Methicillin Resistant *Staphylococcus aureus*

MRSA

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Importance

Staphylococcus aureus is an opportunistic pathogen often carried asymptomatically on the human body. Methicillin-resistant *S. aureus* (MRSA) strains have acquired a gene that makes them resistant to nearly all beta-lactam antibiotics. Resistance to other antibiotics is also common, especially in hospital-associated MRSA. These organisms are serious nosocomial pathogens, and finding an effective treatment can be challenging. Community-associated MRSA strains, which originated outside hospitals, are also prevalent in some areas. While these organisms have generally been easier to treat, some have moved into hospitals and have become increasingly resistant to drugs other than beta-lactams. Animals sometimes become infected with MRSA from humans, and may either carry these organisms asymptomatically or develop opportunistic infections. Most of the MRSA found in dogs and cats seem to be lineages associated with people. Colonization of dogs and cats is often transient and tends to occur at low levels; however, these organisms can be transmitted back to people, and pets might contribute to maintaining MRSA within a household or facility. MRSA can also be an issue in settings such as veterinary hospitals, where carriage rates can be higher, especially during outbreaks in pets, horses and other animals.

Animal-adapted MRSA strains also exist. The livestock-associated lineage MRSA CC398, which apparently emerged in European pigs between 2003 and 2005, has spread widely and infected many species of animals, especially pigs and veal calves, in parts of Europe. CC398 has also been found on other continents, although the reported prevalence varies widely. People who work with colonized livestock or poultry can carry CC398, and these organisms can cause opportunistic infections. Other livestock associated MRSA have also been identified in various locations. CC9 is an especially prominent lineage in Asia.

MecC-bearing MRSA is a new type of MRSA first recognized in 2011. Many of these organisms have been recovered from animals, especially dairy cattle, but they can also infect and colonize humans. Recognizing mecC MRSA is currently problematic, as most of the diagnostic tests used routinely to identify MRSA do not detect these organisms.

Etiology

Staphylococcus aureus is a Gram positive, coagulase positive coccus in the family *Staphylococcaceae.* Methicillin-resistant *S. aureus* strains have acquired resistance to methicillin and other beta lactam antibiotics (e.g., penicillins and cephalosporins) via the mecA or mecC genes.

Most MRSA carry the mecA gene, which resides on a large mobile genetic element called the staphylococcal chromosomal cassette mec (SCCmec). This gene codes for a penicillin binding protein, PBP2a, which interferes with the effects of beta lactam antibiotics on cell walls. It confers virtually complete resistance to nearly all beta-lactam antibiotics including semi-synthetic penicillins such as methicillin, oxacillin, or cloxacillin. (Notable exceptions to this rule are the latest generation of cephalosporin β-lactams, e.g., ceftaroline and ceftobiprole.)

Acquisition of mecA seems to have occurred independently in a number of *S. aureus* lineages. Some lineages have a tendency to colonize specific species, and may be adapted to either humans or animals. Others ("extended host spectrum genotypes") are less host-specific, and can infect a wide variety of species. MRSA strains known as epidemic strains are more prevalent and tend to spread within or between hospitals and countries. Other "sporadic" strains are isolated less frequently and do not usually spread widely. There are also MRSA strains that produce various exotoxins (e.g., toxic shock syndrome toxin 1, exfoliative toxins A or B, and enterotoxins) associated with specific syndromes, such as toxic shock syndrome.

MecC (formerly $mecA_{LGA251}$) is a beta lactam resistance gene that was first recognized in 2011, and is less well understood than mecA. Like mecA, mecC is carried on SCCmec. It codes for a different version of PBP2a, which is also thought to interfere with the effects of beta-lactam antibiotics on cell walls. However, a recent paper suggests that mecC-encoded PBP2a may mediate resistance to some beta-lactam drugs, but not others. This could raise the possibility of treatment with some drugs that are ineffective against mecA-bearing MRSA. Many mecC-bearing organisms seem to belong to lineages of staphylococci associated with animals. Some of these lineages appear to have a wide host range.

There could be other, yet unrecognized, mec variants. Rare mec-independent forms of resistance have also been reported in *S. aureus* (e.g., "BORSA" strains, which do not carry mecA but are borderline resistant to oxacillin in *in vitro* tests). Such isolates may be recognized in laboratory tests that directly examine a colony's resistance to antibiotics (phenotypic methicillin resistance), but not in tests based on the recognition of mecA or mecC.

Other methicillin-resistant *Staphylococcus* species

Phenotypic methicillin resistance, the mecA gene and/or mecC have been reported occasionally in *Staphylococcus* species other than *S. aureus*. These organisms have increasingly become an issue in veterinary medicine. For example, methicillin-resistant *S. pseudointermedius* is now a significant concern in dogs. Such animal-associated methicillin-resistant staphylococci occasionally cause zoonotic infections in humans or colonize people asymptomatically. There are also concerns that they could transfer mecA or mecC to staphylococci normally carried by humans.

For further information about methicillin-resistant staphylococci other than *S. aureus*, please see recent reviews (e.g., Cain, 2013 in the reference list).

Naming conventions for S. aureus strains

MRSA lineages adapted to humans have traditionally been classified into hospital-associated and community-associated strains. Hospital-associated MRSA are known for their resistance to a wide variety of antibiotics, and at one time, did not normally circulate outside hospitals. Community-associated MRSA were, conversely, defined as lineages occurring in people who have not been hospitalized or recently had invasive procedures. They were usually susceptible to many antibiotics other than beta-lactams. Community-associated MRSA first appeared in high-risk populations such as intravenous drug users, people in nursing homes, and people who were chronically ill, but are no longer limited to these groups. Recently, the distinctions between these two groups of organisms have started to blur. Community-associated strains have spread into hospitals, and in some areas, hospital-associated strains may be relatively common in people who have no healthcare-associated links. Multiple antibiotic resistance has also emerged in some community-associated strains.

