Review Article

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Use of antibiotics in animal agriculture & emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) clones: Need to assess the impact on public health

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Widespread use of antibiotics in human, veterinary medicine and agricultural settings has played a significant role in the emergence of resistant MRSA clones due to selection pressure. MRSA has now become established in human population as well as in various animal species. An animal associated clone, MRSA ST 398 has been reported from animal foods and also from human infections in the community as well as from the health care associated infections. Clonal relationship between strains of animal and human origins are indicators of interspecies transmission of clones. Spread of these organisms may pose a great impact on public health if animal associated strains enter into the community and health care settings. Surveillance is important to correlate the genetic changes associated with their epidemiological shift and expansion to predict its impact on public health. Strict regulations on the use of antibiotics in humans as well as in animal food production are required to control the emergence of drug resistant clones. This article reviews the information available on the role of antibiotics in emergence of MRSA strains, their epidemiological shift between humans and animals and its impact on the public health.

Key words Animal agriculture - antibiotic resistance - epidemiological shifts - humanosis - LA-MRSA - MRSA - zoonosis

Introduction

Antibiotics are widely used in humans as well as in veterinary medicine and other agricultural activities. Over the past decades industrial use of these medicines has resulted in an increase in the number and types of microorganisms resistant to drugs, leading to increased public health problems in terms of morbidity, mortality and increased cost of treatments[1-3].

MRSA (methicillin resistant *Staphylococcus aureus*) is an important human pathogen that has developed resistance to methicillin and several other antibiotics. The global prevalence of MRSA in human infections is quite high. It has been reported as variable resistance in parts of USA, 40 per cent in southern Europe, however, less than 1 per cent in northern Europe[4]. In Asian countries the prevalence rates in hospitals has been found as 41 per cent in India, 42 per cent in Pakistan, 18 per cent in Philippines, 38 per cent in Malaysia, 50-70 per cent in Korea, 53-83 per cent in Taiwan and 70 per cent in Hong Kong and Japan[5-7]. According to a report from Australian Group of Antimicrobial Resistance, the prevalence of MRSA in Australia was 31 per cent[8]. Initially considered as

health care associated pathogen, MRSA is now being reported as a cause of community acquired infections around the world[9-11]. There are reports on increase in prevalence CA-MRSA (community acquired MRSA) and emergence of variants of HA-MRSA (health care associated MRSA) and their in-filtration into hospital settings from several countries including India[12-14].

MRSA strains associated with livestock (LA-MRSA) have emerged in farm animals mainly swine, companion animals and persons in contact with these animals[11,15]. Human infections associated with LA-MRSA have also been reported from several countries[16-19]. Animal to human as well as human to animal transmission of resistant strains can have a potential impact on public health if these strains enter into the community and health care settings[16-20]. Here we summarize the information available on the role of antibiotics in emergence of MRSA strains, their epidemiological shift between humans and animals and its impact on the public health.

Antibiotic use and resistance

Antibiotic resistance is a global problem, particularly in developing countries including India[21-23]. Several factors are responsible for the development of resistance in bacteria. Most important of these is the drug selection pressure due to irrational use of antibiotics. In addition to medical use, antibiotics are used in agricultural settings. In animals, antibiotics are used not only for the treatment of infections but also for the prevention of disease and promotion of growth in sub therapeutic doses[21]. It has been reported that the consumption of antibiotics in USA is 100 to 1000 times more in agricultural activities than in human medicine and about 90 per cent of this amount is used for growth promotion and prophylactic purposes whereas only 10 per cent for the treatment of infections[24]. Certain closely related antibiotics which are used as growth promoters in animals are also used for disease control in humans. Microbiological and clinical evidences have shown that non therapeutic use of antibiotics in animals has led to the selection of resistant forms of bacteria particularly in favourable ecosystems[2,24]. These resistant bacteria can be transmitted between animals, to humans in contact with them and also to the environment. It has been documented that the glycopeptide resistant enterococci have emerged after using an antibiotic, avoparcin as growth promoter in animal agriculture[2,24]. The resistant genes then disseminated to other Gram-positive organisms including MRSA. Resistance to glycopeptides is a cause of concern as vancomycin, a glycopeptide, is the drug of choice for the treatment of hospital acquired infections due to multi drug resistant staphylococci. Similarly the use of tylosin in animal feed supplement has resulted in the development of erythromycin resistant staphylococci[2,24]. Use of enrofloxacin (a derivative of fluoroquinolones) in poultry has resulted in emergence of resistance to ciprofloxacin. Use of modern cephalosporins has contributed to the spread of MRSA in pig industries in several European countries[25]. The acquisition of resistance in MRSA of animal origin has been shown to increase prevalence of infections and therapeutic failures in humans[7,10,21,25].

