability of these strains to produce intoxication or food poisoning. *S. aureus* is a major species of primates, although specific ecovars or biotypes can be found occasionally living on different domestic animals or birds [87].

3.5 Virulence factors of *S.aureus*

S. aureus expresses many potential virulence factors:

- surface proteins that promote colonization of host tissues;
- invasins that promote bacterial spread in tissues (leukocidin, kinases, hyaluronidase);
- surface factors that inhibit phagocytic engulfment (capsule, Protein A);
- biochemical properties that enhance their survival in phagocytes (carotenoids, catalase production);
- immunological disguises (Protein A, coagulase);
- membrane-damaging toxins that lyse eucaryotic cell membranes (hemolysins, leukotoxin, leukocidin);
- exotoxins that damage host tissues or otherwise provoke symptoms of disease (SEA-G, TSST, ET);
- inherent and acquired resistance to antimicrobial agents [88, 89].

3.6 Pathogenesis of *S. aureus*

The pathogenicity of *Staphylococcus aureus* is due to the toxins, invasiveness and antibiotic resistance. *S.aureus* is major cause of nosocomial and community acquired infections [68].

Beyond its ability to exist as a commensal, *S. aureus* is also a versatile pathogen capable of causing a wide range of diseases from localized skin and soft tissue infections to life threatening septicemia [90]. It is also a major food poisoning bacteria [91] (Table 2).

Table 2 Clinical manifestations associated with *Staphylococcus aureus* infections [92].

Types of infections	
Direct infection	
(a) Skin infections	folliculitis, carbuncle, impetigo, cellulitis, abscess, ...
(b) Deep infections	
Blood stream infections	arthritis, osteomyelitis bacteriemia, sepsis metastatic infections : endocarditis, meningitis, osteomyelitis, arthritis, pericarditis, lung abscess, ...
Toxin-mediated diseases	food poisoning scaled skin syndrome toxic shock syndrome with multiple organ failure

Staphylococcus aureus can survive in various environments and has a wide range of natural reservoir [93]. It shows a high tolerance to variations in pH, which confers an advantage for colonizing body sites characterized by a mildly acidic pH, like skin, mouth, vagina, urine and abscesses, where it may cause severe infections [94].

3.6.1 Skin and Soft Tissue Infections

Staphylococcus aureus has long been recognized as a leading cause of skin and soft-tissues infections including abscesses, atopic dermatitis, carbuncles, cellulitis, furuncles, folliculitis, impetigo, pemphigus, psoriasis... In particular, necrotizing soft-tissue infections may be rapidly fatal because of the toxin-induced circulatory collapse [92].

3.6.2 Deep-seated infections

Once the bacteria have broken down the natural skin barrier, they can disseminate into more profound sites or migrate directly into the blood. Thus any localized infection has the potential to become the seeding ground for a more severe spread.

S. aureus is able to cause deep-seated related threatening systemic infections such as endocarditis, osteomyelitis, pneumonia, bacteremia and septic shock in which intracellular foci are probably present [95].

3.6.3 Bacteraemia

Staphylococcus aureus is a major cause of bacteremia, and *S. aureus* bacteremia is associated with higher morbidity and mortality, compared with bacteremia caused by other pathogens [96]. The exact incidence of *Staphylococcus aureus* bacteremia (SAB) is difficult to ascertain, as prospective population-based surveillance studies are infrequently performed. In Scandinavian countries, where data from the nationwide surveillance of SAB are routinely collected, the annual incidence is approximately 26/100,000 population. A similar low incidence of 19.7/100,000 population was reported in a Canadian study in 2008, while in countries with a greater burden of methicillin-resistant *S. aureus* (MRSA), incidence rates are generally higher, between 35 and 39/100,000 population. In comparison, even higher rates, approximately 50/100,000 population, are inferred from surveillance data from the United States [97].

3.6.4 Metastatic infections

S.aureus has a tendency to spread to particular sites, including the bones, joints, kidneys, and lungs. Suppurative collections at these sites serve as potential foci for recurrent infections.

Patients with persistent fever despite appropriate therapy should be examined for the presence of suppurative collections [98].

