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Review on superbug

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ABSTRACT

Staphylococcus aureus is a common cause of infection in both hospitals and the community, and it is becoming increasingly virulent and resistant to antibiotics. The recent sequencing of seven strains of S. aureus provides unprecedented information about its genome diversity. Subtle differences in core (stable) regions of the genome have been exploited by multi-locus sequence typing (MLST) to understand S. aureus population structure. Dramatic differences in the carriage and spread of accessory genes, including those involved in virulence and resistance, contribute to the emergence of new strains with healthcare implications. Understanding the differences between S. aureus genomes and the controls that govern these changes is helping to improve our knowledge of S. aureus pathogenicity and to predict the evolution of super-superbugs

Keywords: Staphylococcus aureus, superbugs.

1. INTRODUCTION

Antibiotic-resistant bacteria ("superbugs"), such as Methicillin-resistant Staphylococcus aureus (MRSA) and Clostridium difficile, are found in NHS hospitals but recent attempts to reduce the problem have been quite successful.1Both C. difficile and MRSA are, however, not exclusive to the NHS, existing in British private hospitals and throughout other western healthcare systems. The UK's record is good internationally. For instance, cases doubled in the USA's private healthcare system between 1999 and 2005,and the UK's death rate is half that of the USA's. The introduction of Private Finance Initiative cleaning contractors into the NHS and the associated "cutting corners on cleaning" have been blamed for the problem, as has increased drug resistance due to inappropriate prescribing of antibiotics and patients failing to complete courses of antibiotics. Another viewpoint is that the spread of communicable diseases in hospitals is facilitated by the overcrowding in NHS hospitals with high bed occupancy rates (as the NHS has a low bed: population ratio produced by hospital bed closures and the increasing emphasis on increasing bed 'turnaround time'). The Superbug NDM1which stands for New Delhi metallo-beta-lactamase is started to spread in the world. NDM-1 is a superbug that is resistant to antibiotics. More specifically, it is an enzyme found inside bacteria. MRSA is an abbreviation for methicillin-resistant Staphylococcus aureus bacteria (fig. 2). This bacterium is known to cause skin infections along with many other types of infections.

MRSA is called a "super bug" because the infections caused by this organism are resistant to many common antibiotics like the ones belonging to the beta-lactam family, including methicillin and penicillin. MRSA belongs to the large group of bacteria known as Staphylococci, often referred to as Staph.

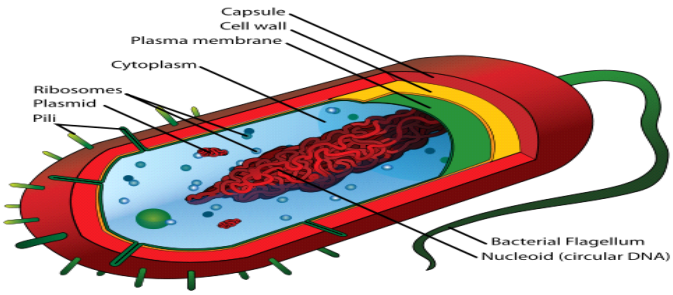


Fig.1 SUPERBUGS (An intro to bacteria, infectious diseases, and antibiotic resistance)

The Superbug NDM1 (in fig.3) which stands for New Delhi metallo-beta-lactamase is started to spread in the world. NDM-1 is a superbug that is resistant to antibiotics. More specifically, it is an enzyme found inside bacteria.

Fig.2 MRSA (methicillin-resistant Staphylococcus aureus bacteria)

Fig.3 NDM1-Esch. Coli

2. SUPERBUG THREAT RISES

Elective surgeries and cancer treatments will become too risky if superbugs continue to gain strength and antibiotic effectiveness keeps waning - unless Australia maintains low levels of resistance. Infectious disease experts are calling for better surveillance to monitor outbreaks and for the medical fraternity to stop "squandering" antibiotics in the face of the global threat.

Fig 4. Superbug threat rises

The call for more rigorous action comes after 33 people died and 3000 were infected by a rare E. coli strain believed to have originated in contaminated vegetables in Germany this month. Unlike hospital "superbugs" - common types of bacteria that morph into antibiotic- resistant strains - this form of E. coli was passed on through food and gained its "superbug" status from the toxic gene it had inherited. Peter Collignon, director of the Australian National University's infectious diseases unit, said causes of the superbug rise included increased air travel, feeding antibiotics to livestock and the "excessive" use of antibiotics to treat illness.

