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Review Paper

Methicillin-Resistant Staphylococcus Aureus: A Brief Review

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Abstract

Methicillin-resistant Staphylococcus aureus (MRSA) is a bacterium responsible for several difficult-to-treat infections in humans. It is also called multidrug-resistant Staphylococcus aureus and oxacillin-resistant Staphylococcus aureus (ORSA). MRSA is any strain of Staphylococcus aureus that has developed, through the process of natural selection, resistance to beta-lactam antibiotics, which include the penicillins (methicillin, dicloxacillin, nafcillin, oxacillin, etc.) and the cephalosporins. Strains unable to resist these antibiotics are classified as methicillin-sensitive Staphylococcus aureus, or MSSA. The evolution of such resistance does not cause the organism to be more intrinsically virulent than strains of Staphylococcus aureus that have no antibiotic resistance, but resistance does make MRSA infection more difficult to treat with standard types of antibiotics and thus more dangerous.MRSA is especially troublesome in hospitals, prisons and nursing homes, where patients with open wounds, invasive devices, and weakened immune systems are at greater risk of infection than the general public.

Keywords: MRSA, causes, molecular genetics, laboratory diagnosis, prevention.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) are a type of staphylococcus or "staph" bacteria that are resistant to many antibiotics. Staph bacteria, like other kinds of bacteria, normally live on the skin and in the nose, usually without causing problems.

MRSA is different from other types of staph because it cannot be treated with certain antibiotics such as methicillin. Staph bacteria only become a problem when they cause infection. For some people, especially those who are weak or ill, these infections can become serious.

MRSA infections are more difficult to treat than ordinary staph infections. This is because the strains of staph known as MRSA do not respond well to many common antibiotics used to kill bacteria.

When methicillin and other antibiotics do not kill the bacteria causing an infection, it becomes harder to get rid of the infection. MRSA bacteria are more likely to develop when antibiotics are used too often or are not used correctly. Given enough time, bacteria can change so that these antibiotics no longer work well. This is why MRSA and other antibiotic-resistant bacteria are sometimes called "super bugs."

Methicillin-resistant *Staphylococcus aureus* (MRSA) were first reported in the early 1960's and are now regarded as a major hospital acquired pathogen worldwide. The term methicillin resistant is historically used to describe resistance to any of this class of antimicrobials.

Today in the USA approx. 35% of hospital strains of *Staph. aureus* are resistant to methicillin (or other penicillin antibiotics), and in recent years the emergence of vancomycin-resistant *Staph. aureus* (VRSA) has caused additional concern.

Resistance occurs when the organism has a mecA gene producing an altered penicillin binding protein, PBP2a (also known as PBP2') and either an oxacillin MIC of 2mg/l or a methicillin MIC of 4mg/l. Infected and colonised patients are the reservoir of MRSA both in hospitals and the community with transmission generally being via contact with health workers. Effective, rapid laboratory diagnosis and susceptibility testing is critical in treating, managing and preventing MRSA infections.

The prevention of horizontal transmission of MRSA has become increasingly important as the prevalence of this pathogen increases. Oral carriage of MRSA may serve as a reservoir for re-colonization of other body sites or for cross- infection to other patients or health care workers. At least two cases have been reported of cross-infection from a general dental practitioner to patients[1]. The practitioner had probably been colonised whilst a patient in hospital. Nursing homes are another important source of colonization and infection and two cases of acute parotitis caused by MRSA in elderly patients have been described[2].

Attempts are frequently made to eradicate carriage of MRSA from either patients or medical staff colonized by this organism. However, clinical experience has shown that oropharyngeal carriage of MRSA can be difficult to eradicate[3].

Therefore, it is important that consideration be given to the oral cavity if eradication of colonisation by MRSA is clinically appropriate. Mupirocin is rarely effective alone in clearing oropharyngeal colonization. Successful eradication of throat carriage of MRSA in a health-care worker has been achieved by the use of rifampicin and fusidic acid, in addition to topical mupirocin[4].

However, eradication of throat carriage of MRSA has been achieved with use of topical chlorhexidine(0.2%) in addition to normal control measures of patient isolation, nasal mupirocin and chlorhexidine body washes[5]. Within the oral cavity MRSA may preferentially colonise denture surfaces. One group of workers[6] found 10% of unselected denture-wearing patients carrying MRSA on their dentures which proved difficult to eradicate with conventional denture clearing agents.

