African Journal of Biotechnology Vol. 11(61), pp. 12429-12435, 31 July, 2012
Available online at http://www.academicjournals.org/AJB
DOI: 10.5897/AJB12.141
ISSN 1684–5315 ©2012 Academic Journals

Review

Commensal *Staphylococcus* spp., *Acinetobacter* spp. and *Stenotrophomonas maltophilia* as reservoirs of antibiotic resistance genes

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Accepted 23 April, 2012

***Staphylococcus* species, *Acinetobacter* species and *Stenotrophomonas maltophilia* are of particular importance as they sometimes reside as flora on the intact skin and nasal passages of man and farm animals. Studies around the globe have shown them as "friends and foes" especially in immunocompromised individuals as they occur as commensals but sometimes as pathogens that infect, causing morbidity and consequently higher therapeutic cost. The occurrence of antibiotic resistance gene(s) in their genomes and their phenotypic display of resistance make them difficult to control and places a high demand on the assessment of such genes in the bacteria. In doing this, the less considered (commensals) have been described more recently as a reservoir for antibiotic resistance genes. The transfer of heavy metal and antibiotic resistance genes from *Staphylococcus* spp., a Gram positive bacterium to *S. maltophilia* and *Acinetobacter* species, Gram negative bacteria confer the resilience to control measures that is peculiar with the former on the latter. This attribute in *Acinetobacter* spp. and *S. maltophilia* have encouraged their inclusion in drug screening research. Intermittent assessment of resistance genes in the ecosystem should be embraced to foster appropriate measures against their spread.**

Key word: Commensal, resistance genes, *Staphylococcus*, *Acinetobacter*, *Stenotrophomonas maltophilia.*

INTRODUCTION

Commensal bacteria are becoming increasingly important in the emergence of antibiotic resistance (Marshall et al., 2009; Halawani, 2011). Recent epidemiological reports on some bacteria have shown that many seeming non-pathogenic (commensal) bacteria have been implicated as aetiologies of extended spectrum drug resistant infections (Marshall et al., 2009). These have been described as acquired traits among such commensals which might have originated from their pathogenic counterparts (Pallechi et al., 2008). They thereby, feed on the antibiotics meant to kill or inhibit them (Dantas et al., 2008). It is true that the previously known determinant of antibiotic resistance is believed to be mainly nosocomial, while less consideration is being accorded to the environmental reservoirs (Nwosu, 2001; Seveno et al., 2002). A thorough analysis of the human commensal and/or his environment will reveal their implications as reservoirs of antibiotic resistance gene(s). Some schools of thought believe that commensals take up their antibiotic resistance genes from the environment (D'Costa et al., 2006) where they exist in large amounts (Seveno et al., 2002).

In any location being considered, culturable bacteria are usually the source of the antibiotic resistance genes, while non culturable bacteria (sometimes non-pathogenic) which are the majority (Head et al., 1998; Torsvik et al., 1998; Whitman et al., 1998; Beja et al., 2002) are less considered (Suzuki et al., 1997; Hugenholtz et al., 1998). This might position the environment as a worthwhile location for consideration as the possible custodian of antibiotic resistance; genes as most

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of these non culturable bacteria reside there. Using culturable microbiota is justifiable as it gives the idea of the resident gene pools within the environment in question. Meanwhile, this does not rule out the residence of these genes in humans as considerable antibiotic resistance genes may be transferred from the human or animal microflora to pathogens (Salyers et al., 2004; Dethlefsen et al., 2007). Either in cultured or uncultured bacteria, resistance genes and their phenotypic expression remains a challenge to be overcome in the environment, animals and humans. This review focuses on the commensal bacteria as reservoirs of antibiotic resistance genes with specific emphasis on *Staphylococcus* spp., *Acinetobacter* spp. and *Stenotrophomonas maltophilia* which are of peculiar epidemiological importance as flora and pathogens of human.

RESERVOIRS OF ANTIBIOTIC RESISTANCE GENES: COMMENSAL OR PATHOGENS

Resistance to antibiotics by bacteria and its intrinsic factors like resistance genes remain a concern to public health around the globe (Levy, 2000; Deshpande and Joshi, 2011). The distribution and/or dissemination of such bacteria are also of paramount concern to human, especially by his on-dwelling commensals, on his farm animals, in his environments: cultivated or uncultivated; remote (Sjolund et al., 2008) or near and in pathogens on the infected or convalescent (Jury et al., 2010). In whichever case, commensal or pathogen, each has been implicated as possible reservoirs of antibiotic resistance genes (de Araujo et al., 2006; Upadhyaya et al., 2011). The only difference is perhaps in the recognition previously accorded them. While pathogenic species have been known adequately in their carriage of antibiotic resistance genes and subsequent phenotypic expression of the genes, which have made treatment difficult (Lipsky, 2007) or limit therapeutic options available; less recognition is accorded the role of commensals (Marshall et al., 2009), yet they have been reservoirs of myriads of virulence and drugs resistance genes. Therefore, according both commensals and pathogens due recognition becomes imperative in the fight against antibiotic resistance.