3. ANTIBIOTIC RESISTANCE

Antibiotic resistance is a type of drug resistance where a microorganism is able to survive exposure to an antibiotic. While a spontaneous or induced genetic mutation in bacteria may confer resistance to antimicrobial drugs, genes that confer resistance can

be transferred between bacteria in a horizontal fashion by conjugation, transduction, or transformation. Thus a gene for antibiotic resistance which had evolved via natural selection may be shared. Evolutionary stress such as exposure to antibiotics then selects for the antibiotic resistant trait. Many antibiotic resistance genes reside on plasmids, facilitating their transfer. If a bacterium carries several resistance genes, it is called multidrug resistant (MDR) or, informally, a superbug or super bacterium. Genes for resistance to antibiotics, like the antibiotics themselves, are ancient. [1] However, the increasing prevalence of antibiotic-resistant bacterial infections seen in clinical practice stems from antibiotic use both within human medicine and veterinary medicine. Any use of antibiotics can increase selective pressure in a population of bacteria to allow the resistant bacteria to thrive and the susceptible bacteria to die off. As resistance towards antibiotics becomes more common, a greater need for alternative treatments arises. However, despite a push for new antibiotic therapies there has been a continued decline in the number of newly approved drugs.[2] Antibiotic resistance therefore poses a significant problem.

3.1 Causes

The widespread use of antibiotics both inside and outside of medicine is playing a significant role in the emergence of resistant bacteria.[3] Although there were low levels of preexisting antibiotic resistant bacteria before the widespread use of antibiotics [4,5] evolutionary pressure from their use has played a role in the development of muiltidrug resistance varieties and the spread of resistance between bacterial species.[6] Antibiotics are often used in rearing animals for food and this use among others leads to the creation of resistant strains of bacteria. In some countries antibiotics are sold over the counter without a prescription which also leads to the creation of resistant strains. In supposedly well-regulated human medicine the major problem of the emergence of resistant bacteria is due to misuse and overuse of antibiotics by doctors as well as patients.[7] Other practices contributing towards resistance include the addition of antibiotics to the food of livestock. [8,9] Household use of antibacterials in soaps and other products, although not clearly contributing to resistance, is also discouraged (as not being effective at infection control).[10] Also unsound practices in the pharmaceutical manufacturing industry can contribute towards the likelihood of creating antibiotic resistant strains.[11] Certain antibiotic classes are highly associated with colonisation with superbugs compared to other antibiotic classes. The risk for colonisation increases if there is a lack of sensitivity (resistance) of the superbugs to the antibiotic used and high tissue penetration as well as broad spectrum activity against "good bacteria". In the case of MRSA, increased rates of MRSA infections are seen with glycopeptides, cephalosporins and especially quinolones.[12,13] In the case of colonisation with C difficile the high risk antibiotics include cephalosporins and in particular quinolones and clindamycin.[14,15] In a paper published in the recent edition of the journal Nature, researchers at McMaster University say they have discovered that antibiotic-resistant genes existed in soil bacteria at the same time that now-extinct mammoths, early horses and bison roamed Canada's North.

3.1.1 In medicine

The volume of antibiotic prescribed is the major factor in increasing rates of bacterial resistance rather than compliance with antibiotics.[16] A single dose of antibiotics leads to a greater risk of resistant organisms to that antibiotic in the person for up to a year.[17] Inappropriate prescribing of antibiotics has been attributed to a number of causes including: people who insist on antibiotics, physicians simply prescribe them as they feel they do not have time to explain why they are not necessary, physicians who do not know when to prescribe antibiotics or else are overly cautious for medical legal reasons. [18] For example, a third of people believe that antibiotics are effective for the common cold [19] and 22% of people do not finish a course of antibiotics primarily due to that fact that they feel better (varying from 10% to 44% depending on the country).[20] Compliance with once daily antibiotics is better than with twice daily antibiotics. Sub optimum antibiotic concentrations in critically ill people increase the frequency of antibiotic resistance organisms. While taking antibiotics doses less than those recommended may increase rates of resistance, shortening the course of antibiotics may actually decrease rates of resistance. Poor hand hygiene by hospital staff has been associated with the spread of resistant organisms and an increase in hand washing compliance results in decreased rates of these organisms.