3.6.5 Toxin-mediated diseases

Among the predominant bacteria involved in food-borne diseases, *Staphylococcus aureus* is the leading cause of gastroenteritis resulting from the consumption of enterotoxins-contaminated food. Symptom-onset is abrupt and the disease may be severe enough to warrant hospitalization, but is usually self-limiting and does not require specific therapy.

In contrast, staphylococcal scalded skin syndrome (SSSS; Ritter syndrome) and toxic shock syndrome (TSS) are more severe. Staphylococcal scalded skin syndrome is a rare but well-described disorder in neonates and young children and results from the colonization or infection with a strain of *S. aureus* producing epidermolytic toxins. It ranges in severity from trivial focal skin blistering to extensive, life-threatening exfoliation. Toxic shock syndrome is one of the most feared staphylococcal manifestations and results from the colonization or infection with a strain of *S. aureus* producing the protein TSST-1. The key features of this infection are widespread erythroderma occurring in association with profound hypotension and multiple organ dysfunction [92].

3.7 Antibiotic resistance in *S. aureus*

Staphylococcus aureus has been recognized as one of the most common and devastating human pathogens [99]. In the preantibiotic era, the mortality of patients infected with *Staphylococcus aureus* bacteremia exceeded 80% [100]. The introduction of penicillin in the early 1940s dramatically improved the prognosis of patients with staphylococcal infection. However, as early as 1942, penicillin-resistant staphylococci were recognized, first in hospitals and subsequently in the community [101]. More than 80% of both community- and hospital-acquired staphylococcal isolates were resistant to penicillin by the late 1960s [100]. Methicillin, a penicillinase-resistant semisynthetic penicillin, was introduced in 1961. Less than 1 year later, methicillin-resistant *S. aureus* (MRSA) was reported in a British hospital and in 1963, in Danish hospitals, which subsequently spread to the other parts of the world [93, 102]. Methicillin-resistant strains is an evolved version of *S. aureus* with the capability to survive treatment with beta-lactam antibiotics, including penicillin, methicillin, and cephalosporins [103]. Quinolones were introduced in the 1980s and represented a significant therapeutic advancement in the treatment of patient with infectious caused by *S. aureus* [101]. However, quinolone resistance among *S. aureus* emerged quickly, more prominently among the MRSA, and became a serious clinical problem; the prevalence of quinolone resistance in MRSA ranged from 52 to 62% by 1989, compared with 0–6% in 1987 [101, 104, 105, 106, 107]. From then on, the preferred antibiotic for treating MRSA infections is the glycopeptide vancomycin [108]. However, the dramatic increased usage of this antibiotic lead to development of vancomycin resistant *S. aureus* (VRSA) and vancomycin intermediate *S. aureus* (VISA) [101]. The first clinical isolate of vancomycin-intermediate-resistant *S. aureus* (VISA) was identified in 1997, and these strains have now been reported worldwide [109].

The emerging resistance to vancomycin among gram-positive cocci and the poor tissue penetration and weak antibacterial activity of this glycopeptide, has led researchers to develop novel antistaphylococcal agents. Linezolid, daptomycin, tigecycline, and quinupristin/dalfopristin have been introduced into clinical practice, each with their own clinical pros and cons [110].

Not surprisingly, the spread of MRSA from the hospital to the community setting, coupled with the emergence of VISA and VRSA, has become a major cause of concern among clinicians and microbiologists. The treatment options available for these infections are now severely compromised and thus new classes of antimicrobial agents effective against MRSA, VISA and VRSA are urgently required [109].

4. Conclusion

Multidrug-resistant bacteria are becoming more common and due to their multiplicity of mechanisms, they are frequently resistant to many if not all of the current antibiotics. This daunting spectre has been the target of many research efforts into conventional antibiotics and alternative approaches.

A vast number of potential antimicrobial alternatives including phages, BCWH, and AMP are under investigation to overcome the growing issue of bacterial resistance to antibiotics.

The enormous demand has triggered worldwide efforts in developing novel antibacterial alternatives. Bacteriophages (phages), bacterial cell wall hydrolases (BCWH), essential oils and antimicrobial peptides (AMP) are among the most promising candidates.

