Methicillin-Resistant Staphylococcus aureus and New Delhi Metallo beta-lactamases: types of antibiotic resistance, methods of prevention

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Abstract

Methicillin was known as an antibiotic that was used to treat many infections caused by Staphylococcus aureus, but in a short period of time this antibiotic entered the medical field and eventually led to the emergence of methicillin-resistant strains of bacteria, and it is believed that methicillin resistance resulted from the bacterial acquisition of a gene that encodes a protein capable of. This strain is known as methicillin-resistant aureus, MRSA. However, the danger of antibiotic resistance does not stop there, especially if we know the emergence of new strains of bacteria that are resistant to the most powerful antibiotics, namely New Delhi Metallo beta-lactamases. In this article, we will talk about the two types of antibiotic resistance, methods of prevention and reduction of resistance, and a brief history of each of them.

Keywords: MRSA; Methicillin-Resistant Staphylococcus aureus; Anti-Bacterial Agents; Staphylococcal Infections; beta-lactamase NDM-1

الملخص

لم يتم استخدام الميثيسيلين كمضاد حيوي لعلاج العديد من الالتهابات التي تسببها المكورات العنقودية الذهبية ، ولكن في فترة قصيرة من الزمن ، دخل هذا المضاد الحيوي إلى المجال الطبي أدى في النهاية إلى ظهور سلالات من البكتيريا المقاومة للميثيسيلين ، ويعتقد أن مقاومة الميثيسيلين نتجت عن اكتساب البكتيريا للجين الذي يشفر بروتينًا قادرًا على هذه السلالة المعروفة باسم مقاومة الميثيسيلين المذهبة ، MRSA. ومع ذلك ، فإن خطر مقاومة المضادات الحيوية لا يتوقف عند هذا الحد ، خاصة إذا علمنا ظهور سلالات جديدة من البكتيريا المقاومة لأقوى المضادات الحيوية ، وهي (New Delhi Metallo beta-lactamases). في هذه المقالة سوف نتحدث عن نوعين من مقاومة المضادات الحيوية ، وطرق الوقاية والحد من المقاومة ، وتاريخ موجز لكل منهما.

الكلمات الدالة
Introduction

Staphylococcus aureus, a human pathogen, has a variety of virulence factors and the ability to acquire resistance to most antibiotics. This ability is compounded by the continual emergence of a new clone, making S. aureus a “super glitch.” Clinical use of methicillin has led to methicillin-resistant Staphylococcus aureus (MRSA) (1).

Where these bacteria have a high ability to acquire resistance determinants to antibiotics, especially after the entry of generations of antibiotics into the field of medical use, and the fact that Staphylococcus aureus has a high pathogenicity among the types of staphylococci, the acquisition of resistance determinants in these bacteria poses a great challenge to the treatment and control of the diseases they cause These bacteria (2).

Methicillin is a penicillin antibiotic that was previously used to treat bacterial infections caused by organisms of the genus Staphylococcus. It was active against certain types of Staphylococci, including Staphylococcus aureus, which are resistant to penicillin, but this type of bacteria has shown resistance to the antibiotic methicillin. Known as MRSA, it is known as Methicillin-resistant Staphylococcus Arues in a short period of time when this antibiotic is used in the treatment of S. aureus (3).

1.1 –Antibiotics

Antibiotics belong to a broader group of antimicrobial compounds and are used to treat infections caused by microorganisms, including fungi and parasites (3,5). Table 1 shows the types of common antibiotics.

Table (1) shows some types of common antibiotics and their most important properties.
<table>
<thead>
<tr>
<th>tetracycline derivatives</th>
<th>sexual diseases</th>
<th>Antibacterial</th>
<th>Doryx, Doxidar</th>
<th>Doxycycline</th>
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<tr>
<td>feline newborns</td>
<td>sexual diseases</td>
<td>Antibacterial</td>
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<td>Azithromycin</td>
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1.1.1 **Resistance to Antibiotics Vital: Antibiotic Resistance**

Is the ability of microbes such as bacteria, fungi, and viruses, and parasites that cause for no diseases to survive and adapt to the environment in which, despite eating several types of antibiotics and be resistant to the treatment of a not well, which needs to change the treatment and only anti-cover types multiple of bacteria (4). However, Staphylococcus aureus resistant to methicillin MRSA About the often-unnecessary use of antibiotics for long periods

1.1.2 - Causes of antibiotic resistance:
A - Excessive use of antibiotics.
B - A shortage of antibiotics that are being developed.
C - Weak infection control in hospitals and clinics.
D - Excessive use of antibiotics in fish and livestock farms (5).