3.1.2 Role of other animals

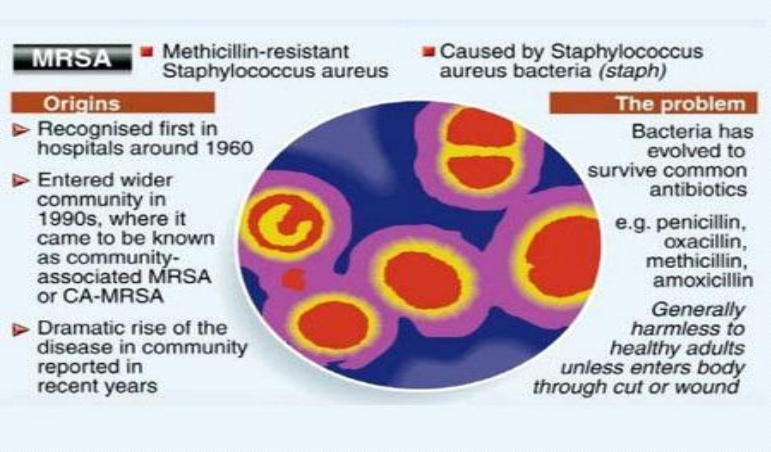
Drugs are used in animals that are used as human food, such as cows, pigs, chickens, fish, etc., and these drugs can affect the safety of the meat, milk, and eggs produced from those animals and can be the source of superbugs. For example, farm animals, particularly pigs, are believed to be able to infect people with MRSA.[26] The resistant bacteria in animals due to antibiotic exposure can be transmitted to humans via three pathways, those being through the consumption of meat, from close or direct contact with animals, or through the environment.[21] The World Health Organization concluded that antibiotics as growth promoters in animal feeds should be prohibited in the absence of risk assessments. In 1998, European Union health ministers voted to ban four antibiotics widely used to promote animal growth (despite their scientific panel's recommendations). Regulation banning the use of antibiotics in European feed, with the exception of two antibiotics in poultry feeds, became effective in 2006. In Scandinavia, there is evidence that the ban has led to a lower prevalence of antimicrobial resistance in (non-hazardous) animal bacterial populations. In the USA federal agencies do not collect data on antibiotic use in animals but animal to human spread of drug resistant organisms has been demonstrated in research studies. Antibiotics are still used in U.S. animal feed—along with other ingredients which have safety concerns. Growing U.S. consumer concern about using antibiotics in animal feed has led to a niche market of "antibiotic-free" animal products, but this small market is unlikely to change entrenched industry-wide practices. In 2001, the Union of Concerned Scientists estimated that greater than 70% of the antibiotics used in the US are given to food animals (for example, chickens, pigs and cattle) in the absence of disease. In 2000 the US Food and Drug Administration (FDA) announced their intention to revoke approval of fluoroquinolone use in poultry production because of substantial evidence linking it to the emergence of fluoroquinolone resistant campylobacter infections in humans. The final decision to ban fluoroquinolones from use in poultry production was not made until five years later because of challenges from the food animal and pharmaceutical industries.[22] Today, there are two federal bills (S. 549 and H.R. 962) aimed at phasing out "non-therapeutic" antibiotics in US food animal production.

4. RESISTANT PATHOGENS

Some bactria attain the resistance against the antibiotics. Some antibiotic resistant bacterias are given below-

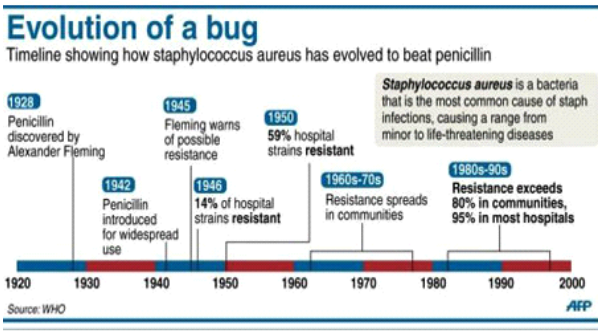
4.1 Staphylococcus aureus

MRSA infection is caused by methicillin-resistant staph bacteria. Known as a "superbug," MRSA treatment can be very challenging. Methicillin-resistant Staphylococcus aureus (MRSA) - commonly known as **"Staph,"** is an infection- causing strain of Staphylococcus bacteria that is **resistant** to a range of antibiotics, particularly Methicillin. The trend towards drug resistance to antibiotics such as Penicillin was first noticed in 1950's. Subsequently it was noticed that the bug Staph also developed drug resistance to other penicillin like antibiotics called erythromycin, streptomycin, and tetracycline.