Several different genetic techniques are currently used to classify *S. aureus* strains and lineages, including pulsed-field gel electrophoresis (PFGE), multilocus sequence typing (MLST), DNA sequencing of the X region of the protein A gene (spa typing), SCCmec typing and multilocus variable-number tandem repeat (VNTR) analysis (MLVA). Additional methods were used in the past. Consequently, a single *S. aureus* isolate can have more than one valid name, depending on the test used for typing. Examples of strain names are USA100, CMRSA1 or EMRSA1, based on PFGE typing; ST followed by a number (e.g., ST398) based on MLST typing; or “t” followed by a number (e.g., t011) in spa typing. *S. aureus* are also grouped into clonal complexes (e.g., CC398), which contain genetically related ST types. Naming conventions are complex, and strains given a single name in one system are sometimes separated into more than one type in another system. Isolates may also be identified with a combination of tests for a more complete description. MRSA ST8 t064 SCCmecIV, for instance, is a genetic type that has been found in some horses. Names such as ST9 or CC398 are used for both methicillin-resistant and methicillin-susceptible *S. aureus* of that genetic type. However, the isolates referred to in this factsheet are all MRSA unless otherwise noted.

Genetic typing of MRSA has primarily been used for epidemiological purposes. For example, it can be used to determine whether an isolate found in a veterinary hospital is a livestock-associated or human-associated lineage. It is also becoming important in distinguishing human hospital-associated and community-associated strains of MRSA, which tend to differ in their antibiotic resistance patterns.

Species Affected

Colonization or infection with MRSA has been reported in a number of mammalian species, from domesticated livestock and companion animals (e.g., cattle, small ruminants, camelids, horses, dogs, cats, rabbits, hamsters) to captive (e.g., zoo) or free-living wild species. Among wild animals, MRSA has been found in both terrestrial and aquatic species. Some mammals are reservoir hosts for MRSA, while others are usually infected sporadically, after contact with organisms carried by another species. MRSA has also been found in birds, including poultry, pigeons, psittacines and wild birds. Although MRSA has been reported in turtles, colonization with either methicillin-resistant or methicillin-sensitive *S. aureus*) seems to be rare in reptiles.

Lineages in pigs

Pigs seem to be true reservoir hosts for MRSA CC398, a clonal complex which includes ST398 and some isolates of other MLST types. This lineage has also been called “non-typeable MRSA” (NT-MRSA) because most isolates cannot be typed by PFGE (although they can be typed by other methods), or livestock-associated MRSA (LA-MRSA). CC398 does not seem to be particularly host specific, and it has been detected in other species, such as horses, cattle (especially veal calves), sheep, goats, poultry, commercial and pet rabbits, cats, dogs, and wild rats and field mice/ voles (*Microtus arvalis*) from colonized farms. Other MRSA lineages have also been associated with pigs in some areas. Some are widespread and common (e.g., the livestock-associated lineage CC9 in parts of Asia), while others have been reported from limited numbers of animals or geographic regions. ST5 was the most common lineage found in pigs in several U.S. studies, although CC398 and other lineages were also detected. Pigs can also become colonized with human-associated strains, and in some cases, it is still inconclusive whether a lineage is adapted to pigs or people.

Lineages in ruminant livestock

In cattle, some MRSA strains seem to be of human origin, and MRSA CC398 has also been found; however, there also seem to be some bovine-associated strains. Similarly, human-adapted MRSA, CC398 and isolates that might be host-adapted have been reported in small ruminants.

Lineages in horses

Various MRSA lineages, including both human- and livestock-associated strains, have been found in horses. CC8 is reported to be the most common lineage in some areas (e.g., Australia, parts of North America), while CC398 is sometimes found in horses in Europe. Some MRSA might be adapted to circulate in horses.

Lineages in pets

There do not seem to be any MRSA lineages adapted to cats and dogs; these species seem to be colonized or infected only sporadically, mainly by lineages associated with humans. CC398 is also found sometimes. Rare MRSA isolated from pet hamsters were thought to have been acquired from people, and CC398 was reported in a pet rabbit in Europe.

Lineages in birds

Poultry colonized with CC398 and CC9 have been found in Europe. There is limited information about MRSA in other birds.

Lineages in wild species

In several clinical case reports, captive wild animals were thought to have acquired MRSA from humans. Both livestock-associated and human-associated MRSA have been reported, at low prevalence, in free-living wildlife. Wild Norway rats (*Rattus norvegicus*) in a Canadian inner city neighborhood carried some MRSA strains indistinguishable from human isolates in the area, but also some strains that are normally livestock-associated, such as CC398.

MecC MRSA

MecC-bearing *S. aureus* has been isolated from various animals, including livestock (e.g., dairy cattle, beef cattle, sheep, farmed rabbits), farmed red deer (*Cervus elaphus*), pets (dogs, cats, guinea pigs), diverse free-living and captive wildlife, and at least one bird (a chaffinch, *Fringilla coelebs*). Many isolates have belonged to CC130, which appears to be associated with animals. This lineage is especially common in cattle, but appears to have a wide host range. Other lineages that bear mecC (e.g., CC425, CC49) have also been found.

Zoonotic potential

A number of MRSA strains predominantly colonize people and circulate in human populations. They include the common hospital-associated (mecA) clones CC5, CC8, CC22, CC30 and CC45, and additional community-associated strains. There is evidence that these organisms can be transferred to animals, and re-transmitted from this source to humans.

People can also be infected or colonized with some MRSA clonal complexes maintained in animals, such as CC398. Colonization with these organisms can either be transient or persist for longer periods. [Note: People can also be colonized or infected with methicillin-sensitive CC398; however, this lineage is distinct from livestock-associated methicillin-resistant CC398, and seems to be adapted to circulate in people.] Some mecC-bearing MRSA isolated from humans appear to be linked to contact with livestock; however, there are reports of mecC MRSA in people without apparent animal contact.

Isolates shared between humans and animals have been reported in a number of environments, including veterinary hospitals, households and healthcare facilities (e.g., nursing homes). In some environments (e.g., veterinary hospitals), either people or animals may be the original source of shared isolates.

Geographic Distribution

MRSA can be found worldwide, but the specific lineages can differ between regions. Human hospital-associated strains tend to occur in all countries, although they can be rare in some areas (e.g., some Nordic countries) where eradication programs have been implemented. Human community-associated strains are common in some locations such as North America, but uncommon in others. MRSA types in dogs and cats are influenced by the predominant human lineages in the region.