1.1.3 - The Spread of Antibiotic Resistance:

The spread of antibiotic resistance currently poses a major public health threat facing humanity today. Bacteria that are resistant to many drugs are reported annually, while the development of new antibiotics is declining. Emphasis has been placed on limiting the spread of antibiotic resistance by limiting the use of antibiotics in health care, veterinary applications and meat production, which has led to a reduction in the exposure of pathogens to antibiotics, thus reducing the selection of resistant strains (5).
Figure (1) shows how antibiotic resistance spreads

2.1- Methicillin

It is an antibiotic of the penicillin group, which was previously used in the treatment of bacterial infections caused by organisms of the genus Staphylococcus. It is derived from penicillin, as it contained a modification of the original structure of penicillin, which made it resistant to a bacterial enzyme called penicillinase beta-lactamase, where this was produced. The enzyme is inactivated by most strains of Staphylococcus aureus and inactivates certain types of penicillin by hydrolysis of the beta-lactam ring which is central to the antimicrobial activity of these drugs (6,7).
2.2 Staphylococcus aureus

Staphylococcus Aureus is a gram-positive, nonmotile bacterium. It was called by this name (staphylococcus) because it gathers in the form of irregular balls that resemble a bunch of grapes when viewed under the microscope. They are completely red and are facultatively anaerobic (can live in the presence or absence of oxygen). Staphylococcus aureus usually lives normally on human skin, in the nasal cavity (Figure 4) or in the respiratory tract. However, it can cause a range of diseases, from minor skin infections such as pimples, impetigo, abscesses (Fig. 5), boils, cellulitis, folliculitis, scalded skin syndrome and anaphylactic shock syndrome (Fig. 6), in addition to Life-threatening diseases such as pneumonia, meningitis, osteomyelitis and septicemia. It is one of the most common causes of hospital-acquired illnesses. Staphylococcus aureus is an opportunistic pathogen responsible for many suppurative infections in both humans and animals (8).
Figure No. (4) Nose ulcers

Figure No. (5) Abscess

Figure (6) Anaphylactic shock syndrome (8)
1.4 Methicillin-resistant Staphylococcus aureus (MRSA)

This type of bacteria is characterized by its resistance to many types of known antibiotics, and this type of bacteria lives naturally in the nose and on the skin, and does not cause any harm to humans, and a wound or surgical procedure may lead to a large multiplication of bacteria and cause infection. Where the symptoms of infection depend on the location of the infection, it often causes skin sores and boils, and may cause some more serious health complications in some cases when it is transmitted to the bloodstream, lungs, or urinary system, and this type of bacteria is highly contagious (8).

![Methicillin-resistant Staphylococcus aureus (MRSA)](image)

**Figure 4 shows methicillin-resistant Staphylococcus aureus (MRSA).**

1.4.1 -kinds

There are several types, the most important of which are:

- **A**: MSSA, which is an abbreviation for (Methicillin-Sensitive Staphylococcus aureus).
- **B**: VRSA: It is an abbreviation for Vancomycin Resistant staphylococcus aureus.
- **C**: ORSA: It is an abbreviation for Oxycillin Resistant Staphylococcus aureus.
- **D**: CA-MRSA, which is an abbreviation for Community Acquired-Methicillin Resistant staphylococcus aureus.
- **E**: HA-MRSA: It is an abbreviation for Hospital Acquired-Methicillin Resistant staphylococcus aureus.
1.4.2 Mechanism of MRSA Resistance:

The mechanism of methicillin resistance in Staphylococcus aureus is twofold: the first is the production of beta-lactamase enzymes, and the second is the presence of the mecA gene. (8,9).

This gene uniquely encodes a penicillin-binding protein (PBP) that binds to Meticillin and thus promotes bacterial survival by preventing the antibiotic from inhibiting cell wall synthesis (9).

1.4.3 Ways of spread of MRSA:

Staphylococcus aureus can spread through contact with pus from an infected wound, or contact with objects used by an infected person, such as towels or sports equipment. People with diabetes, injecting drug users, and people with heart disease should take extra precautions to avoid contact with the Staphylococcus aureus. Because they are more vulnerable, bacteria are also transmitted through the hands of health care workers, where the introduction of bacteria into the bloodstream can lead to various complications, including endocarditis and meningitis, and if spreads widely, it can cause septicemia(8).

1.4.4 Symptoms and diagnosis:

• bacteremia.