A brief survey showed that commensal bacteria play vital roles as reservoirs of antibiotic resistance genes and transmission (Blake et al., 2003). Byarugaba et al. (2011) reported a high level resistance exhibited by certain commensal bacteria of animal origin with the range of 46.8 to 96% resistances to tetracycline, erythromycin and ampicillin. Epstein et al. (2009) also reported 17% prevalence of methicillin resistant *Staphylococcus intermedius* which showed about 2% higher than earlier observations (Morris and Anderson, 2006; Vengust and Anderson, 2006; Abraham and Morris, 2007), showing the rise in resistance in commensal subgroup just like their pathogenic counterparts. Class 1 integrons (mobile genetic elements) are one of the major contributors of the horizontal dissemination of antibiotic resistance genes in a diversity of enteric bacteria (Frost et al., 2005). Hence, the need for the identification of bacterial antibiotic resistance reservoirs in the environment and the transfer rate of antibiotic resistance genes into other bacteria becomes relevant (Amabile-Cuevas and Chicurel, 1992; Guardabassi et al., 2000; IFT, 2006). Sommer et al. (2009) observed that most of the antibiotic resistance genes harboured by the human microflora were distantly related (60.7% at the nucleotide level and 54.9% at the amino acid level) to antibiotic resistance genes which are far detected in pathogenic isolates. This observation justifies the need for perspective assessment of the antibiotic resistance genes among such important commensal bacteria as *Staphylococcus* spp., *Acinetobacter* spp. and *S. maltophilia*, due to their proximity as commensal to human and their implication in the life threatening multiple drug resistant infections (Lo et al., 2002; Kobashi et al., 2007; Rasheed and Awole, 2007).

Staphylococcus species

Quite a number of pathogenic strains of Staphylococci resides in commensal strains and position them as pertinent entities in infection control. Besides, a recognized commensal organism can become pathogenic in a favourable condition *in vivo* (Yana and Polk, 2004). By-passing the host's non-specific immune system to establish an infection by commensals follows the same trend as their pathogenic counterparts and depends on the original site of the flora and/or the route of entry to the site of infection, the intrinsic pathogenic attributes (virulence) of the bacterium, the inoculums' size which determines the survival quotients and the host (s)' immune status (Chang et al., 2005; Li et al., 2005). Injury to the skin allows the seeming harmless skin-resident commensal *Staphylococcus* spp. to exhibit their difficult-to-resist nature in the peritoneum and joints (Ibrahem, 2010). These attributes generate a notion that commensalism is just a phase in pathogenicity cycle, especially in *Staphylococcus aureus.*

The dual mode of living by *Staphylococcus* species between commensalism and parasitism is a complex one in reality. However, it is a possibility which justifies that commensal *Staphylococcus* species on healthy skin and nasal passage (Adegoke and Komolafe, 2008) appear as flora waiting for opportunity to exhibit the intrinsic pathogenic tendencies. Hence, *S. aureus* have been implicated in various clinical (systemic) cases (Adegoke and Komolafe, 2009) and its ability to survive on fomite (Adegoke and Okoh, 2011) encouraged their spread from one person to another. This scenario is also true for coagulase negative Staphylococci (CNS), especially

Staphylococcus epidermidis that have been described as an “accidental pathogen” of man (Otto, 2009). The pathogencity of *S. epidermidis* is enhanced by its marker of invasive surface protein (Arrecubieta et al., 2009). *Staphylococcus haemolyticus* is also a notorious commensal and pathogen of farm animals (Fischetti et al., 2000; Rasheed and Awole, 2007), but the former is a known commensal in endodontic region and pathogen of endodontic infection (Vianna et al., 2005). More importantly, these organisms have been reported as a repository of resistance genes, even in their commensal phase (Kozitskaya et al., 2004; Otto, 2009).