Animal agriculture

Animal agriculture refers to the industrialized production of livestock including cattle, poultry and fish. Recent studies have shown that use of antibiotics as prophylactic agents and growth promoters in these animals has resulted in the emergence of drug resistant micro-organisms including MRSA, causing serious and difficult to treat infections in animals as well as in humans[2, 24].

MRSA : Evolution and epidemiological expansion

MRSA is known for its extraordinary adaptable nature and ability to develop resistance to antibiotics[26]. Resistance is acquired mainly through horizontal gene transfer. MRSA are defined by the presence of *MecA* gene on a mobile genetic element called Staphylococcal chromosomal cassette mec (SCC*mec*)[26] *MecA* gene encodes for penicillin binding protein PBP2a which confers resistance to most of the beta lactam antibiotics including semi-synthetic penicillins. Gene transfer may occur between different *Staphylococcus* species and even strains from diverse host origins[26]

MRSA are subcategorized as health care associated MRSA (HA-MRSA) and community acquired MRSA (CA-MRSA) depending upon the circumstances of acquiring the disease. HA-MRSA infections occur mostly among hospitalized patients or the patients who have undergone invasive medical procedures. These strains usually cause life threatening infections such as pneumonia, blood stream infections, surgical site infections and toxic shock syndrome. CA-MRSA infections mostly cause skin infections, necrotizing pneumonia, boils, pus filled lesions and occur among persons without any established risk factors for their acquisition. Some clonal lineages of MRSA can infect

and colonize a wide variety of animal species and are known as extended host spectrum genotypes of MRSA[27,28]. MRSA strains differ in their pathogenic potential with regard to their affiliation to humans or animals. Risk factors for acquisition of MRSA in animals are similar to those for human acquisition, mainly contact with a colonized human or animal, hospitalization and usage of antibiotics. When the companion animals are infected or colonized with human strains, it is considered humanosis while the strains emerging from the diverse animal species and causing human infections known as zoonosis. Generally companion animal strains of MRSA differ from those in livestock and food production animals[27]. Clones of MRSA are differentiated using molecular methods such as pulsed field gel electrophoresis, SCC *mec* typing, multilocus sequence typing and *spa* typing[29,30]. Majority of HA-MRSA carry SCC*mec* type I, II, III cassettes and lack *PVL* genes while CA-MRSA strains carry SCC*mec* type IV, V cassettes and contain *PVL* genes, however, several sub types and their variants are emerging[13,14]. Most of the livestock associated MRSA particularly ST 398 have been found to contain SCC*mec* type IV, V cassettes[27].

MRSA infections in animals

MRSA was first recognized in animal infections in 1972 in milk from mastitic cows in Belgium[31]. Since then, various reports on animal diseases due to MRSA have been published from diverse animal hosts. MRSA ST 398 has been reported in farm animals and companion animals from various countries. It is most prevalent in pigs[32-34]. Other MRSA lineages which have been commonly reported from poultry and horses are ST5, ST8 and ST22[3]. The presence of MRSA has also been reported from animal food products, however, implications of human infections by its consumption is not very common[35].

Animal associated MRSA infections in humans

Animal associated MRSA infections in humans were first reported during 2003-2005 in Netherlands[16]. MRSA ST 398 which was initially isolated from pigs has now been reported in humans and has accounted for up to 25 per cent of the total MRSA infections in certain countries[16]. LA-MRSA ST 398 has been reported in CA as well as HA infections from wounds and ventilator associated pneumonia[15,16,36]. People with occupational exposure to livestock particularly pigs and cattle have shown a high prevalence of nasal colonization with MRSA ST 398[16,19].