References

- [1] Murphy SC. Malaria and global infectious diseases: why should we care? *Virtual Mentor*. 2006; 8(4):245-50.
- [2] World Health Organization. 2013 Mortality and global health estimates. Geneva, Switzerland: World Health Organization.
- [3] Noah D, Fidas G, editors. *The Global Infectious Disease Threat and Its Implications for the United States* [Internet]. Washington, DC: US Department of State & National Security Council, National Intelligence Council; 2000. Available from: <http://fas.org/irp/threat/nie99-17d.htm>
- [4] Abulreesh HH, Organji SR. The prevalence of multidrug-resistant staphylococci in food and the environment of Makkah, Saudi Arabia. *Res J Microbiol*. 2011; 6(6):510-523.
- [5] Foxman B. The epidemiology of urinary tract infection. *Nat Rev Urol*. 2010; 7:653-60.

- [6] Kaper JB, Nataro JP, Mobley HL. Pathogenic *Escherichia coli*. *Nature Rev Microbiol*. 2004; 2:123-40.
- [7] Kim KS. Current concepts on the pathogenesis of *Escherichia coli* meningitis: implications for therapy and prevention. *Curr Opin Infect Dis*. 2012; 25:273-8.
- [8] Pitout JD. Extraintestinal pathogenic *Escherichia coli*: an update on antimicrobial resistance, laboratory diagnosis and treatment. *Expert Rev Anti Infect Ther*. 2012;10:1165-76.
- [9] Rayner C, Munckhof WJ. Antibiotics currently used in the treatment of infections caused by *Staphylococcus aureus*. *Intern Med J*. 2005; 35 Suppl 2:S3-16.
- [10] Deresinski S. Methicillin-resistant *Staphylococcus aureus*: an evolutionary, epidemiologic and therapeutic odyssey. *Clin Infect Dis*. 2005; 40:562-573.
- [11] Ippolito G, Leone S, Lauria FN, Nicastrì E, Wenzel RP. Methicillin-resistant *Staphylococcus aureus*: The superbug. *Int. J. Infect. Dis*. 2010; 14 (Suppl. 4): S7-S11.
- [12] Hiramatsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover FC. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. *J Antimicrob Chemother*. 1997; 40(1):135-6.
- [13] Centers for Disease Control and Prevention (CDC). *Staphylococcus aureus* resistant to vancomycin--United States, 2002. *MMWR Morb Mortal Wkly Rep*. 2002; 51(26):565-7.
- [14] Lancellotti M, de Oliveira MP, de Avila FA. Research on *Staphylococcus* sp. in biofilm formation in water pipes and sensibility to antibiotics. *Braz J Oral Sci*. 2007; 6: 1283-1288.
- [15] Acco M, Ferreira FS, Henriques JAP, Tondo EC. Identification of multiple strains of *Staphylococcus aureus* colonizing nasal mucosa of food handlers. *Food Microbiol*. 2003; 20:489-493.
- [16] Stefani S, Goglio A. Methicillin-resistant *Staphylococcus aureus*: related infections and antibiotic resistant. *Int. J. Infect. Dis*. 2010; 14 (Suppl. 4): S19-S22.
- [17] Wulf M, Voss A. MRSA in livestock animals-an epidemic waiting to happen? *Clin. Microbiol. Infect*. 2008; 14: 519-521.
- [18] Escherich T. Die Darmbakterien des Neugeborenen und Säuglings. *Fortschritte der Medizin*. 1885; 3, 515-522 and 547-554.
- [19] Meng J, Schroeder, C M. *Escherichia coli*. In: Simjee S, editor. *Foodborne diseases*. Totowa, NJ: Humana Press; 2007. p. 1-25.
- [20] Levine MM. *Escherichia coli* That Cause Diarrhea: Enterotoxigenic, Enteropathogenic. 1987; 155(3), 377-389.
- [21] Flatamico P, Smith J. *Escherichia coli* infections. In: Riemann H, Cliver D, editors. *Food Infection and Intoxication*. Elsevier Inc; 2006. p. 205 - 239.