Methicillin was introduced to treat Staph infection in 1959 and initially it was very successful in treating the much dreaded penicillin-resistant hospital acquired Staphylococcus aureus infections. This success was short lived and in 1961, Methicillin resistance was acquired by Staphylococcus aureus and the first such case was reported from a hospital in the UK.Today outbreaks of MRSA infection is the most dreaded hospital or community acquired infection and can be a nightmare for a hospital or the whole community and a major public health problem. The latter strains are slightly different to what first appeared in the hospitals.

Although many clones of MRSA have appeared in different countries but the broad consensus is that there are 11 major MRSA clones within five groups of related genotypes. Methicillin resistance in Staph bacteria has been found to be due to a (penicillin-binding) protein encoded by the Methicillin-resistant gene (mecA). This gene has, with time, continued to evolve and this has resulted in various strains of MRSA becoming resistant to different antibiotics such as penicillin, amoxicillin and oxacillin. A 2009 research has revealed that many antibiotic-resistant genes and toxins are collectively transferred from one bacterium to another and this explains the speed at which antibiotic resistance develops in Staph bacteria earning it the dubious but awe- inspiring name of "superbug". At any given time different strains of Staph bacteria normally exist on the skin, or on the nose, of nearly one third of human population. However if the presence of the bacteria does not make a person sick then he is reported to be a 'carrier' who is merely 'colonized' and not infected. Staph bacteria is harmless in most people but they may pass it on to others through shared items such as towels or clothing. The bacteria usually finds its way into a person's body through cuts or bruises. In older people, or in those with low immunity, the organism can cause serious illnesses. Recently MRSA has been in the news for causing serious and even fatal infections in the young. The majority of MRSA infections can be classified as HA-MRSA (hospital- or health-care-acquired) and CA-MRSA (communityacquired).Most MRSA infections occur in health- care setups such as hospitals, nursing homes and dialysis centers. They are known as health care-associated MRSA (HA-MRSA). This type of infection has been plaguing hospitals for several years now.



4.2 Streptococcus and Enterococcus

Streptococcus pyogenes (Group A Streptococcus: GAS) infections can usually be treated with many different antibiotics. Early treatment may reduce the risk of death from invasive group A streptococcal disease. However, even the best medical care does not prevent death in every case. For those with very severe illness, supportive care in an intensive care unit may be needed. For persons with necrotizing fasciitis, surgery often is needed to remove damaged tissue. Strains of *S.* pyogenes resistant to macrolide antibiotics have emerged, however all strains remain uniformly sensitive to penicillin.

4.3 Pseudomonas aeruginosa

Pseudomonas aeruginosa is a highly prevalent opportunistic pathogen. One of the most worrisome characteristics of P. aeruginosa consists in its low antibiotic susceptibility. This low susceptibility is attributable to a concerted action of multidrug efflux pumps with chromosomally-encoded antibiotic resistance genes (for example, mexAB-oprM, mexXY etc.) and the low permeability of the bacterial cellular envelopes. Besides intrinsic resistance, P. aeruginosa easily evolve specific resistance either by mutation in chromosomally-encoded genes, or by the horizontal gene transfer of antibiotic resistance determinants. Evolution of multidrug resistance by P. aeruginosa isolates requires several genetic events that include acquisition of different mutations and/or horizontal transfer of antibiotic resistance genes. Hypermutation favours the selection of mutation-driven antibiotic resistance in P. aeruginosa strains producing chronic infections, whereas the clustering of several different antibiotic resistance genes in integrons favours the concerted acquisition of antibiotic resistance determinants. Some recent studies have shown that phenotypic resistance associated to biofilm formation or to the emergence of small-colony-variants may be important in the response of P. aeruginosa populations to antibiotics treatment.

4.4 Clostridium difficile

Clostridium difficile is a nosocomial pathogen that causes diarrheal disease in hospitals world wide. Clindamycin-resistant C. difficile was reported as the causative agent of large outbreaks of diarrheal disease in hospitals in New York, Arizona, Florida and Massachusetts between 1989 and 1992. Geographically dispersed

outbreaks of C. difficile strains resistant to fluoroquinolone antibiotics, such as Cipro (ciprofloxacin) and Levaquin (levofloxacin), were also reported in North America in 2005.

4.5 Salmonella and E. coli

Escherichia coli and Salmonella come directly from contaminated food. When both bacterium are spread, serious health conditions arise. Many people are hospitalized each year after becoming infected, and some die as a result.