In a subsequent study, eradication of the long-term carriage of MRSA from denture-wearing patients was successful only after heat sterilizing or remaking the dentures that had become persistently colonized by MRSA[7]. More recently, 19% of elderly institutionalised veteran populations were shown to be colonized by MRSA in the oral cavity, compared with a prevalence of 20% in the nares. Interestingly, 4% of subjects were culture positive for oral MRSA without evidence of nasal carriage[8].

Carriage of MRSA is not restricted to the chronically ill or institutionalized patients. One study[9] showed that a small portion of children (5 from 307) carried MRSA, a larger proportion than a more recent study (4 from 539)[10]. Another group demonstrated that MRSA clones may colonise the oral cavity of healthy children for relatively long periods of time (5 years), challenging the hypothesis that staphylococci are transient members of the oral flora[11]. Surprisingly little work has been performed on factors affecting oropharyngeal colonization by MRSA.

However, MRSA strains have spread in many hospitals isolates worldwide since 1970s[12]. The nose and oral cavity are the most common reservoir site for Staphylococci[13], and colonization of organism in this part of the body lead to dissemination to other body surfaces. Hospital personnel tend to have higher colonization rates than the general population[14].

Colonized residents and personnel are sources for dissemination of organism and they can serve as reservoirs for MRSA and may harbor the organism for many months[15]. Colonization may be either transient or persistent[13]. It is recommended that every hospital or institute plans own institution strategy in controlling *Staph. aureus* infection.

Methicillin-resistant *Staphylococcus aureus* (MRSA) represents a challenge for all healthcare institutions. Previously limited to large institutions, outbreaks of MRSA are now quite common in all hospital settings[16,17]. These strains are not only resistant to multiple antibiotics, but also act as a reservoir for multiple drug resistant genes.

The spread of Staphylococci from person to person[18] is more difficult to prevent. An example of this is the surgical infection, which can be caused by relatively few organisms, because foreign bodies and devitalized tissue may be present. The problem of infection has been persistent in the surgical world even after the introduction of antibiotics. Pathogens that infect surgical site can be acquired from the hospital environment or other infected patients. Its increasing incidence is a growing concern with emergence of virulent, antibiotic resistant strains in the community settings[19].

Causes: MRSA, like all staph bacteria, can be spread from one person to another through casual contact or through contaminated objects. It is commonly spread from the hands of someone who has MRSA. This could be anyone in a health care setting or in the community. MRSA is usually not spread through the air like the common cold or flu virus, unless a person has MRSA pneumonia and is coughing.

MRSA that is acquired in a hospital or health care setting is called healthcare - associated methicillin - resistant *Staphylococcus aureus* (HA-MRSA). In most cases, a person who is already sick or who has a weakened immune system becomes infected with HA-MRSA. These infections can occur in wounds or skin, burns, and IV or other sites where tubes enter the body, as well as in the eyes, bones, heart, or blood.

In the past MRSA infected people who had chronic illnesses. But now MRSA has become more common in healthy people. These infections can occur among people who are likely to have cuts or wounds and who have close contact with one another, such as members of sports teams. This type of MRSA is called community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA).

Serious staph infections are more common in people with a weakened immune system. This includes patients who: i. Are in hospitals and long-term care facilities for a long time, ii. Are on kidney dialysis (hemodialysis), iii. Receive cancer treatment or medicines that weaken their immune system, iv. Inject illegal drugs, v. Had surgery in the past year.

MRSA infections can also occur in healthy people who have not recently been in the hospital. Most of these MRSA infections are on the skin or less commonly lung infections. People who may be at risk are: i. Athletes and other people who may share items such as towels or razors, ii. Children in day-care, iii. Members of the military, iv. People who have gotten tattoos.

MRSA Infections in Hospital

MRSA infections are a particular problem in hospitals. As with ordinary strains of *Staphylococcus aureus*, some patients harbour MRSA on their skin or nose without harm (such patients are said to be 'colonised').

However, these patients may develop infections if the MRSA spread to other parts of the body (eg if MRSA spread from the colonised nose to a wound). When this happens the resulting infection is described as 'endogenous'.

