Emerging Drug-resistant Superbugs

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Antimicrobial agents are drugs, chemicals and substances that either kill or inhibit the growth of microorganisms including susceptible bacteria (Gilbert and McBain, 2003). Unfortunately, bacteria could change in a way that they can survive in the presence of the antimicrobials. Susceptible bacteria get eliminated while resistant clones stay alive, continue to multiply and cause more damages. When bacteria resist the effects of an antimicrobial agent, it is referred to as resistant. If a bacterial strain is exceedingly resistant to almost every known and antibiotics available, it is informally called "a superbug" or "a super bacterium" implying a super fighter against antimicrobial agents (Reinhardt, 2010). While bacteria could be harmless and sometimes helpful, superbugs are mostly pathogenic bacterial strains and infections with superbugs usually result in increased severity of diseases, prolonged hospitalized stay, higher cost of treatment and increased mortality rate. Existing-clinical outcomes demand the new alternative treatments, particularly new medications that could overcome the development of multi-resistance in superbugs. Fearfully, superbugs are so talent that they can build up or acquire a resistance to most antimicrobials available in the markets including novel drugs designed to treat bacteria that have already become resistant to former-generation drugs and then, become stronger.

There are a variety of reasons for the increasing emergence of antimicrobial resistance among bacteria and the main reason is antimicrobial usage in both humans and animals. In humans, antimicrobial agents are often inappropriately taken due to the expectation of rapid infection cure. In many countries around the world, several antibiotics are sold over the counter without a prescription and inappropriate prescribing of antibiotics has been simply issued by physicians. All these misbehaviors enhance the growing of resistance among bacteria leading to ineffective treatment. Similarly, the antimicrobial substances have been widely used in food-animal production for three main purposes including treatment of diseases, prevention of infection and promoting of growth. The latter has appeared to make up the largest portion of total veterinary antimicrobial uses and mainly contribute to the widespread dissemination of antimicrobial resistance among bacteria. Antimicrobial use in farm animals evidently poses superbug risk to humans. This is based on the fact that the greater the length of antimicrobial exposure time, the greater the chance of development of resistance. When the board spectrum antimicrobial agents are used and other bacteria are killed, superbugs can grow better and their infection rate will be promoted. As a rule of thumb, whenever an antimicrobial agent is used, it drives forward the development of resistant bacteria and of course, superbugs.

Up to date, superbugs have emerged around the world and most of them appear as the life threatening pathogens. These emerging-deadly superbugs include:

1. ***Escherichia coli and Klebsiella pneumoniae*** **harboring** ***New Delhi metallo β-lactamase (NDM-1)*** The NDM-1 gene encodes β-lactamase enzymes carbapenemases conferring resistance to a board range of β-lactams. The enzymes are commonly produced by Gram-negative bacteria, in particular *E. coli* and *K. pneumoniae* (Paterson, 2006). The NDM-1 gene was first detected in a *K. peumoniae* isolate from a Swedish patient who travelled to New Delhi in 2008 (Yong et al., 2009) and has emerged as a newest superbug quickly arisen as one of the most feared pathogens. The NDM-1 gene is horizontally transferred and has spread to many countries worldwide in a short time. Special awareness has been raised against the NDM-1 carrying *E. coli* strains that could resist to cabapenems the most powerful-antibiotic group currently available (Queenan and Bush, 2007).

2. ***Methicillin-resistant Staphylococcus aureus (MRSA)*** MRSA is the most recognized superbugs that have become very common in many hospitals throughout the world. Methicillin was introduced in 1959 for treatment of penicillin-resistant *S. aureus* and soon later, MRSA was first detected in 1961 (Ippolito et al., 2010). At first, MRSA was limited to hospitals and healthcare settings and so known as hospital-acquired MRSA infection. Since the late 1990s, the MRSA epidemiology encounter a major change that is the emergence of community-acquired MRSA strains with rapid spread and causing fatal diseases (Ippolito et al., 2010). Most MRSA strains exhibit resistance to multiple drugs including penicillin, methicillin, tetracycline, erythromycin and vancomycin (de Lencastre et al., 1996; Smith et al., 1999).

3. ***Multidrug resistant Strptococcus and Enterococcus*** Two major-streptococcal superbugs posing lethal risk include *S. pyrogenes* Group A and *S. pneumoniae*. *S. pyrogenes* Group A or Strep A is notoriously known as a flesh-eating bacterium due to its ability to produce toxins that cause necrotizing fasciitis and the most rapid treatment is removing the damage tissues. *S. pneumonia* resistant to penicillin

and other β-lactams have increasingly caused sickness and death worldwide (Schrag et al., 2001). This superbug has additionally developed resistance to trimethoprim, sulfmethoxazole, azithromycin, tetracyclines, minocycline and fluoroquinolones (Hoenigl et al., 2010). Multi-resistant *E. faecium* is another superbug that is frequently found in hospitals. This superbug is normally not harmful. It will become very dangerous and deadly when enters urinary tract and open wound. Vancomycin-resistant *Enterococcus* (VRE) is prominently known as the leading cause of urinary tract infection and meningitis (Sood et al., 2008).