4.6 Acinetobacter baumannii

On November 5, 2004, the Centers for Disease Control and Prevention (CDC) reported an increasing number of Acinetobacter baumannii bloodstream infections in patients at military medical facilities in which service members injured in the Iraq/Kuwait region during Operation Iraqi Freedom and in Afghanistan during Operation Enduring Freedom were treated. Most of these showed multi drug resistance (MRAB), with a few isolates resistant to all drugs tested.

5. ALTERNATIVES

5.1 Prevention

Rational use of antibiotics may reduce the chances of development of opportunistic infection by antibiotic-resistant bacteria due to dysbacteriosis. In one study the use of fluoroquinolones are clearly associated with Clostridium difficile infection, which is a leading cause of nosocomial diarrhea in the United States, and a major cause of death, worldwide. There is clinical evidence that topical dermatological preparations such as those containing tea tree oil and thyme oil may be effective in preventing transmittal of CA-MRSA. In addition, other phytotherapeutic medicines too can reduce the use of antibiotics or eliminate their use entirely. Vaccines do not suffer the problem of resistance because a vaccine enhances the body's natural defenses, while an antibiotic operates separately from the body's normal defenses. Nevertheless, new strains may evolve that escape immunity induced by vaccines; for example an update Influenza vaccine is needed each year. While theoretically promising, anti-staphylococcal vaccines have shown limited efficacy, because of immunological variation between Staphylococcus species, and the limited duration of effectiveness of the antibodies produced. Development and testing of more effective vaccines is under way. The Australian Commonwealth Scientific and Industrial Research Organization (CSIRO), realizing the need for the reduction of antibiotic use, has been working on two alternatives. One alternative is to prevent diseases by adding cytokines instead of antibiotics to animal feed.

These proteins are made in the animal body "naturally" after a disease and are not antibiotics so they do not contribute to the antibiotic resistance problem. Furthermore, studies on using cytokines have shown that they also enhance the growth of animals like the antibiotics now used, but without the drawbacks of non-therapeutic antibiotic use. Cytokines have the potential to achieve the animal growth rates traditionally sought by the use of antibiotics without the contribution of antibiotic resistance associated with the widespread non-therapeutic uses of antibiotics currently utilized in the food animal production industries. Additionally, CSIRO is working on vaccines for diseases.

5.2 Phage therapy

Phage therapy, an approach that has been extensively researched and utilized as a therapeutic agent for over 60 years, especially in the Soviet Union, is an alternative that might help with the problem of resistance. Phage therapy was widely used in the United States until the discovery of antibiotics, in the early 1940s. Bacteriophages or "phages" are viruses that invade bacterial cells and, in the case of lytic phages, disrupt bacterial metabolism and cause the bacterium to lyse. Phage therapy is the therapeutic use of lytic bacteriophages to treat pathogenic bacterial infections. Bacteriophage therapy is an important alternative to antibiotics in the current era of multidrug resistant pathogens. A review of studies that dealt with the therapeutic use of phages from 1966–1996 and few latest ongoing phage therapy projects via internet showed: phages were used topically, orally or systemically in Polish and Soviet studies. The success rate found in these studies was 80–95% with few gastrointestinal or allergic side effects. British studies also demonstrated significant efficacy of phages against Escherichia coli, Acinetobacter spp., Pseudomonas spp and Staphylococcus aureus. US studies dealt with improving the

bioavailability of phage. Phage therapy may prove as an important alternative to antibiotics for treating multidrug resistant pathogens.

6. RESEARCH

6.1 New medications

Until recently, research and development (R&D) efforts have provided new drugs in time to treat bacteria that became resistant to older antibiotics. That is no longer the case. The potential crisis at hand is the result of a marked decrease in industry R&D, and the increasing prevalence of resistant bacteria. Infectious disease physicians are alarmed by the prospect that effective antibiotics may not be available to treat seriously ill patients in the near future. As bacterial antibiotic resistance continues to exhaust our supply of effective antibiotics, a global public health disaster appears likely. Poor financial investment in antibiotic research has exacerbated the situation. A call to arms raised by several prestigious scientific organisations a few years ago rallied the scientific community, and now the scope of antibacterial research has broadened considerably. The pipeline of new antibiotics is drying up. Major pharmaceutical companies are losing interest in the antibiotics market because these drugs may not be as profitable as drugs that treat chronic (long-term) conditions and lifestyle issues. The resistance problem demands that a renewed effort be made to seek antibacterial agents effective against pathogenic bacteria resistant to current antibiotics. One of the possible strategies towards this objective is the rational localization of bioactive phytochemicals. Plants have an almost limitless ability to synthesize aromatic substances, most of which are phenols or their oxygen-substituted derivatives such as tannins. Most are secondary metabolites, of which at least 12,000 have been isolated, a number estimated to be less than 10% of the total. In many cases, these substances serve as plant defense mechanisms against predation by microorganisms, insects, and herbivores. Many of the herbs and spices used by humans to season food yield useful medicinal compounds including those having antibacterial activity. Traditional healers have long used plants to prevent or cure infectious conditions. Many of these plants have been investigated scientifically for antimicrobial activity and a large number of plant products have been shown to inhibit growth of pathogenic bacteria. A number of these agents appear to have structures and modes of action that are distinct from those of the antibiotics in current use, suggesting that cross-resistance with agents already in use may be minimal. For example the combination of 5'-methoxyhydnocarpine and berberine in herbs like Hydrastis canadensis and Berberis vulgaris can block the MDR-pumps that cause multidrug resistance. This has been shown for Staphylococcus aureus.