CC398 is the predominant MRSA in livestock in some European countries. It is still rare or absent in others, although imported cases may be found occasionally. Other MRSA (e.g., CC1, CC97) have also been found in some herds. Outside Europe, CC398 has been recognized in North America, South America, Asia, the Middle East, Australia and New Zealand. However, its prevalence varies widely, and in some locations, reports of its presence are rare. Livestock-adapted CC9 appears to be the most common MRSA lineage among pigs in many Asian countries, but there are regions where other lineages are more prevalent. Both CC5 and CC398 have been found in North American pigs, and some studies have reported that CC5 (ST5) is the most common MRSA type in U.S. pigs. There is limited information about MRSA in African livestock, but ST5 and ST88 have been reported.

MecC-bearing MRSA have only been reported from Europe, to date; however, this distribution could be an artifact of sampling. One study found no mecC in samples of bulk tank milk from farms in the U.S. (Oregon, Wisconsin and New York).

Transmission

Humans

In humans, *S. aureus* is an opportunistic pathogen. Both methicillin-sensitive and methicillin-resistant strains can be found as normal commensals on the skin (especially the axillae and perineum), the nasopharynx, anterior nares and/or in the gastrointestinal tract. Although other sites can also be colonized, many people carry hospital-associated MRSA in the nares. Colonization with *S. aureus* (or MRSA) can occur any time after birth. Current estimates suggest that approximately 20% of humans are persistent carriers of *S. aureus*, while 30% carry this organism transiently, and the remainder are not colonized.

MRSA are usually transmitted by direct contact, often via the hands. People are infectious as long as the carrier state persists or the clinical lesions remain active. MRSA can also be disseminated on fomites (including food that has been contaminated by human carriers) and in aerosols. *S. aureus* (and presumably MRSA) can be transmitted from the mother to her infant during delivery, and organisms in milk may contribute to intestinal colonization of the infant. MRSA has also been transmitted between people in solid organ transplants.

People usually become colonized with MRSA CC398 after contact with live animals, or less frequently, by contact with animal environments or animals at slaughter. This lineage has also been found in a number of people in Europe who have no apparent livestock-related contact. How these people acquired the organism is still unclear, although proximity to farms appeared to be a risk factor in some studies. CC398 can be transmitted from person to person, especially within households, although this seems to be less efficient than person-to-person spread of human-adapted lineages.

One recent study suggested that mecC-bearing MRSA transmission might be transmitted to household members at relatively low rates.

Animals

MRSA has been recovered from various sites in asymptomatic animals, including the nares, pharynx, mouth, skin, and rectum or cloaca. The organisms can colonize more than one site. Carrier animals may serve as reservoirs for disease in themselves, and they may transmit MRSA to other animals or people. Infection or colonization has been observed in people after as little as 4 hours of close contact with a sick, MRSA colonized foal.

Some MRSA strains, such as CC398, are readily transmitted within the host species to which they are adapted. Inhalation of contaminated dust, which can contain large numbers of organisms, is thought to be a major route of spread in confinement operations. Piglets often become colonized from the sow during the perinatal period, but also acquire these organisms horizontally, from other pigs or the environment, as they grow. The MRSA status of the sow seems to have little influence on her offspring after 40 days. In a given herd, many or most pigs can change their MRSA status more than once from birth to full growth, and the prevalence can differ greatly between different sampling points (e.g., from 8% to 94%). One recent study suggested that, like human MRSA carriers, individual pigs can be classified into non-carriers of CC398, transient carriers and persistent carriers.

The transmission of human-adapted MRSA lineages between animals is poorly understood. One study conducted at a canine rescue facility suggested that these strains might not be transmitted readily between healthy dogs. In a few case reports, family pets seem to have acted as one reservoir for the bacteria, and decolonization of humans was unsuccessful when carriage in these animals was not addressed. The frequency with which this occurs is still poorly understood.

Environmental sources and food products

Laboratory reports documenting *S. aureus* or MRSA survival range from less than 24 hours on some dry surfaces (e.g., < 4 hours on dry metal coins, a few minutes on metal razor blades) to a week, several months or more. Survival is reported to be longer when the organisms are protected by organic matter (e.g., 13 days on pus- or blood-contaminated coins) and/or when their initial concentration is high. Factors such as temperature and humidity also affect persistence. Some studies suggest that survival may be prolonged on some plastics. Organisms have also been recovered after 2-3 weeks from ceramics or fabric. One anecdotal report suggested that MRSA may survive for several months in dust on livestock operations.

Environmental contamination with MRSA has been reported in veterinary practices, sometimes even when MRSA patients were not detected, and on some surfaces in households. Contaminated surfaces in veterinary practices can include items, such as computers, that are touched only by humans. High concentrations of organisms may be found in farm environments, including dust and air within swine barns where large numbers of animals are held. Several studies have demonstrated CC398 in exhausted air from pig or poultry facilities, up to 350 m downwind, as well as on the soil up to 500m downwind. However, some of these studies reported that the concentration of organisms in air outside the barn was very low. Isolation rates were reported to be higher in summer, possibly due to higher ventilation rates from barns. CC398 has also been found in chicken manure, soil fertilized with contaminated manure, and feces from wild rooks in Europe. One study reported detecting MRSA on animal feed collected from a truck before it entered a pig facility in the U.S. In abattoirs that slaughter CC398 carrier pigs, MRSA could be detected in a number of areas by the end of the day, but only limited locations were still contaminated by the next morning.

Both animal-associated and human-associated MRSA strains have been found in meat. MRSA can also occur in raw (unpasteurized) milk and cheese. These organisms might contribute to carriage or infection by skin contact with the meat; however, their significance (if any) is still uncertain.

Disinfection

S. aureus is susceptible to various disinfectants including sodium hypochlorite, alcohols, benzalkonium chloride, iodophors, phenolics, chlorhexidine, glutaraldehyde, formaldehyde, and a combination of iodine and alcohol. This organism can also be destroyed by heat. (However, the exotoxins responsible for food poisoning are relatively heat stable, and can persist after live *S. aureus* has been eliminated.)

Infections in Animals

Incubation Period

The incubation period varies with the syndrome. Animals can be colonized for prolonged periods without developing clinical signs.