Some patients are at increased risk of developing infection. They include those with breaks in their skin due to wounds or indwelling catheters which allow MRSA to enter the body, and those with certain types of deficiency in their immune system, such as low numbers of white cells in their blood.

Individuals colonised with MRSA may also serve as a 'reservoir' of MRSA that may spread to other patients. This may happen, for example, if hospital staff attending to a colonised or infected patient become contaminated or colonised with MRSA themselves (often only briefly) and spread the bacteria to other patients with whom they subsequently have contact. These patients may in turn become colonised and/or infected. The spread of MRSA (or for that matter other bacteria) between patients is called cross-infection. In addition, MRSA may be spread via contaminated equipment or through the environment.

Some strains of MRSA are particularly successful at spreading between patients and may also spread between hospitals, presumably when colonised patients or staff moves from one hospital to another. These strains are known as epidemic MRSA (or EMRSA for short). During the 1990s there was a marked increase in infections caused by MRSA in hospitals in the UK due to the emergence and spread of two particular stains of EMRSA known as EMRSA-15 and EMRSA-16.

MRSA Infections in the Community

Patients may be colonised with MRSA when they leave hospital, and there has long been concern that MRSA might spread from hospitals into the community.

In recent years increasing numbers of cases of MRSA infection in the community have been seen in many countries around the world, particularly the USA. However, investigations of these cases have shown that in many instances, the strains of MRSA found in patients in the community are distinct from those strains seen in hospitals and it now appears that these so called 'community-associated MRSA' have evolved independently of hospital MRSA. Although infections with 'community-associated MRSA' occur frequently in some countries, they are uncommon in the UK.

Studies in the USA and other countries have shown that the 'community-associated MRSA' often cause infections in previously healthy individuals who lack the risk factors seen in hospitalised patients. Many of these strains have a toxin called the Panton-Valentine leucocidin (usually referred to as 'PVL') which may contribute to their increased ability to cause infections.

Luckily, 'community-associated MRSA' are frequently susceptibility to a wide range of antibiotics (apart from those belonging to the penicillin class). As further evidence of their independent evolution, 'community-associated MRSA' are generally susceptible to a wider range of antibiotics than are hospital strains.

Genetics: Antimicrobial resistance is genetically based; resistance is mediated by the acquisition of extrachromosomal genetic elements containing resistance genes. Exemplary are plasmids, transposable genetic elements, and genomic islands, which are transferred between bacteria via horizontal gene transfer[20].

A defining characteristic of MRSA is its ability to thrive in the presence of penicillin-like antibiotics, which normally prevent bacterial growth by inhibiting synthesis of cell wall material. This is due to a resistance gene, *mecA*, which stops β-lactam antibiotics from inactivating the enzymes (transpeptidases) that are critical for cell wall synthesis.

SCC*mec*: Staphylococcal cassette chromosome *mec* (SCC*mec*) is a genomic island of unknown origin containing the antibiotic resistance gene *mecA*[21,22] SCC*mec* contains additional genes beyond *mecA*, including the cytolysin gene *psm-mec*, which may suppress virulence in hospital-acquired MRSA strains[23]. SCC*mec* also contains *ccrA* and *ccrB*; both genes encode recombinases that mediate the site-specific integration and excision of the SCC*mec* element from the *Staph. aureus* chromosome[21,22].

Currently, six unique SCC*mec* types ranging in size from 21–67 kb have been identified[21]; they are designated types I-VI and are distinguished by variation in *mec* and *ccr* gene complexes[20]. Owing to the size of the SCC*mec* element and the constraints of horizontal gene transfer, a limited number of clones is thought to be responsible for the spread of MRSA infections[21].

Different SCC*mec* genotypes confer different microbiological characteristics, such as different antimicrobial resistance rates[24]. Different genotypes are also associated with different types of infections. Types I-III SCC*mec* are large elements that typically contain additional resistance genes and are characteristically isolated from HA-MRSA strains[29,31]. Conversely, CA-MRSA is associated with types IV and V, which are smaller and lack resistance genes other than *mecA*[22,24].

mecA: *mecA* is responsible for resistance to methicillin and other β-lactam antibiotics. After acquisition of *mecA*, the gene must be integrated and localized in the *Staph. aureus* chromosome[21]. *mecA* encodes penicillin-binding protein 2a (PBP2a), which differs from other penicillin-binding proteins as its active site does not bind methicillin or other β-lactam antibiotics[21].