- [22] Doyle MP, Padhyem VV. *Escherichia coli*. In: Doyle MP, editor. *Foodborne bacterial pathogens*. New York: Marcel Dekker Inc; 1989. p. 235-281.
- [23] Adams MR, Moss MO. *Food microbiology*. The Royal Society of Chemistry, Cambridge: UK; 2008.
- [24] Jay JM, Loessler M J, Golden DA. *Modern food microbiology*. 7th ed. Springer: New York; 2005.
- [25] Bell C, Kyriakides A. *E. coli* - practical approach to organism and its control in foods. Blackie Academic and professional : New York; 1998.
- [26] Balows A, Hausler W J, Herrmann K L, Isenberg HD, Shadomy HJ. *Manual of clinical microbiology*. 5th ed. American Society for Microbiology: Washington, DC; 1991.
- [27] Ørskov F, Ørskov I. *Escherichia coli* serotyping and disease in man and animals. *Canadian Journal of Microbiology*. 1992; 38(7), 699-704.
- [28] Scheutz F, Cheasty T, Woodward D, Smith HR. Designation of O174 and O175 to temporary O groups OX3 and OX7, and six new *E. coli* O groups that include Verocytotoxin-producing *E. coli* (VTEC): O176, O177, O178, O179, O180 and O181. *Acta Pathologica Microbiologica et Immunologica Scandinavica*. 2004; 112(9), 569-584.
- [29] Mol O, Oudega B. Molecular and structural aspects of fimbriae biosynthesis and assembly in *Escherichia coli*. *FEMS Microbiology Reviews*. 1996; 19(1), 25-52.
- [30] Barlow RS, Hirst RG, Norton RE, Ashhurst-Smith C, Bettelheim KA. A novel serotype of enteropathogenic *Escherichia coli* (EPEC) as a major pathogen in an outbreak of infantile diarrhoea. *J Med Microbiol*. 1999; 48(12):1123-5.
- [31] Nataro JP, Kaper JB. Diarrheagenic *Escherichia coli*. *Clinical Microbiology Reviews*. 1998; 11(1), 142.
- [32] Seth A. Antimicrobial and phytochemical analysis of common Indian spices against food borne pathogens. *Advanced BioTech*. 2011; 11(5), 22-27.
- [33] Sussman M. *Escherichia coli*: Mechanisms of Virulence. Cambridge University Press; 1997. 11p.
- [34] Ramanathan H. *Food Poisoning A Threat to Humans*. Marsland Press; 2010. 27p.
- [35] Doughari HJ, Ndakidemi PA, Human IS, Benade S. Virulence factors and antibiotic susceptibility among verotoxin non O157: H7 *Escherichia coli* isolates obtained from water and wastewater samples in Cape Town, South Africa. *African Journal of Biotechnology*. 2011; 10(64): 14160-8.
- [36] Abhilash M. Osmotolerance Studies of Uropathogenic *Escherichia coli*. *The Internet Journal of Aesthetic and Antiaging Medicine*. 2009; 2(1).
- [37] Ngwai YB, Akpotu MO, Obidake RE, Sounyo AA, Onanuga A, Origbo SO. Antimicrobial Susceptibility of *Escherichia coli* and other Coliforms Isolated from Urine of Asymptomatic Students in Bayelsa State, Nigeria. *African Journal of Microbiology Research*. 2010; 5(3): 184-191.
- [38] Sansonetti P. *Bacterial Virulence*. Volume 2 *Infection Biology*. John Wiley & Sons; 2010. 78 p.
- [39] Dworkin M, Falkow S. *The Prokaryotes*: Vol. 4: Bacteria: Firmicutes, *Cyanobacteria*. 3rd ed. Springer; 2006. 5p.
- [40] Brzuszkiewicz EB. Genome Sequence of *Escherichia Coli* 536: Insights into Uropathogenicity through Comparison with Genomes of *Escherichia Coli* MG1655, CFT073, and EDL933. Doctorate thesis. University of Goettingen: Warsaw, Poland; 2005.