Therefore, the antibiotic resistance among staphylococci is, no doubt, a major global public health problem in both hospital and community. Large number (12.5%) of multidrug resistant Staphylococci were reported amidst other bacterial species in high vaginal swab (Adegoke and Okoh, 2011). The ubiquity of the human commensal *S. epidermidis* makes it a successful carrier and reservoir of antibiotic resistance genes, which are sometimes transferred to *S. aureus*, the trend noted to influence the rise in the spread of community acquired methicillin resistance *S. aureus* (MRSA) (Ma, 2002). Rising skin colonization by ciprofloxacin resistant strains of *S. epidermidis* is usually accompanied by the excretion of ciprofloxacin, among other antibiotics in sweat during chemotherapy (Dancer, 2004). This encourages increased skin colonization by ciprofloxacin-resistant *S. epidermidis* (Raad, 1998) as ciprofloxacin-sensitive *S. epidermidis* would have been wiped out. Sometimes, the outcome of mecA gene presence translates into the expression of resistance to the β-lactams by commensal *S. aureus* (Antignac and Tomaz, 2009). In another instance involving *Staphylococcus sciuri*, only the inactivation of penicillin binding protein brings about the expression of phenotypic resistance with *mecA* genes’ availability (de Lencastre et al., 2007; Zapun et al., 2009). The proximity of various *Staphylococcus* spp. to human makes resistance gene in them, a concern (Dethlefsen et al., 2007; Cohn and Middleton, 2010). Antibiotic use and environmental factors contribute to the emergence and spread of such resistance, especially in *S. aureus*, which is a common cause of life-threatening infections in both human and farm animals (Cohn and Middleton, 2010). Therefore, animal-derived products remain a potential source of MRSA (EFSA, 2008).

The presence of the peculiar resistance genes in ready-to-eat food stuff has immense epidemiological importance (EFSA, 2008); as they may contribute to human or animal microflora resistance gene load. Going down memory lane, with the effect of the beta lactamase enzyme that resulted in resistance to some beta lactam antibiotics by some bacteria including Staphylococci, methicillin was discovered and introduced into infection control arsenal in 1960s. It was observed to have stability against the enzyme with accompanying good therapeutic *S. aureus.* This scenario soon extended to vancomycin later introduced for treating MRSA (Hiramatsu et al., 1997; Olayinka et al., 2005; Adegoke and Okoh, 2011), and was only thought to be limited to clinical strain but was later discovered to have extended to community acquired strains or commensals (Olayinka et al., 2004). Concomitant MRSA and VRSA have resulted in therapeutic failure in about 85.7% orthopaedic procedure (Ariza et al., 1999). Hence, resistance genes and the phenotypic expression of resistance in Staphylococci has long and till date been a cause for global concern as an epidemiological threat (Finland et al., 1950; Finland, 1955; Shittu et al., 2011) deserving priority attention. However, records of resistance gene assessment among commensal *Staphylococcus* species are not available in many regions of the world including South Africa.

Acinetobacter spp.

Twelve genospecies of *Acinetobacter* earlier distinguished by Bouvet and Grimont in 1986 have risen to 33, out of which 24 have been named (Vaneechoutte et al., 2008). Species like *Acinetobacter baumannii, Acinetobacter calcoaceticus, Acinetobacter haemolyticus, Acinetobacter johnsonii, Acinetobacter junii* and *Acinetobacter lwoffii* (Bouvet and Grimont, 1986) belong to the first classified twelve. The *A. baumannii* exists in soil and water. They are also known for their ability to survive a wide range of atmospheric and environmental conditions (Gusten et al., 2002; Simor et al., 2002; Jawad et al., 2004). In comparison with other bacteria, *Acinetobacter* is most consistently observed in the environment and on the animals, but mostly as commensal found in 97% of natural surface water (Bifulco et al., 1989; Rusin et al., 1997; Jellison et al., 2001). A very good example is *A. baumannii* commonly found on the skin and nasal passages of animals as well as in soil (Seifert et al., 1997). Other species like *A. calcoaceticus* inhabit vegetables besides water and soil. Many of the species in the genus are systemic pathogens of human (Peleg et al., 2008) and are human parasites (La Scola and Raoult, 2004).

Beside their presence in dual mode in man, *Acinetobacter* species are important biotechnological tools, and have been utilized extensively in the synthesis of enzymes and other life-sustaining macromolecules and for degradation of recalcitrant compounds (Chan et al., 2011). However, the presence of antibiotic resistance genes in large proportion in either commensal or pathogenic species of *Acinetobacter* makes the organism of immense concern (Deshpande and Joshi, 2011). This is owing to its potentials as pathogen in immuno-compromised individuals (Rise, 2006; Chen et al., 2008). Resistance to many conventional antibiotics considered to be in the last line of defence has been observed in large percentage of *A. baumannii* (Zarakolu et al., 2006) which poses a great challenge to selection of the appro-

priate therapeutic option (Rise, 2006). This *Acinetobacter* which is usually a commensal but sometimes a pathogen has been reported to harbour sulphonamide resistance gene (sulII gene) in its commensal state in the environment (Agerso and Petersen, 2007) and tetracycline resistance genes (Segal et al., 2005) through any of the existing two-way mechanism of tetracycline resistance (Lau et al., 2008). Despite this potentials, the organism is least considered as test isolates in antimicrobial drug studies involving medicinal plants. Future research in this area is hereby encourages to consider the use of *Acinetobacter* spp. in the overall public health interest.