Clinical Signs

MRSA can cause the same syndromes as *S. aureus*, which can be carried asymptomatically, or involved in a wide variety of opportunistic, suppurative infections. MRSA has been specifically isolated from various skin and wound infections including abscesses, dermatitis including severe pyoderma, postoperative wound infections, fistulas, and intravenous catheter or surgical implant infections. The presence of suture material or orthopedic implants seems to be linked to persistent infections in dogs and cats. MRSA has also been found in other conditions including pneumonia, rhinitis, sinusitis, otitis, keratitis, bacteremia, septic arthritis, osteomyelitis, omphalophlebitis, metritis, mastitis (including gangrenous mastitis) and urinary tract infections. Both *Bordetella bronchiseptica* and MRSA were isolated from the nasal and oropharyngeal tract of puppies after an outbreak of fatal respiratory disease; the role of MRSA in the outbreak was uncertain.

Most swine herds colonized with CC398 do not develop any clinical signs; however, this organism has occasionally been isolated from skin infections, including one outbreak of exudative dermatitis (which is usually caused by *S. hyicus*). There are a few reports of its involvement in more serious illnesses, such as septicemia in a litter of newborn piglets. There might be MRSA that are more virulent for pigs. A CC30 strain, thought to be livestock-associated, was recently isolated from several sick pigs in Ireland. In species other than pigs, CC398 has been found in asymptomatically colonized animals as well as in various purulent conditions, similarly to other MRSA.

MecC-bearing MRSA have been found in apparently healthy cattle, but have also been associated with cases of mastitis in this species. These organisms have been detected in various purulent conditions in cats, dogs, rabbits, guinea pigs and other species. MecC-bearing MRSA were isolated from one wild hedgehog with severe dermatitis, and another hedgehog with septicemia.

Post Mortem Lesions

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The post-mortem lesions of MRSA infections are those seen with any purulent bacterial infection, and vary with the organ system or tissue involved.

Diagnostic Tests

MRSA can be diagnosed by culturing *S. aureus* and identifying methicillin resistant strains with genetic assays and/or antibiotic susceptibility tests. Diagnostic samples in clinical cases are collected from affected sites and/or blood, as for any purulent or septicemic condition. How to best identify colonized animals is still under investigation, and might differ between species. Some studies have found that most (though not all) colonized dogs can be identified by sampling the nares; however, one study recently reported that the mouth might be a particularly sensitive site in dogs and cats, alone or in combination with other locations. The nasal cavity is sampled most often in horses, and one study found that collecting these samples from the nasal vestibulum may be optimal. Adding skin sampling may improve the chance of detecting MRSA in a minority of horses. Nasal swabs are often collected from pigs. Two studies suggested that swabbing the skin behind the ears was a sensitive technique at the herd level, and one survey indicated that tonsils might be a useful site in less intensively raised pigs. Sites that have been sampled in poultry include the trachea, cloaca and nose shell. Environmental samples, including air/dust samples, may be useful for determining herd status on livestock farms. When collecting samples from individual animals, colonization can be difficult to distinguish from transient contamination unless repeated samples are taken.

S. aureus can be cultured in a number of media. On blood agar, colonies are usually beta-hemolytic. Enrichment media, as well as selective plates for MRSA, are available. On microscopic examination, *S. aureus* is a Gram positive, non-spore forming coccus, which may be found singly and/or in pairs, short chains and irregular clusters. Biochemical tests are used to differentiate it from other staphylococci. *S. aureus* can also be identified with assays such as the API Staph Ident system.

The presence of the mecA or mecC gene currently defines MRSA. MecA can be identified by PCR (or other genetic assays), and a latex agglutination test can detect PBP2a, the product of mecA. Commercial PCR or latex agglutination tests to identify mecA-bearing MRSA will not usually recognize isolates that contain mecC. Some in-house PCR tests for mecC have been developed, and assays that can recognize both mecA and mecC have been described in the literature.

Phenotypic antibiotic susceptibility tests (e.g., disk diffusion or MIC determination) can detect MRSA containing either mecA or mecC. However, mecC strains are difficult to recognize, as many isolates exhibit only marginally elevated resistance *in vitro*. Phenotypic tests generally use oxacillin or cefoxitin, although the organism is still traditionally described as resistant to methicillin. Cefoxitin can detect some isolates not recognized by oxacillin, including some mecC strains, and testing isolates with both drugs has been recommended. In some cases, the recognition of a strain as MRSA by phenotypic methods, with a negative result in a PCR assay to detect mecA, might indicate the presence of a mecC strain. However, phenotypic tests can overestimate the prevalence of MRSA, because isolates that do not carry mecA or mecC (and thus, are not considered MRSA) can be resistant. It is also possible to miss rare mecA-bearing MRSA if the resistance gene is not expressed at sufficiently high levels *in vitro*.

MRSA lineages and strains can be identified with molecular tests such as PFGE, MLST, MLVA, SCCmec typing, spa typing and other assays. This information can be useful for purposes such as tracing outbreaks; identifying the most likely source of colonization (e.g., livestock associated or human-associated) or distinguishing human community-associated and hospital-associated MRSA. Some isolates may be untypeable by certain methods. Notably, PFGE cannot identify CC398. A combination of methods may be needed to identify a strain.

Treatment

Antibiotics, topical treatments and other measures have been used successfully to treat clinical cases. In some cases, surgical implants were also removed. Antibiotic therapy should be based on susceptibility testing; however, all mecA-bearing MRSA strains are considered to be resistant to penicillins, most cephalosporins (except the latest generation of cephalosporins, ceftaroline and ceftobiprole), cephems and other ß-lactam antibiotics, regardless of susceptibility testing results. *S. aureus* that carry mecA but appear phenotypically susceptible to methicillin can revert to resistance if the patient is treated with beta-lactam drugs. Most CC398 MRSA are resistant to tetracyclines, but the susceptibility patterns of these isolates otherwise vary (although many are also resistant to trimethoprim). Some MRSA can appear sensitive to clindamycin during routine sensitivity testing, but carry a gene that allows them to become resistant during treatment. In one study, inducible clindamycin resistance was very common among erythromycin-resistant, clindamycin-susceptible MRSA isolates from dogs and cats in Canada.