- [41] Todar K. Pathogenic *E. coli*. Online Textbook of Bacteriology. Department of Bacteriology: University of Wisconsin-Madison; 2007.
- [42] Hilbert DW, editor. Antibiotic Resistance in Urinary Tract Infections: Current Issues and Future Solutions, Urinary Tract Infections. [Internet]. 2011. Available from: <http://cdn.intechweb.org/pdfs/20573.pdf>
- [43] Livermore DM. β -Lactamase-mediated resistance and opportunities for its control. *Journal of Antimicrobial Chemotherapy*. 1998; 41(D): 25–41.
- [44] Drawz SM, Bonomo RA. Three decades of beta-lactamase inhibitors. *Clinical Microbiology Reviews*. 2010; 23(1): 160-201.
- [45] Bradford PA. Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. *Clinical Microbiology Reviews*. 2001; 14(4): 933-51.
- [46] Lee SY, Kotapati S, Kuti JL, Nightingale CH, Nicolau DP. Impact of extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* species on clinical outcomes and hospital costs: a matched cohort study. *Infection Control and Hospital Epidemiology*. 2006; 27: 1226-1232.
- [47] Ortega M, Marco F, Soriano A, Almela M, Martínez JA, Muñoz A, Mensa J. Analysis of 4758 *Escherichia coli* bacteraemia episodes: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome. *Journal of Antimicrobial Chemotherapy*. 2009; 63 (3): 568-574.
- [48] Prober CG. Cephalosporins: An Update. *Neoreviews*. 1998; 19(4): 118 -127.
- [49] Orden JA, Ruiz-Santa-Quiteria JA, García S, Cid D, de la Fuente R. In vitro activities of cephalosporins and quinolones against *Escherichia coli* strains isolated from diarrheic dairy calves. *Antimicrobial Agents and Chemotherapy*. 1999; 43: 510–513.
- [50] Beg QZ, Al-hazimi AM, Ahmed MQ, Fazaludeen MF, Shaheen R. Resistant bacteria a threat to antibiotics. *Journal of Chemical and Pharmaceutical Research*. 2011; 3 (6): 715-724.
- [51] Courpon-Claudinon A, Lefort A, Panhard X, Clermont O, Dornic Q, Fantin B, Mentré F, Wolff M, Denamur E, Branger C. COLIBAFI Group. Bacteraemia caused by third-generation cephalosporin-resistant *Escherichia coli* in France: prevalence, molecular epidemiology and clinical features. *Clinical Microbiology and Infection*. 2011; 17(4): 557-565.
- [52] Bean DC, Livermore DM, Hall LM. Plasmids imparting sulfonamide resistance in *Escherichia coli*: implications for persistence. *Antimicrobial Agents and Chemotherapy*. 2009; 53 (3): 1088-1093.
- [53] Perreten V, Boerlin P. A new sulfonamide resistance gene (sul3) in *Escherichia coli* is widespread in the pig population of Switzerland. *Antimicrobial Agents and Chemotherapy*. 2003; 47: 1169-1172.
- [54] Huovinen P, Sundström L, Swedberg G, Sköld O. Trimethoprim and sulfonamide resistance. *Antimicrobial Agents and Chemotherapy*. 1995; 39:279–89.
- [55] Darrell JH, Garrod LP, Waterworth PM. Trimethoprim: laboratory and clinical studies. *Journal of Clinical Pathology*. 1968; 21: 202-209.
- [56] Fleming MP, Datta N, Gruneberg RN. Trimethoprim resistance determined by R factors. *British Medical Journal*. 1972; 1: 726-728.
- [57] Randrianirina F, Soares JL, Carod JF, Ratsima E, Thonnier V, Combe P, Grosjean P, Talarmin A. Antimicrobial resistance among uropathogens that cause community-acquired urinary tract infections in Antananarivo, Madagascar. *Journal of Antimicrobial Chemotherapy*. 2007; 59: 309-312.
- [58] Hammerum AM, Heuer OE. Human health hazards from antimicrobial-resistant *Escherichia coli* of animal origin. *Clinical Infectious Diseases*. 2009; 48(7): 916-921.
- [59] Belavic JM. Drug news: Fluoroquinolone-induced tendinopathy. *The Nurse Practitioner*. *The American Journal of Primary Health Care*. 2009; 34(1): 17 – 18.
- [60] Hansen GT. The Mutant-Prevention Concentration (MPC): Ideas for restricting the development of fluoroquinolone resistance. Thesis of Doctorate in Science: University of Saskatchewan. 2005.
- [61] Oteo J, Aracil B, Hoyo JF, Perianes J, Gómez-Garcés JL, Alós JI. Do the quinolones still constitute valid empirical therapy for community-acquired urinary tract infections in Spain? *Clinical Microbiology and Infection*. 1999; 5: 654-656.
- [62] Wang H, Dzink-Fox JL, Chen M, Levy SB. Genetic characterization of highly fluoroquinolone-resistant clinical *Escherichia coli* strains from China: Role of *acrR* mutations. *Antimicrobial Agents and Chemotherapy*. 2001; 45(5): 1515-21.
- [63] Naber KG, Llorens L, Kaniga K, Kotey P, Hedrich D, Redman R. Intravenous doripenem at 500 milligrams versus levofloxacin at 250 milligrams, with an option to switch to oral therapy, for treatment of complicated lower urinary tract infection and pyelonephritis. *Antimicrobial Agents and Chemotherapy*. 2009; 53(9): 3782-3792.
- [64] Karczmarczyk M, Martins M, Quinn T, Leonard N, Fanning S. Mechanisms of Fluoroquinolone Resistance in *Escherichia coli* Isolates from Food-Producing Animals. *Applied and Environmental Microbiology*. 2011; 77(20): 7113-20.
- [65] Chapple CR, Steers WD. *Practical Urology: Essential Principles and Practice*: Springer edition; 2011.
- [66] Nicolle LE. Pivmecillinam in the treatment of urinary tract infections. *Journal of Antimicrobial Chemotherapy*. 2000; 46 (A): 35-39.
- [67] Crossley KB, Jefferson KK, Archer GL, Fowler VG. (2009). *Staphylococci in Human Disease*. 2nd ed John Wiley & Sons; 2009.
- [68] Bhatia A, Zahoor S. *Staphylococcus aureus* Enterotoxins: A Review. *Journal of Clinical and Diagnostic Research*. 2007; 1(2):188-197.
- [69] Sambanthamoorthy K.. Role of Msa in the Regulation of Virulence and Biofilm Formation in *Staphylococcus aureus*. ProQuest Edition; 2007.