S. maltophilia

Antibiotic resistance genes, either inherent or acquired, are major internal forces behind the antibiotic resistance exhibited by *S. maltophilia* (Zhang et al., 2001; Mckay et al., 2003; Alonso et al., 2004). Various strains of *S. maltophilia* including commensals from the environment, opportunistic pathogens from the immunocompromised sick or convalescent and those linked with persistent terminal clinical conditions bear resistant genes (Nicodemo and Paez, 2007) that serves as a clog in chemotherapeutic wheel. A good example is found in Canadian hospital where *S. maltophilia* was recovered from all the trapped air from the hospital rooms and erythromycin resistance genes was detected in them (Di Bonaventura et al., 2004). Various observations of the resistance genes in *S. maltophilia* have been made. Song et al. (2010) in Korea discovered the antibiotic resistance gene *sul1* in class 1 integron in place of sul gene which determine cotrimoxazole (trimethoprim-sulfamethazole) resistance in *S. maltophilia* isolates and that resistance to antibiotics might be as a result of multiple antibiotic resistance genes. Sanchez et al. (2009) remarked that the presence of genes coding for long existing Qnr determinant in *S. maltophilia* confers antibiotic resistance on the organism against the supposed drug of choice. They also emphasized that the organism has proven proficient in the acquisition of novel antibiotic resistance genes via horizontal transfer.

This is evident by the reports that myriad of genes found in *S. maltophilia* Sm777 possess a cluster of genes for antibiotic and heavy metal resistance (Pages et al., 2008) purportedly transferred from Gram-positive bacteria (Alonso et al., 2000), for the first time, to the best of our knowledge. In the same premise, the efflux pump D, E, F (SmeDEF), multidrug efflux pump contributes to the intrinsic multidrug resistance in *S. maltophilia and* justifies the need to access the bacteria from time to time for effective planning. Emphatically, some of these genes are inherent, while others are acquired intra- and inter-specifically. This observation of the affirmative presence of pools of genes, especially for antibiotic resistance among others in commensal (Schwarz et al., 2001) and their transfer to other commensals or pathogens through various means (Ray et al., 2009) emphasizes their importance in epidemiology and infection control (Marshall et al., 2009). A good instance here as mentioned earlier is the antibiotic resistance gene transfer from Gram positive to Gram negative bacteria and vice versa reported by Alonso et al. (2004). The indirect hazard arises through transfer of resistance genes which are easily accomplished naturally by the organism, bypassing certain difficult steps and passing the gene to a bacterium, pathogenic for humans, either directly, or via another commensal bacterium (Popa et al., 2011). This becomes hazardous.

In United States, the inappropriate use of antibiotics is identified as a selective force for this hazard. About 50% of the antibiotics being used are not only for therapy but to enhance growth (Institute of Food Technologists, 2006; Pruden et al., 2006). Tetracycline, for example, has been used extensively in veterinary medicine, besides their normal application in human medicine (Chopra and Roberts 2001) in such a way that it has hastened the emergence of resistance. Consequently, widespread resistance has been reported in various communities of human and animals (Institute of Food Technologists 2006; Pruden et al. 2006), though most of these were discovered to be supported by efflux mechanism and the protein production (Chopra and Roberts, 2001). A study conducted by Yang et al. (2010) on antibiotic resistance owing to the effect of agriculture in Colorado showed among other things, large count of tetracycline-resistant bacteria and tetracycline resistance genes like *tet (B), tet (C), tet (W)* and *tet (O)* in wastewater samples and non-farm environments. This study pointed to the fact that wastewater from animal breeding farms may serve as the source for the spread of antibiotic resistance genes to other environment (Huys et al., 2009).

For most animal-based antibiotic resistant bacteria, the number of animal per space and their feeding platform and compositions affect their bacterial strain carriage, for example, Dhlamini (2002) reported that 87% of subsistent poultry systems in KwaZulu-Natal incorporate herbal formula along with trace amount of commercially prepared antibiotics in the poultry feed for treatment. This suggests that the observed resistance commensal strains and genes found in farm animals from developing and developed countries would differ due to different farm approaches.

CONCLUSION

The non availability of proper record on the assessment of antibiotic resistance genes among the commensal bacteria belonging to *Staphylococcus* spp., *Acinetobacter* spp. and *S. maltophilia* is a recurring decimal in developing countries including South Africa. The ongoing studies in our group in the Nkonkobe Municipality of the

Eastern Cape Province of South Africa will shed some light and provide insights into this phenomenon. The use of *Acinetobacter* species and *S. maltophilia* as test organisms in antimicrobials researches is hereby advocated due to their impact on public health, and intermittent assessment of their antibiotic resistance gene(s) to foster adequate plan in preventing sudden emergence of multiple drug resistant infection in large proportion is hereby advocated as a subject of intensive investigation in our group.

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