According to one recent study, isolates that carry mecC seem to differ from mecA-bearing MRSA in their patterns of resistance to beta-lactam antibiotics, and might be treatable with some drugs ineffective against mecA MRSA. Penicillin-clavulanic acid was effective against the isolate used in this particular study.

Local treatment with antiseptic compounds such as chlorhexidine or povidone iodine may be helpful in some types of infections. A few published reports in animals describe successful treatment by meticulous wound management without antimicrobials. Animals treated with topical therapy alone must be monitored closely for signs of localized progression or systemic spread.

Certain antimicrobials, such as vancomycin and tigecycline, are critically important for treating human illnesses caused by MRSA. In some cases, they may the drugs of last resort. The use of these drugs in animals may place selection pressure on isolates that can infect humans. Thus, they are controversial for treating MRSA-infected animals, and should be avoided if at all possible. Recent publications should be consulted for the current list of critically important drugs.

Control

Disease reporting

Reporting requirements for MRSA differ between countries. National and/or local authorities should be consulted for specific information for each region.

Prevention

Veterinary hospitals should establish guidelines to minimize cross-contamination by MRSA and other methicillin-resistant staphylococci. Some routine precautions include hand hygiene, infection control measures (with particular attention to invasive devices such as intravenous catheters and urinary catheters), and environmental disinfection. Barrier precautions should be used when there is a risk of contact with body fluids or when an animal has a recognized MRSA infection. These animals should be isolated. MRSA-infected wounds should be covered whenever possible.

Researchers have recommended that veterinary hospitals initiate surveillance programs for MRSA. Screening at admission allows isolation of carriers, the establishment of barrier precautions to prevent transmission to other animals, and prompt recognition of opportunistic infections caused by these organisms. However, screening all animals can be costly and may not be practical in some practices. An alternative is to screen targeted populations, such as animals with non-antibiotic responsive, non-healing or nosocomial infections, and admitted animals belonging to healthcare workers, known MRSA-positive households and others at elevated risk of colonization. Animals that have been in contact with either MRSA cases or infected/ colonized staff should be tested. If staff are screened for any reason (e.g., during an outbreak), this must be undertaken only with full consideration of privacy and other concerns.

On farms, CC398 can be spread during livestock movements, and may be introduced when buying new stock. MRSA-negative farms, in particular, should attempt to buy stock from MRSA negative sources. Biosecurity measures, including dedicated clothing and showering in, may decrease the risk of MRSA introduction to a farm by human visitors, or reduce transmission between units. Because CC398 has been detected in rodent pests living on pig farms, these animals should be considered in control programs. The potential risks of MRSA in manure may also need to be addressed. Avoiding routine antimicrobial use in food animals might reduce selection pressures, and lower the prevalence of these organisms in livestock. One study found that, in the Netherlands, white veal farms which reduced the use of antibiotics had a lower CC398 prevalence compared to control farms, although the organism was not eliminated. In this study, there was no benefit to professional cleaning and disinfection before introduction of the calves, compared to normal cleaning routines. However, the authors caution that this should not be generalized to all cleaning and disinfection regimens.

The best method to eliminate MRSA carriage in animals in poorly understood, and could differ between species. Dogs, cats, horses and some other animals (including some captive dolphins and walruses) have been known to spontaneously eliminate MRSA when the environment is regularly cleaned and disinfected, and re-infection is prevented. Temporary contact isolation (e.g., having a pet sleep in a crate on an easily cleaned/ disinfected surface, rather than with the owner) and social distancing, together with good hygiene, might also be helpful. Kenneling a colonized pet, preferably in isolation, might be considered in some situations. The efficacy of decolonization with antimicrobials is uncertain. It is not recommended for routine use in pets, but may be considered in individual cases to control transmission, e.g., when an animal remains a persistent carrier or infection control measures are impossible. A variety of antimicrobials (including systemic drugs) have been used to decolonize animals in individual cases, but their efficacy is still unknown. One group suggests that, in the absence of studies describing effective decolonization methods, topical agents such as chlorhexidine might be tried initially. Some authors have noted that topical treatment of nasal carriage with mupirocin or other drugs is likely to be impractical in pets.

Attempts to eliminate MRSA on colonized horse farms and in equine veterinary hospitals have included infection control measures, screening and segregation of animal carriers, and decolonization of human personnel. One horse farm also treated two horses with antibiotics when they remained long-term carriers. Some veterinary hospitals and two farms reported elimination of the organism circulating at the time, while other hospitals found that nosocomial infections were reduced or temporarily eliminated, but the organism persisted in the facility. Various isolates were involved in these reports, including human-adapted strains, a CC8 lineage associated with horses, and CC398.

Several studies have described efforts to eliminate CC398 from colonized swine farms. Removing all pigs and cleaning and disinfecting the facilities, before restocking, reduced CC398 prevalence on some farms; however, this organism seemed to be completely eliminated from few farms (e.g., one of 6 herds in one study). On at least one farm, the organisms were reintroduced in new stock. One group reported that shampooing and disinfecting the skin of pregnant sows, before farrowing, temporarily reduced MRSA prevalence in the sows and their piglets, but did not result in long-term reductions. In Norway, a human-adapted (ST8) MRSA was eradicated from a lightly colonized swine herd, as an adjunct measure while people on the farm were decolonized. In this case, control measures included the removal of animals that tested positive, as well as animals in adjacent pens, together with environmental cleaning and disinfection. Two studies reported that biofilters at exhaust vents reduced dust and airborne MRSA emissions from swine facilities, although the organisms were not necessarily eliminated at all times.

Programs to exclude MRSA in imported animals are unusual; however, CC398 is currently rare in Sweden, and a Swedish advisory board has recommended that imported breeding boars and semen be tested for MRSA. These recommendations suggest that boars be quarantined until 3 tests are negative, and colonized pigs or semen not be introduced. In addition, they advise all in/ all out production for finishing pigs, to limit the possibility of spread in these animals.