Transmission of MRSA between humans and animals

Historically, MRSA infections in companion animals involved HA MRSA strains and the direction of spread was linked from humans to animals as the strains causing infections in these animals were closely related to human strains prevalent in the community and the hospitals of the same geographical regions[37,38]. Currently the situation is changing with the MRSA strains evolving within the animal kingdom and colonizing and infecting humans[27]. Transmission of strains from humans to animals and back from animals to humans is possible through direct contact[39]. Price *et al*[40] investigated clonal lineages of ST 398 from various host species and demonstrated their route of transmission from humans to animals. Studies suggested that MRSA ST 398 was originated in humans as methicillin-sensitive *S. aureus* (MSSA) ST 398, transmitted to livestocks and acquired resistance to anibiotics tetracycline and methicillin[40]. Studies on SCC *mec* types of these lineages describe a strong evidence of selection of antibiotic resistance associated with food animal production *i.e*. use of antibiotics for growth promotion and prevention of diseases[40]. Relatedness of human strains of MRSA ST 398 to LA-MRSA ST 398 was defined by multilocus sequence typing (MLST), s*pa* typing and whole genome sequence typing of strains[20,27,40]. These resistant strains may have been reintroduced into the human populations presenting LA associated MRSA infections[19]. Evidences also suggest that MRSA can be transmitted in both the directions, however, the frequency and overall relevance are not clearly understood[9]. Association between animal and human carriage of MRSA ST 398 and antimicrobial usage has also been reported[39,41]. This epidemiological shift involving transmission of strains from humans to animals and back from animals to humans is a matter of public health concern[18].

Public health significance of LA-MRSA

LA-MRSA represents a concern in both human and animal health. Healthy colonized animals may act as MRSA reservoirs and source of transmission to other animals. In livestock it usually causes mastitis and soft tissue infection which may enter the food chain subsequently affecting the public health and economy. On the other hand, persons in direct contact with MRSA colonized livestock are at high risk of becoming colonized with LA-MRSA. These in turn,

may become the source of transmission to other humans consequently spreading the infection in the community at large. In the process, genetically diverse CA-MRSA may evolve. When patients colonized with these clones are admitted in health care centres, infection may spread to other patients and health care workers resulting in serious public health consequences.

WHO Reports and recommendations on containment of antibiotic resistance

According to a report on medical impact of antimicrobial use in food animals, published by the WHO[2] "the use of antibiotics in animal agriculture poses a significant risk to human health due to selection of cross-resistance in bacteria to antibiotics used in humans". It results in "increased severity of infections" and "increased frequency of treatment failures". It has been reported that "major transmission pathway of resistant bacteria is from food animals to humans" and can happen through direct contact with animals, consumption of meat, drinking contaminated water or the transfer of resistant genes between animal and human pathogens[2]. In view of public health safety, the WHO recommended certain guidelines and policies for the use of antibiotics in food animals for the containment of resistance emerging in common pathogens[1,2]. In the key message of the recommendations the prudent use of antibiotics has been emphasized by stopping non therapeutic use of drugs particularly those drugs which are used to treat human diseases or related to such drugs in animals, by regulating sales/ distribution of antibiotics, monitoring surveillance of infections at farms, in community and at health care institutes and by imparting education and training to personnel associated with animal agriculture.

Indian scenario

Animal agriculture, poultry and dairy farming are major industries in India. A large number of people working in these farms are in close contact with livestock. The use of antibiotics in animal agriculture was not strictly regulated by law in India; however, certain restrictions are there on the use of antibiotics in poultry products and seafood for export purposes[42]. Efforts are being made to meet the challenges of antibiotic resistance in India by monitoring and promoting rational drug use by imparting education and training, conducting surveillances, setting up international partnership programmes and making national antibiotic policies with the Government to regulate the use of antibiotics in humans as well as in veterinary medicine[23,42]. There is a paucity of data on antimicrobial use in food animals and very little information is available on animal associated MRSA infections and its impact on public health in India. Reports on high prevalence (54%) of CA-MRSA strains with Scc *mec* types IV and V isolated from patients with no documented risk factors indicate towards a need of epidemiological surveillance to control the spread of infections at large[14]. According to a study from Global Antibiotic Resistance Partnership (GARP)-India Working Group[23] and the recommendations of Ministry of Health and Family Welfare task force report[42], a national policy has been announced for containment of antimicrobial resistance in the country.

Conclusions

MRSA has become established in human populations as well as in various animal species. Recent evidences indicate towards a link between the use of antibiotics and emergence of MRSA clones. Irrational use of antibiotics in the treatment of human diseases and non therapeutic use of antibiotics in animals may have played a significant role in the emergence of resistant clones due to selection pressure. Such resistance may pose a great impact on public health if animal associated strains enter into the community and health care settings. Strict regulations on the use of antibiotics in human medicine as well as in animal food production are required to control the emergence of drug resistant clones. Clonal relationship between strains of animal and human origins are indicators of interspecies transmission of clones. Surveillance is important to correlate the genetic changes associated with the epidemiological shift and expansion to predict its impact on public health.

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