4. ***Multidrug-resistant P. aeruginosa*** *and* ***Acinetobactor baumannii (MRAB)*** Both *P. aeruginosa* and *A. baumannii* are opportunistic pathogens that are the important causes of hospital acquired infection. These superbugs have become predominant in most intensive care settings and some strains cannot be treated with any systemic antibiotics available. *P. aeruginosa* has been disreputably known for its highly intrinsic resistance to multiple drugs due to the synergy of low permeability cell and the expression of multidrug efflux systems envelope. This superbug has a great ability to form biofilms that slow down the intracellular penetration of antimicrobial molecules once again leading to resistance to various antimicrobials (Costerton et al., 1999).

Infection with *A. baumannii* is commonly associated with patients with immunosuppression and having invasive, of which death rate is high up to 80% (Turton et al., 2006). The apparent resistance in the MRAB strain has limited drug choice for treatments especially carbapenems.

5. Multidrug-resistant and Extensively drug-resistant tuberculosis (MDR- and XDR-TB) Tuberculosis is a dreadful disease that is acquired by inhalation. MDR-TB is caused by strains of *Mycobacterium tuberculosis* and has become a leading cause of death among HIV-infected individuals. This superbug is resistant to one of two first-line antibiotics isoniazid and rifampicin and can be treated with second-line drugs (i.e. kanamycin, amikacin and capreomycin) that are more expensive and have more side-effects (Jugheli et al., 2009). XDR-TB is a subset of MDR-TB that is additionally resistant to fluoroquinolones and one of the powerful second-line drugs (Jain and Dixit, 2008). Emergence of XDR-TB has raised a serious concern of restricted antitubercular drugs for a future TB treatment.

6. Multidrug-resistant Clostridium difficile

C. difficile is a commensal bacterium in human intestine that does not cause any significant disease when it is present in small number. Once the normal intestinal flora is disrupted in particular by a board spectrum antibiotic, *C. difficile* will overgrow and produce several toxins leading to severe illness i.e. pseudomembranous colitis (PMC). This phenomenon usually takes place after long-term hospitalization with use of clindamycin, ampicillin, amoxicillin, and cephalosporins (Mylonakis et al., 2001). This superbug is considered the most serious cause of antibiotic-associated diarrhea and informally called "a spore spread superbug" (Lawley et al., 2009). Its spores are heat-tolerant and resistant to alcohol and several routine disinfectants (except bleach). To date, *C. diffile* strains resistant to many front line antimicrobial agents i.e. clindamycin, ciprofloxacin, levofloxacin, metronidazole, linezolid have been isolated (Loo et al., 2005; Rupnik et al., 2009).

7. ***Multidrug-resistant E. coli*** **025b-ST131** Multi-resistant *E. coli* strains are frequently found and do not seem to provoke much excitement until an outbreak occurs. Whenever this superbug is spread, serious public health problem will arise and some death will be always reported. The well-known *E. coli* superbug produces Extended-Spectrum β-Lactamase (ESBL) and is almost untreatable (Hsieh et al., 2010). A new-virulent drug resistant strain of *E. coli* serogroup 025b sequence type 131 (ST131) has emerged as an important extraintestinal pathogen that is usually contaminated with animal feces, transferred to food of animal origin and also associated with infection of gastrointestinal tract. ST131 exhibits resistance to many β-lactams, which is mostly related to CTX-M-15 the most commonly-identified CTX-M mediating resistance to penicillin, cephalosporins and monobactams (Johnson et al., 2010). This superbug also commonly exhibits resistance to antibiotics in groups of fluoroquinolones, sulphamethoxazole and trimethoprim (Johnson et al., 2009; Johnson et al., 2010).

8. ***Multidrug-resistant Salmonella*** Highly drug resistant-*Salmonella* has increased and is now recognized as a lethal-food poisoning superbug commonly associated with meat and meat products. In general, transfer of resistance trait in this superbug is very efficient through a mobile genetic elements class 1 integrons and several conjugative R-plasmids (Khemtong and Chuanchuen, 2008; Wannaprasat et al., 2011). Concerns are now growing on a *Salmonella* superbug, *S.* Typhimurium DT104, which exhibits resistance to at least four antibiotics and is now becoming more resistant.

Arising of resistance among bacteria is considered a dynamic process. The constantly-evolving resistance mechanisms enforce scientists and experts to continually develop new antimicrobial agents. However, it does not seem to be enough to keep up with the rapid development of bacterial resistance. Emergence of deadly superbugs raises a great concern that there will be eventually no antimicrobials effective for infection treatment and calls for the attention that it is now a crucial time to develop strategies to preserve the efficacy of antimicrobial agents for future generations. In fact, the rigorous hygiene may be the best way to stop superbugs from spreading and producing damages since multidrug-resistant bacteria could be simply controlled by the comprehensive sanitation e.g. strictly cleaning and disinfecting of all medical equipment and rooms, thoroughly hand washing, early checking the patient for superbugs. It comes to the fact that the patients that use the most antimicrobials are livestock. Even though antimicrobial agents clinically important to human medicine are suggested to be used in farm animals only for medical purposes, this is still far away from what actually happens in today-veterinary practices. As it is necessary to use antimicrobial agents to protect both animal and human health, awareness of using these substances should be priorities in both human and veterinary medicine.

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