Morbidity and Mortality

Outbreaks or clusters of clinical cases have been reported occasionally among horses at veterinary hospitals, and some studies suggest that MRSA may be an emerging pathogen in this species. Reports of infections in companion animals, mainly as postoperative complications and wound infections, also appear to be increasing. In addition to MRSA carriage or contact with carriers, risk factors include repeated courses of antibiotics, hospitalizations (with a longer stay associated with higher risk), intravenous catheterization, orthopedic implants and surgery. Studies from some areas have reported that, when *S. aureus* is found in wounds from dogs, cats and horses, a high percentage of these organisms may be methicillin resistant.

The mortality rate is expected to vary with the syndrome, e.g., lower mortality in superficial infections and higher case fatality rates in septicemia and other serious invasive diseases. At several veterinary referral hospitals, 92% of dogs with infections mainly affecting the skin and ears were discharged, with no significant differences in the survival rate compared to methicillin-sensitive *S. aureus*. In another study, 84% of horses with MRSA infections at 6 veterinary hospitals in Canada survived to discharge. The mortality rate was 20% in an outbreak of exudative dermatitis caused by CC398 in young pigs.

Prevalence of MRSA carriage in animals

Dogs and cats

Colonization with MRSA seems to be uncommon in healthy dogs and cats not linked to a source of this organism. Studies from North America, Europe, Asia and other areas have reported carriage rates of 0-4% among healthy dogs and cats in the community. One U.S. animal shelter found that colonization (< 1%) was not elevated in this environment. Higher carriage rates, up to 11%, have been reported in dogs and cats sampled on admission to veterinary hospitals, possibly due to previous contacts with veterinary facilities. Elevated rates have also been found in some animal facilities such as veterinary clinics or kennels, especially during outbreaks; and in some (though not all) studies of households where humans carried or were infected with MRSA. One study reported that the risk of carriage was increased in dogs belonging to veterinary students.

The colonization status can differ for each animal in a multi-pet household or institution: individual animals may be persistent carriers, sporadically colonized or unaffected. Some studies suggest that carriage in most dogs and cats is likely to be transient, and typically disappears if infections and colonization in human contacts are controlled.

Horses

MRSA carriage appears to be low among healthy horses, with typical colonization rates less than 5-10%. The rates have been lower when horses are tested in the community (where carriage rates of 0% to 2% were reported by several studies from North America, Europe and Asia), and higher in those horses tested upon admission to equine clinics and veterinary hospitals. Colonization rates within veterinary hospitals have been estimated to range from 2% to 16% in most cases, but rates can be much higher (e.g., 40%, 55%) during some outbreaks. One Canadian study reported that infections in the community were clustered, with 13% or 5% of the horses colonized on two farms, and no MRSA detected on eight other farms. Another group found that 61% of the horses on a U.S. racehorse farm were colonized at one visit; however, no MRSA was detected 8 weeks later. While colonization in many horses appears to be transient, one article reported that the duration of carriage ranged from approximately 2 months to approximately 2 years if there were no interventions.

Pigs

Colonization with CC398 is very common among pigs in some parts of Europe, but uncommon in other areas. The reported herd level prevalence varies from < 1% to 71%, with animal level prevalence reported to be as high as 44% in some studies. Carriage rates have often been higher when pigs were sampled at abattoirs rather than on farms, probably because some animals become colonized or contaminated during transport. Reported carriage rates for livestock-associated MRSA (CC9 or other lineages) in Asian countries have also varied widely, from < 5% to approximately 42%, with herd-level prevalence up to 59% in some areas. In Canada, one study found that 25% of swine, and 45% of farms were colonized with MRSA, mainly CC398 but also CC5. Studies from the U.S. have reported overall colonization rates of 0% to 17% in pigs sampled directly on farms (mainly CC5 but also CC398 and other lineages). Herd level prevalence in these studies ranged from 0% to 30%, and 10-100% of the pigs were colonized on affected farms. Some U.S. studies reported that many farms declined to participate, which could affect whether these rates are representative of commercial operations overall. Two studies from Africa reported MRSA colonization rates of 1% (Senegal) or 12.5% (South Africa) in pigs. A survey from Peru found that 40% of the pigs on one of 6 large farms carried CC398, while 5% of the scavenging pigs in villages carried a human community-associated strain.

Studies from Europe and Asia have reported that larger herds are more likely to be infected with livestock-associated MRSA than small herds. Having a CC398-positive supplier is strongly associated with herd colonization by this organism, although some colonized farms have suppliers that are MRSA-free. The farming system/ management factors also seems to affect the risk of infection, and some studies have also suggested other risk factors for CC398 carriage, such as use of zinc as a food additive. In some herds, the highest MRSA prevalence seems to occur around the time of weaning, then declines; however, the pattern may differ between herds. Genetic factors may influence whether a pig is likely to carry *S. aureus*, and one study suggested that a subset of persistently colonized pigs might be the primary contributors to maintenance and transmission of this organism on a farm, with other animals colonized only transiently or not at all.

Cattle

CC398 carriage rates in cattle vary widely, depending on the overall prevalence of this organism in a country, and the type of production system. Where this organism is common, veal calves (especially white veal calves) are often carriers. In some areas, up to 90% of the veal calf farms and 28-64% of the calves can be colonized. Within a high risk area, factors that appear to influence prevalence include farm hygiene, antibiotic use, and farm size, with higher rates of carriage on larger farms.

CC398 carriage rates are reported to be considerably lower in beef and dairy operations. In Belgium, where MRSA colonization is common in veal calves, carriage rates were reported to be 5% in beef cattle (10-30% of farms colonized) and 1% in dairy cows (10% of farms). Other surveys have reported isolating MRSA from <5% to 15% of dairy cattle or bulk tank milk in Europe, and 9% of beef cattle at slaughter in Germany.

Studies of bulk tank milk in the U.S. suggest that the farm level prevalence of MRSA in this area is low (< 1% to 4%). Some studies from the U.S. and Canada did not detect MRSA in beef cattle, although it has been reported in meat. Surveys in South Korea found MRSA (mainly isolates adapted to humans) in <1% to 6% of milk samples, and 4% or 14% of dairy farms. In Brazil, one group found MRSA in 3% of milk samples.

Poultry

MRSA was detected in 2% to 35% of chicken flocks in a number of studies from Europe. Some reports suggest that the prevalence may be higher on broiler farms than layers. A German national monitoring scheme found MRSA in 20% of turkeys, and localized studies in Germany have reported that up to 25-90% of turkey flocks may be colonized in some regions. CC398 was often detected in these studies, although other lineages were also found.