- [70] Siegrist J, editor. *Staphylococcus aureus* in the Focus. Microbiology Focus 3.4 - Sigma-Aldrich. [Internet]. 2011. Available from: http://www.sigmaaldrich.com/etc/medialib/docs/Fluka/Brochure/1/mibi_focus_3_4.Par.0001.File.tmp/mibi_focus_3_4.pdf.
- [71] Ekkelenkamp MB, Rooijackers SHM, Bonten MJM. Staphylococci and micrococci. In: Cohen J, Powderly W, Opal S, editors. Infectious Diseases. 3rd ed. Expert consult premium edition; 2010.
- [72] Deák T, Farkas J. Microbiology of Thermally Preserved Foods: Canning and Novel Physical Methods. DEStech Publications, Inc edition; 2013. P. 37 & 38.
- [73] Ludwig W, Schleifer KH, Whitman WB. (). Revised road map to the phylum Firmicutes. In: De Vos et al. editors. Bergey's Manual of Systematic Bacteriology, vol. 3. The Firmicutes. 2nd, ed. New York: Springer-Verlag; 2009. pp.1-17.
- [74] Bergeron M, Dauwalder O, Gouy M, Freydiere AM, Bes M, Meugnier H, Benito Y, Etienne J, Lina G, Vandenesch F, Boisset S. Species identification of staphylococci by amplification and sequencing of the tuf gene compared to the gap gene and by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. European Journal of Clinical Microbiology & Infectious Diseases. 2011; 30(3): 343-54.
- [75] Tortora GJ, Funke BR Case CL. Microbiology: an introduction. 7 th edition. San Francisco: Benjamin Cummings; 2002. 885p.
- [76] Ryan K.J. Staphylococci. In: Ryan KJ, Ray CG, editors. Sherris medical microbiology: an introduction to infectious diseases.4 th ed. New York: McGraw-Hill; 2004. 261-271p.
- [77] Freeman-Cook L, Freeman-cook KD, Alcamo IE. *Staphylococcus aureus* infections: Deadly diseases and epidemics. Infobase Publishing edition; 2006. 26-29p.
- [78] Manu DK. Antimicrobial effectiveness of Phenyllactic acid against foodborne pathogenic bacteria and *Penicillium* and *Aspergillus* molds. Thesis of Master of Science: Iowa State University; 2012. 21p.
- [79] MinorTE, Marth, EH. Staphylococci and their significance in foods. Elsevier Scientific Pub. Co. edition; 1976.
- [80] Wilkinson BJ. Biology. In: Crossley KB, Archer GL, editors. The staphylococci in human disease. New York: Churchill Livingstone; 1997. 1-38p.
- [81] Hait J. *Staphylococcus aureus*. In Lampel KA, Al-Khaldi S, Cahill SM, editors. 2nd ed. Bad Bug Book; 2012. 12-16p.
- [82] Schmitt M, Schuler-Schmid U, Schmidt-Lorenz W. Temperature limits of growth, TNase, and enterotoxin production of *Staphylococcus aureus* strains isolated from foods. International Journal of Food Microbiology. 1990; 11: 1-19.
- [83] Bergdoll MS. *Staphylococcus aureus*. In: Doyle MP., editor. Foodborne Bacterial Pathogens. New York: Marcel Dekker Inc; 1989. 463-523p.
- [84] Gao J, Stewart GC. Regulatory elements of the *Staphylococcus aureus* protein A (Spa) promoter. Journal of Bacteriology. 2004; 186(12): 3738-3748.
- [85] Halpin-Dohnalek MI, Marth EH. *Staphylococcus aureus*: Production of extracellular compounds and behavior in foods—a review. Journal of Food Protection. 1989; 52: 267-282.