As such, PBP2a can continue to catalyze the transpeptidation reaction required for peptidoglycan cross-linking, enabling cell wall synthesis in the presence of antibiotics. As a consequence of the inability of PBP2a to interact with β-lactam moieties, acquisition of *mecA* confers resistance to all β-lactam antibiotics in addition to methicillin[21].

mecA is under the control of two regulatory genes, *mecI* and *mecR1*. MecI is usually bound to the *mecA* promoter and functions as a repressor[20,22]. In the presence of a β-lactam antibiotic, MecR1 initiates a signal transduction cascade that leads to transcriptional activation of *mecA*[20,22]. This is achieved by MecR1-mediated cleavage of MecI, which alleviates MecI repression[20]. *mecA* is further controlled by two co-repressors, BlaI and BlaR1. *blaI* and *blaR1* are homologous to *mecI* and *mecR1*, respectively, and normally function as regulators of *blaZ*, which is responsible for penicillin resistance[21,25]. The DNA sequences bound by MecI and BlaI are identical[21], therefore, BlaI can also bind the *mecA* operator to repress transcription of *mecA*[25].

Laboratory Diagnosis

Diagnostic microbiology laboratories and reference laboratories are key for identifying outbreaks of MRSA. New rapid techniques for the identification and characterization of MRSA have been developed. This notwithstanding, the bacterium generally must be cultured via blood, urine, sputum, or other body fluid cultures, and cultured in the lab in sufficient quantities to perform these confirmatory tests first. Consequently, there is no quick and easy method to diagnose a MRSA infection.

Therefore, initial treatment is often based upon 'strong suspicion' by the treating physician, since any delay in treating this type of infection can have fatal consequences. These techniques include Real-time PCR and Quantitative PCR and are increasingly being employed in clinical laboratories for the rapid detection and identification of MRSA strains[26,27]. Another common laboratory test is a rapid latex agglutination test that detects the PBP2a protein. PBP2a is a variant penicillin-binding protein that imparts the ability of *Staph. aureus* to be resistant to oxacillin[28].

Laboratory screening for MRSA is a complex balance between speed of result, sensitivity, specificity and cost. Currently the majority of screening is carried out using plate based methods. Surveys suggest that this methodology group accounts for >90% of the screening tests performed.

However a number of alternative methods including broth based methods, chromogenic media, rapid screening kits, molecular assays and automated systems are increasingly being used. Isolation from screening swabs can be a lengthy procedure, due to the number of 'contaminating' organisms that are present in swabs from non-sterile sites.

Broth based enrichment media are commonly employed to increase sensitivity. However this is at the expense of speed of result. NaCl is generally added to the base broth along with either methicillin, oxacillin, [and more recently] cefoxitin. Indicator compounds can also be used to give an early indication of the presence of MRSA.

Solid Agar Media: There are no universal standardised methods for screening and isolation of MRSA using solid agar media. Many selective media are available, and these rely on inhibitors such as NaCl and/or antibiotics to aid selection, together with a pH indicator to highlight presumptive.

Examples are Mannitol Salt Agar containing 7% NaCl with either 4mg/L methicillin or 2mg/L oxacillin; Oxacillin Resistant Screening Agar with 5.5% NaCl and 2mg/L oxacillin; Baird Parker Medium with 8mg/L ciprofloxacin; Mueller Hinton Agar with 4% NaCl and 6mg/L oxacillin. Sensitivity at 24hrs incubation is variable with 48hrs incubation often required for an acceptable result.

Recently developed chromogenic media combine primary growth and selectivity with differentiation from coagulase negative staphylococci. These media show improved specificity when compared with traditional media. Sensitivity is also improved but requires 48hrs incubation to achieve >85%.

The majority of molecular methods used for the detection of MRSA are in-house, relying on multiplexed PCR primers detecting genes specific for *Staph. aureus* (nuc,fem) and mecA detecting methicillin resistance. Most are only suitable for use with pure cultures and not screening of swabs due to the presence of coagulase negative staphylococci carrying the methicillin resistant gene mecA. Newer commercially available amplification assays targeting mecA in combination with other specific markers such as coagulase and have shown encouraging results.