Exotic species

While MRSA has been reported in free-living wildlife, carriage rates currently appear to be low (< 5%). There have been sporadic reports of clinical cases in captive wildlife, but the organism was often suspected or demonstrated to have been acquired from human caretakers. Two reports from European zoos found no MRSA colonization among the animals in their collections, while another study detected MRSA (mecC) only among captive mara *(Dolichotis patagonum*). A recent study reported that 69% of the captive chimpanzees in one U.S. colony were colonized with a human community-associated MRSA. Anecdotal reports suggest that these organisms might also be common in other captive nonhuman primates.

MecC-bearing MRSA

The prevalence of mecC-bearing lineages in animals is still unclear. These isolates are not readily detected with the tests used routinely to recognize MRSA. In various studies performed since 2011, the proportion of mecC isolates has ranged from < 1% to 69%. Some studies suggest that these organisms may be relatively common in dairy cattle; however, a meta-analysis indicated that their overall prevalence in all species might be less than 1%.

Infections in Humans

Incubation Period

The incubation period for *S. aureus* infections in humans is highly variable. In susceptible patients, clinical cases may become apparent 4 to 10 days after exposure; however, opportunistic infections can also occur after an indefinite period of asymptomatic carriage.

Clinical Signs

MRSA is an opportunist, like other *S. aureus*, and can cause the same types of infections. While many people are colonized asymptomatically, mecA-bearing MRSA can be involved in various skin and soft tissue infections, as well as invasive conditions such as pneumonia, endocarditis, septic arthritis, osteomyelitis, meningitis and septicemia. Hospital-acquired MRSA strains are major causes of nosocomial infections associated with indwelling medical devices and surgical sites. Human community-acquired-MRSA strains have mainly been associated with superficial skin or soft tissue disease, although they have also caused sepsis, necrotizing fasciitis, necrotizing pneumonia and other conditions. MRSA strains that carry the exotoxin TSST-1 have been found in cases of toxic shock syndrome, especially in Japan. Other toxin-expressing MRSA strains (exfoliative toxins A or B) can cause staphylococcal scalded skin syndrome, a disease characterized by widespread blistering and loss of the outer layers of the epidermis. Understanding of mecC-bearing MRSA is still limited; however, this organism has also been identified in conditions ranging from wound infections to fatal sepsis.

MRSA strains that produce enterotoxins while growing in food can cause acute staphylococcal gastroenteritis (food poisoning). Antibiotic resistance is generally irrelevant in this condition, because the preformed toxin is eaten in food and the organism is not present in the body. Rare reports have suggested the possibility of overgrowth by enterotoxin-producing *S. aureus* in the intestines of some patients treated with antibiotics.

Zoonotic MRSA can presumably cause the same types of infections as human-associated MRSA strains. Asymptomatic colonization is common, but opportunistic infections also occur. CC398 has mainly been found in superficial skin and soft tissue infections, but some case reports describe conditions such as aggressive wound infection, necrotizing fasciitis, destructive bone and joint infections, sinusitis, endocarditis, nosocomial bacteremia, pneumonia, and severe invasive infection with multiorgan failure.

Diagnostic Tests

Infections in humans are diagnosed by culture and identification of the organism, as in animals. In colonized people, MRSA may be found in multiple locations. The nares are sampled most often, but the addition of other sites, such as the pharynx or skin (e.g., groin) may improve the detection rate. Staphylococcal food poisoning is diagnosed by examination of the food for the organisms and/or toxins.

Treatment

Factors such as the location, severity and progression of the infection, as well as the age and health of the patient, can affect the type of treatment chosen. Skin infections are sometimes treated with techniques that do not require systemic antibiotics (e.g., incision and drainage for abscesses). Treatment may also require adjunct measures such as the removal of catheters.

Antibiotics must be selected based on susceptibility testing. While mecA-bearing MRSA are resistant to nearly all beta-lactam antibiotics, they are generally not resistant to the latest generation of cephalosporins (e.g., ceftaroline and ceftobiprole). Resistance to other drugs is typically high in hospital-acquired MRSA, and lower in community-acquired strains, although resistance has been increasing in the latter group. Some new antibiotics effective against MRSA have recently been introduced. Some of the drugs used to treat serious infections caused by multiple drug resistant MRSA strains include vancomycin, telavancin, linezolid, tedizolid, teicoplanin, tigecycline, quinupristin/dalfopristin and daptomycin. Resistance has been reported to some of these antibiotics, including vancomycin.

Prevention

Hand washing, avoidance of direct contact with nasal secretions and wounds, barrier precautions when handling animals with illnesses caused by MRSA, environmental cleaning and other infection control measures are expected to reduce the risk of acquiring MRSA from infected or colonized animals. Skin lesions should be covered to prevent them from becoming infected. A few studies have suggested that face masks reduce the risk of colonization when working with livestock, compared to gloves alone. People who are unusually susceptible to MRSA, such as immunocompromised persons and post-surgical patients, should be educated about the risks of zoonotic MRSA and the role of good hygiene, such as hand washing before and after contact with pets, and avoidance of direct contact with nasal secretions and wounds.

Infection control measures, particularly hand washing, are also important in preventing the transmission of MRSA from humans to other people or animals. Outpatients with MRSA skin lesions should keep them covered with clean, dry bandages. In some circumstances, such as the inability to adequately cover a MRSA-infected wound, close contact should be avoided. The Netherlands and Scandinavian counties have greatly reduced the incidence of hospital-associated human MRSA by screening and decolonization of hospital staff, and screening of patients on admission. High risk patients, including people who work with pigs or veal calves, are isolated until the screening test demonstrates that they are MRSA-free. MRSA outbreaks are investigated aggressively, and antibiotic use is restricted. Opinions in other countries vary on the relative benefits of various MRSA control measures in hospitalized patients.