Archaeocins is the name given to a new class of potentially useful antibiotics that are derived from the Archaea group of organisms. Eight archaeocins have been partially or fully characterized, but hundreds of archaeocins are believed to exist, especially within the haloarchaea. The prevalence of archaeocins is unknown simply because no one has looked for them. The discovery of new archaeocins hinges on recovery and cultivation of archaeal organisms from the environment. For example, samples from a novel hypersaline field site, Wilson Hot Springs, recovered 350 halophilic organisms; preliminary analysis of 75 isolates showed that 48 were archaeal and 27 were bacterial.

In research published on October 17, 2008 in Cell, a team of scientists pinpointed the place on bacteria where the antibiotic myxopyronin launches its attack, and why that attack is successful. The myxopyronin binds to and inhibits the crucial bacterial enzyme, RNA polymerase. The myxopyronin changes the structure of the switch-2 segment of the enzyme, inhibiting its function of reading and transmitting DNA code. This prevents RNA polymerase from delivering genetic information to the ribosomes, causing the bacteria to die. One of the major causes of antibiotic resistance is the decrease of effective drug concentrations at their target place, due to the increased action of ABC transporters. Since ABC transporter blockers can be used in combination with current drugs to increase their effective intracellular concentration, the possible impact of ABC transporter inhibitors is of great clinical interest. ABC transporter blockers that may be useful to increase the efficacy of current drugs have entered clinical trials and are available to be used in therapeutic regimes[23].

6.2 Applications

Antibiotic resistance is an important tool for genetic engineering. By constructing a plasmid which contains an antibiotic resistance gene as well as the gene being engineered or

expressed, a researcher can ensure that when bacteria replicate, only the copies which carry along the plasmid survive. This ensures that the gene being manipulated passes along when the bacteria replicates. The most commonly used antibiotics in genetic engineering are generally "older" antibiotics which have largely fallen out of use in clinical practice. These include:

- ampicillin
- kanamycin
- tetracycline
- chloramphenicol

Industrially the use of antibiotic resistance is disfavored since maintaining bacterial cultures would require feeding them large quantities of antibiotics. Instead, the use of auxotrophic bacterial strains (and function-replacement plasmids) is preferred.

7. CONCLUSION

Antibiotic resistance is a type of drug resistance where a microorganism is able to survive exposure to an antibiotic. While a spontaneous or induced genetic mutation in bacteria may confer resistance to antimicrobial drugs, genes that confer resistance can be transferred between bacteria in a horizontal fashion by conjugation, transduction, or transformation. Thus a gene for antibiotic resistance which had evolved via natural selection may be shared. Evolutionary stress such as exposure to antibiotics then selects for the antibiotic resistant trait. Many antibiotic resistance genes reside on plasmids, facilitating their transfer. If a bacterium carries several resistance genes, it is called multidrug resistant (MDR) or, informally, a superbug or super bacterium. Certain antibiotic classes are highly associated with colonisation with superbugs compared to other antibiotic classes. The risk for colonisation increases if there is a lack of sensitivity (resistance) of the superbugs to the antibiotic used and high tissue penetration as well as broad spectrum activity against "good bacteria". In the case of MRSA, increased rates of MRSA infections are seen with glycopeptides, cephalosporins and especially quinolones. In the case of colonisation with C difficile the high risk antibiotics include cephalosporins and in particular quinolones and clindamycin. The volume of antibiotic prescribed is the major factor in increasing rates of bacterial resistance rather than compliance with antibiotics. A single dose of antibiotics leads to a greater risk of resistant organisms to that antibiotic in the person for up to a year.

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