There have been a number of developments with bioluminescence in particular the use of adenylate kinase (AK), an enzyme found in all cells that produce ATP from ADP. AK measurement is more sensitive than ATP-based systems and allows routine detection of 50 organisms or more in a sample. Early performance data shows results equivalent to conventional plate culture methods whilst providing results within 5 hours.

Traditionally confirmation of *Staph. aureus* is performed using the slide coagulase test (clumping factor) and the tube coagulase test (free coagulase). Positives on the slide coagulase test should be confirmed with the tube coagulase test. DNase media plates can also be used but positives require additional confirmation.

Agglutination kits are widely available and can be used to confirm *Staph. aureus* by detecting protein A and clumping factor, although some strains of MRSA have low levels of these proteins. Newer kits now work by also detecting surface

antigen. Other latex kits detect PBP2a which occurs within the cell membrane and requires lysis of the cells for detection.

A wide range of commercial biochemical kits are available, both manual and automated. These are based on an array of biochemical tests giving a profile assessed against databases/tables. Many automated systems combine biochemical identification of *Staph. aureus* with antibiotic sensitivity panels for the confirmation of MRSA.

Methods for methicillin and oxacillin susceptibility testing are extensive and published data is contradictory with regard to recommendations. There is no single method that is suitable for all MRSA strains. Standard methods are published by the British Society for Antimicrobial Chemotherapy (BSAC) and in the USA, by the Clinical Laboratory Standards Institute (CLSI), previously known as NCCLS.

Minimum Inhibitory Concentration [MIC] by the dilution method has traditionally been the reference method. BSAC recommend the use of Mueller Hinton or Columbia agar with 2% NaCl and 10^4 cfu/ml inoculum incubated at 30°C. CLSI recommend Mueller Hinton Agar with 2% NaCl and 10^4 cfu/ml inoculum incubated at 33-35°C. Molecular methods which detect the mecA gene are replacing MIC as the reference method.

Antibiotic sensitivity testing using disc diffusion methods remain the most widely used but results are influenced by a range of factors including medium, NaCl concentration, temperature, inoculum and test agent.

A number of recent studies using cefoxitin disc diffusion method suggest greater reliability than with oxacillin. No special medium or incubation temperature is required and the test is less affected by hyper-producers of penicillinase.

The most recent CLSI supplement (M100-S14) suggests the use of 30µg cefoxitin discs using a breakpoint of <= 19mm as indicative of resistance of *Staph. aureus* to oxacillin. Other media based methods include agar, broth based breakpoint methods (2mg/L oxacillin, 4mg/L methicillin) and agar screening methods recommended by CLSI (Approved standard M7-A6).

History

Staphylococcus aureus is a species of bacterium commonly found on the skin and/or in the noses of healthy people. Although it is usually harmless at these sites, it may occasionally get into the body (eg through breaks in the skin such as abrasions, cuts, wounds, surgical incisions or indwelling catheters) and cause infections. These infections may be mild (eg pimples or boils) or serious (eg infection of the bloodstream, bones or joints).

MRSA stands for methicillin-resistant *Staphylococcus aureus*, which is a type of *Staphylococcus aureus* that is resistant to the antibacterial activity of methicillin and other related antibiotics of the penicillin class. The treatment of infections due to *Staphylococcus aureus* was revolutionised in the 1940s by the introduction of the antibiotic penicillin.

However,, most strains of *Staphylococcus aureus* are now resistant to penicillin. This is because *Staphylococcus aureus* can make a substance called ß-lactamase (pronounced beta-lactamase), that degrades penicillin, destroying its antibacterial activity. In the early 1960s, a new type of penicillin antibiotic called methicillin was developed. Methicillin was not degraded by ß-lactamase and so could be used to treat infections due to ß-lactamase-producing strains of *Staphylococcus aureus*. Subsequently, methicillin was replaced by newer and better penicillin-type antibiotics (such as flucloxacillin) that were also not affected by ß-lactamase.