Decolonization of humans is not always be successful, and it can be controversial. It may be recommended in some situations or groups of patients, but not others. A variety of agents, including various combinations of intranasal agents (e.g., mupirocin and fusidic acid), topical antiseptic washes (e.g. chlorhexidine) and systemic antimicrobials have been used in people. MRSA can be resistant to any of these agents, including chlorhexidine. Other family members may need to be decolonized concurrently, and in some cases, carriage in companion animals may need to be considered. When an animal is thought to be involved, it may be advisable to use multiple typing methods to ensure that the strains in the animal and humans are identical. In one recent case, such techniques demonstrated that a dog was not the reservoir for the reintroduction of MRSA to a human household after decolonization, although the strains initially appeared to be the same. The organism may also be reintroduced by carriage in other parts of the body, from the environment, from community members outside the household, or other sources. People who work with CC398-colonized livestock often become recolonized from this source.

The best procedure to follow when a resident animal becomes colonized in a healthcare facility has not been standardized. In one outbreak, options presented to the facility included removing the animal until it cleared the bacterium, or allowing it to remain, with or without antibiotic treatment, and with continued monitoring (culture) and the encouragement of good hand hygiene among human contacts.

Morbidity and Mortality

Hospital-associated MRSA is one of the most prevalent nosocomial pathogens worldwide. Most infections occur in high risk patients, including the elderly and people with open wounds. Healthcare-associated MRSA infections have recently declined in many countries throughout the world. However, infections caused by community-associated MRSA are becoming more prevalent in some areas.

As with many bacterial infections, the case fatality rate differs with the syndrome. Mortality also depends on success in finding an effective antibiotic for the strain, and the general health of the patient. While CC398 can cause severe illness, some studies have suggested that this lineage might be less virulent than lineages adapted to humans. An alternative explanation is that most people colonized with CC398 are generally younger and in better health, and may be less susceptible to opportunistic pathogens.

MRSA carriage - human lineages

Human healthcare workers worldwide are at an increased risk for colonization with MRSA, due to occupational exposure. Carriage rates in this population are estimated to be approximately 2-5% overall, but range from 1% to 15%, and differ between regions. In the general population, MRSA carriage rates are often estimated to be < 1% to 5%, although they can be higher in some populations. Schools and daycare centers appear to be common sites for the dissemination of community-associated lineages. Most transmission of these organisms occurs within households, due to frequent close contact. Community-associated MRSA are also an increasing problem in U.S. hospitals.

MRSA carriage - livestock associated lineages

MRSA carriage rates are elevated in farmers, veterinary personnel and other people who are occupationally exposed to animals colonized with MRSA. Reported colonization rates among veterinarians, veterinary students and/or veterinary staff in Europe, North America, Asia and Australia have ranged from 0% to 22%, with occasional reports as high as 44%. Some but not all surveys found that carriage rates were higher in livestock and/or horse practitioners than small animal practitioners. Long term studies of veterinarians exposed to CC398 suggest that most people either carry this organism transiently or are not colonized, while a smaller number (20-26% in 2 studies) are consistently colonized.

Reported CC398 carriage rates among farm workers in Europe range from < 5% to 44%, and are exceptionally as high as 72-100%. The highest rates are often reported in people exposed to veal calves or swine, due to the high rates of colonization in these species; however, this organism has been found in up to 37% of poultry workers in some areas. Elevated rates of CC398 carriage have also been reported in household members not directly exposed to livestock; however, these rates are lower. Colonization with CC398 often seems to be transient in people with sporadic or short term contact, but more persistent when exposure is frequent and continuous. It may persist for a time in the latter group even when exposure stops. MRSA may be uncommon in people exposed to horses on farms. Few horses carried MRSA in one Belgian survey, and only 2% of their caretakers were carriers.

Reports from Asia suggest that carriage rates for livestock-associated MRSA (e.g., CC9) in farm workers may be lower overall than in Europe, ranging from 2% to 19%. Higher rates have sometimes been reported in certain categories of farms. For instance, one study reported colonization in 37% of workers on large farms, and 9% of workers on small farms. Studies from Europe and Asia have found that, while slaughterhouse workers or butchers can have elevated carriage rates compared to the general population, they appear less likely to be colonized than farm workers.

Studies in North American farm workers have also been published, although some sampled small numbers of people. One U.S. study detected MRSA in 64% of swine workers on a farm colonized with CC398, but no colonized workers (or pigs) on another farm. A larger study by this group found that approximately 21% of swine workers carried MRSA, but most (87%) of the positive samples came from 4 MRSA-positive farms. In North Carolina, <5% of people who worked in industrial and antibiotic-free swine or poultry operations carried MRSA. Another study found no evidence for increased MRSA carriage in people with livestock (pig, cattle and poultry) contact in Iowa. Most of the participants in this study were family farm owners with moderate numbers of pigs A study of 35 relatively small breeding pig farms in Connecticut detected MRSA in 2 of 9 participating workers; however, these isolates were typical human-associated strains in people who had risk factors for colonization. In Canada, the prevalence of CC398 carriage among the general population of Manitoba and Saskatchewan was < 0.5% in 2007-2008, and one study detected MRSA in 20% of swine workers tested. Several U.S. studies have reported that community members living in close proximity to swine operations had an elevated risk of carriage with MRSA; however, these strains were not proven to be livestock associated lineages, and the influence of other factors (e.g., socioeconomic status or direct livestock contact) on the results is still unclear.

MecC MRSA

MecC-bearing MRSA are difficult to identify with routinely used MRSA tests, and their prevalence in humans is uncertain. Most studies suggest that they currently comprise less than 2% of all MRSA isolated from people, with a range of 0% to 6%. However, records from Denmark, where *S. aureus* bacteremia has been tracked since 1958, suggest that their prevalence may be increasing. One study from Sweden suggested that mecC MRSA lineages may be relatively poor colonizers of humans, and carriage may be transient.

Internet Resources

Association for Professionals in Infection Control and Epidemiology. Guidelines for the Control of MRSA

British Small Animal Veterinary Association. MRSA

Centers for Disease Control and Prevention (CDC). MRSA Resources

CDC. Guidelines for Hand Hygiene in Health-Care Settings.

CDC. Healthcare-associated Infections (HAI)

Public Health Agency of Canada. Pathogen Safety Data Sheets

Multi Locus Sequence Typing [database]

Spa-MLST Mapping [database]

The Merck Manual

The Merck Veterinary Manual

U.K. Veterinary Medicines Directorate Guidelines on LA-MRSA

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