- [86] Hauschild T, Stepanović S. Identification of *Staphylococcus* spp. by PCR-Restriction Fragment Length Polymorphism Analysis of dnaJ Gene. Journal of Clinical Microbiology. 2008; 46(12): 3875-9.
- [87] Murray P, Baron EJ, Pfaller MA, Tenoer FC, Tenover RH. Manual of Clinical Microbiology. 8th. Ed. Washington, DC :American Society of Microbiology; 2003.
- [88] Podbielska A, Gałkowska H, Olszewski WL. Staphylococcal and enterococcal virulence – a review. Central European Journal of Immunology. 2011; 36 (1): 56-64.
- [89] Sibbald MJ, Ziebandt AK, Engelmann S, Hecker M, de Jong A, Harmsen HJM, Raangs GC, Stokroos I, Arends JP, Dubois JYF, van Dijk JM. Mapping the pathways to staphylococcal pathogenesis by comparative secretomics. Microbiology and Molecular Biology Reviews. 2006; 70 (3): 755-788.
- [90] Miller HK. Characterization of the Lone Extracytoplasmic Function Sigma Factor, σ_S , and its Role in the *Staphylococcus aureus* Virulence and Stress Responses. Doctorate thesis in Philosophy: University of South Florida; 2012.
- [91] Bore E, Langsrud S, Langsrud O, Rode TM, Holck A. Acid-shock responses in *Staphylococcus aureus* investigated by global gene expression analysis. Microbiology. 2007; 153: 2289-2303.
- [92] Lemaire S. Intracellular *Staphylococcus aureus*, an emerging link to persistent and relapsing infections: factors influencing the activity of antimicrobials against intracellular *S. aureus*. Thesis Ph.D in Pharmaceutical Sciences: Louvain Catholic University; 2008.
- [93] Chambers HF. The changing epidemiology of *Staphylococcus aureus*? Emerging Infectious Diseases. 2001; 7(2): 178-182.
- [94] Baudoux P, Bles N, Lemaire S, Mingeot-Leclercq MP, Tulkens PM, Van Bambeke F. Combined effect of pH and concentration on the activities of gentamicin and oxacillin against *Staphylococcus aureus* in pharmacodynamic models of extracellular and intracellular infections. Journal of Antimicrobial Chemotherapy. 2007; 59(2): 246-253.
- [95] Moreillon P, Que YA, Glauser MP. *Staphylococcus aureus* (including staphylococcal toxic shock). In: Mandell GL, Bennett JE, Dolin R. editors. Mandell, Douglas, & Bennett's Principles and Practice of Infectious Diseases. Vol 2. 6th ed. Philadelphia: Churchill Livingstone; 2005. pp 2321-2351.
- [96] Naber CK. *Staphylococcus aureus* bacteremia: epidemiology, pathophysiology, and management strategies. Clinical Infectious Diseases. 2009; 48 (4): S231- S 237.
- [97] Van Hal SJ, Jensen SO, Vaska V L, Espedido BA, Paterson DL, Gosbell IB. Predictors of Mortality in *Staphylococcus aureus* Bacteremia. Clinical Microbiology Reviews. 2012; 25(2): 362-386.
- [98] Chatterjee I. Senescence of Staphylococci: metabolic and environmental factors determining bacterial survival and persistence. Thesis of doctorate in rerum naturalium. University of Saarland: Homburg/Saar, Germany; 2005.
- [99] Rubin RJ, Harrington CA, Poon A, Dietrich K, Greene JA, Moiduddin A. The economic impact of *Staphylococcus aureus* in New York City hospitals. Emerging Infectious Diseases. 1999; 5: 9-17.