Unfortunately, shortly after the introduction of methicillin, certain strains of *Staphylococcus aureus* emerged that were resistant to methicillin (and also to the newer drugs such as flucloxacillin) These methicillin-resistant *Staphylococcus aureus* became known as 'MRSA' for short, and although methicillin is no longer prescribed, having been replaced by flucloxacillin, the term MRSA continues to be used. Although other types of antibiotics can still be used to treat infections caused by MRSA, these alternative drugs are mostly not available in tablet form and must be administered through a drip inserted into a vein or by injection.

Methicillin-resistant *Staphylococcus aureus* was discovered in 1961 in the United Kingdom. It made its first major appearance in the United States in 1981 among intravenous drug users. MRSA is often referred to in the press as a "superbug". The number of MRSA infections in the United States has been increasing significantly.

A 2007 report in Emerging Infectious Diseases, a publication of the Centers for Disease Control and Prevention (CDC), estimated the number of MRSA infections in hospitals doubled nationwide, from approximately 127,000 in 1999 to 278,000 in 2005, while at the same time annual deaths increased from 11,000 to more than 17, 000[29].

Another study led by the CDC and published in the October 17, 2007 issue of the Journal of the American Medical Association estimated that MRSA would have been responsible for 94, 360 serious infections and associated with 18,650 hospital stay-related deaths in the United States in 2005[30,31]. These figures suggest that MRSA infections are responsible for more deaths in the U.S. each year than AIDS[32].

It has been argued that the observed increased mortality among MRSA-infected patients may be the result of the increased underlying morbidity of these patients. Several studies,

however, including one by Blot and colleagues, that have been adjusted for underlying disease still found MRSA bacteremia to have a higher attributable mortality than methicillin-susceptible *Staphylococcus aureus* (MRSA) bacterrmia[33].

MRSA is sometimes sub-categorized as community-acquired MRSA (CA-MRSA) or healthcare associated MRSA (HA-MRSA), although the distinction is complex. Some researchers have defined CA-MRSA by the characteristics of patients whom it infects, while others define it by the genetic characteristics of the bacteria themselves.

The first reported cases of CA-MRSA began to appear in the mid-1990s in Australia, New Zealand, the United States, the United Kingdom, France, Finland, Canada and Samoa, and were notable because they involved people who had not been exposed to a healthcare setting[34].

In 1997, four fatal cases were reported involving children from Minnesota and North Dakota[34]. Over the next several years, it became clear that CA-MRSA infections were caused by strains of MRSA that differed from the older and better studies health care-associated strains[35].

Prevention

There are several steps that may be undertaken to minimise the spread of MRSA between patients. i. Hospital staff should wash their hands scrupulously before and after having physical contact with patients, using soap or rapidly acting antibacterial alcohol solutions. ii. Patients colonised or infected with MRSA may be kept away from other patients by being placed in separate rooms, either alone or with other patients who also have MRSA. Access to such rooms should be restricted to essential personnel. iii. Hospital staff should wear gloves and disposable gowns prior to having physical contact with MRSA patients. Before leaving the room, they should discard these safely, and wash their hands. iv. Visitors and carers likely to have a lot of physical contact with patients should also wear disposable gloves and gowns. All visitors should wash their hands before leaving the room. v. MRSA can survive on inanimate objects or surfaces such as linen, sinks, floors and even mops used for cleaning. For this reason, areas where MRSA patients are nursed should be thoroughly cleaned using disinfectants.

Conclusion

The increasing prevalence of MRSA infections in the hospitals, other care centres and lately in the community has become a worldwide phenomenon. The wide spread dissemination of multiple - drug resistant strains and antibiotic clones of the bacterium facilitated by inherent or acquired molecular/genetic element is worrying as it complicates diagnosis and chemotherapy. More so, the presence of wide array of virulence and potential risk and spreading factors compounds morbidity and control measures. There is need for adequate policy framework on infection control that will reflect the current realities on the epidemiologic characters of MRSA as well as strict implementation of such control program to checkmate the spread of MRSA infections.

MRSA is no longer only an infection that is acquired in hospitals [HA-MRSA], although this remains a primary source of transmission. Increasingly MRSA can be acquired in the community [CA-MRSA] and indeed from pets [PA-MRSA?]. This perhaps is the more worrying trend due to the potentially large host population and emphasises the need for significantly increased controls of how and when antibiotics are used.

Widespread delivery of antibiotics outside clinically significant uses can only lead to further selection of organisms resitant to higher levels of antibiotics.

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