- [100] Fast M, Bunzeluk K. Population-level interventions to reduce the development and transmission of community-associated antimicrobial resistance: A perspective from the National Collaborating Centre for Infectious Diseases. *Canadian Journal of Infectious Diseases & Medical Microbiology*. 2010; 21(3): 119-22.
- [101] Lowy FD. Antimicrobial resistance: the example of *Staphylococcus aureus*. *Journal of Clinical Investigation*. 2003; 111(9): 1265–1273.
- [102] Choudhury R, Panda S, Singh DV. Emergence and dissemination of antibiotic resistance: a global problem. *Indian Journal of Medical Microbiology*. 2012; 30(4): 384-90.
- [103] Rohani MY, Raudzah A, Lau MG, Zaidatul AA, Salbiah MN, Keah KC, et al. Susceptibility pattern of *Staphylococcus aureus* isolated in Malaysian hospitals. *International Journal of Antimicrobial Agents*. 2000;13(3): 209-213.
- [104] Schaefer S. Methicillin-resistant strains of *Staphylococcus aureus* resistant to quinolones. *Journal of Clinical Microbiology*. 1989; 27: 335–336.
- [105] Shalit I, Berger S A, Gorea A, Frimerman H. Widespread quinolone resistance among methicillin-resistant *Staphylococcus aureus* isolates in a general hospital. *Antimicrobial Agents and Chemotherapy*. 1989; 33(4): 593–594.
- [106] Trucksis M, Hooper DC, Wolfson JS. Emerging resistance to fluoroquinolones in staphylococci: an alert. *Annals of Internal Medicine*. 1991; 114: 424–426.
- [107] Wadsworth SJ, Kim KH, Satishchandran V, Axelrod P, Truant AL, Suh B. Development of new antibiotic resistance in methicillin-resistant but not methicillin-susceptible *Staphylococcus aureus*. *Journal of Antimicrobial Chemotherapy*. 1992; 30: 821–826.
- [108] Ng ST, Lim CY, Tan CS, Abd Karim A, Haron A, Ahmad N, Murugaiyah V, editors. Emergence of vancomycin-resistant *Staphylococcus aureus* (VRSA). [Internet]. *WebmedCentral Infectious Diseases 2: WMC002787*. 2011. Available from: http://www.webmedcentral.com/article_view/2787.
- [109] Appelbaum PC. The emergence of vancomycin-intermediate and vancomycin-resistant *Staphylococcus aureus*. *Clinical Microbiology and Infection*. 2006; 12 (1): 16-23.
- [110] Kontou P, Kuti JL, Nicolau DP. Ceftobiprole : The first anti-MRSA cephalosporin antibiotic. *Formulary*. 2008; 32: 66-78.