Bacteremia, also known as "blood poisoning", can occur when bacteria enter the bloodstream and begin to colonize, causing many symptoms, including: nausea, vomiting, diarrhea, confusion, and the diagnosis of strep disease is by blood culture for bacteria (9).

• Inflammation of the internal heart.

Endocarditis occurs when the endocardium of the heart becomes damaged, allowing bacteria in the bloodstream to lodge on the heart valves or the lining and cause infection. Endocarditis is not characterized by a single symptom but can be detected by many symptoms such as fever, joint pain, loss of appetite, cough, where this diagnosis is usually made by taking a sample of the patient's blood to be tested for bacteria (9).

• Inflammation of the soft tissues.
Staph infection leads to several different types of soft tissue infection such as: impetigo, abscesses, cellulitis, skin infection is also characterized by redness, swelling, and these diseases are diagnosed by observing symptoms and sometimes laboratory tests.

**Pneumonia.**

When Staphylococcus aureus infects the lungs, the resulting disease is pneumonia, which includes many symptoms such as: fever, chest pain, increased breathing, cough accompanied by phlegm. Pneumonia is diagnosed by symptoms and a chest examination, and cultures from sputum tests may also be used (10).

1.4.5 Treats

If this germ is diagnosed, the treatment varies according to a set of factors:

Type of infection, site of infection, severity of symptoms, antibiotics to which MRSA (web8) responds.

1.4.5.1 Measures to deal with MRSA infection include:

A- Culture and sensitivity test of dried materials.

b- Wound care and hygiene.

1.4.5.2 Medication options for MRSA and soft tissue infections include:

a- Tetracycline drug.

B- Sulfamethoxazole, Trimethoprim, Clindamycin.

C- Cephazoline, Cephalexin.

d- Linezolid, Daptmycin (11-15).

1.4.6- Prevention:

• Wash hands with soap and water.

• Covering wounds.

• Not sharing personal items.
• Washing covers and clothes.

• Isolation of infected patients.

• Ensuring the cleanliness of health care centers (8).

1.5 New Delhi metallo-beta-lactamase 1 NDM-1[1] is an enzyme that makes bacteria resistant to a wide range of beta-lactam antibiotics. These include antibiotics of the carbapenem family, which are the mainstay for treating antibiotic-resistant bacterial infections. The NDM-1 gene is one large member of this gene family that encodes carbapenem contact beta-lactamase enzymes contact carbapenem's. The bacteria that produce carbapenems are often referred to in the media as "germs" because the infections they cause are difficult to treat. These bacteria are usually sensitive only to polymyxins and tigecycline(16).

NDM-1 was first detected in a Klebsiella pneumoniae isolate from a Swedish patient of Indian origin in 2008(17). It was later detected in bacteria in India, Pakistan, France (18), Turkey (19), China (20) Japan (21) and Egypt (19) The most common bacteria that make this enzyme are Gram negative, such as Escherichia coli and Klebsiella pneumoniae, but the NDM-1 gene can spread from one bacteria strain to another horizontal gene transfer (16) The Indian Ministry of Health has disputed the August 2010 result of the Lancet study that the gene originated in India, calling this conclusion "unfair" and stating that Indian hospitals are perfectly safe for treatment.(22) Linking this new drug-resistant gene to India has been described by Indian politicians as "malicious propaganda" and multinational corporations have blamed it for what they describe as a selective malignancy. A BJP politician instead argued that the magazine article was fake and represented an attempt to scare medical tourists away from India.

The Indian Ministry of Health issued a statement "strongly refuting" the designation of the enzyme "New Delhi"( 23) Co-author of the 2010 Lancet study based at the University of Madras, stated that he disagreed with the part of the article advising people to avoid elective surgeries in India (22)

In contrast, an editorial in the March 2010 issue of the Journal of the Physicians Association of India blamed the emergence of this gene for widespread misuse of antibiotics in the
Indian health care system, stating that Indian doctors "have not yet taken the issue of antibiotic resistance seriously." And they pointed out the lack of control over the prescription of antibiotics by doctors and even pharmacists. (24) The Times of India states that there is general agreement among experts that India needs an improved policy to control the use of antibiotics and a central registry of antibiotic-resistant infections (24).

**Death cases**

The first reported death from bacteria expressing the NDM-1 enzyme was recorded in August 2010, when a Belgian man who was infected while undergoing treatment in a hospital in Pakistan died despite administering colistin. A doctor involved in his treatment said: "He was in a car accident during a trip to Pakistan. He was taken to hospital with a serious leg injury and then brought back to Belgium, but he was already injured." (25) In another case, an Indian national died in hospital due to a similar injury.

**1.4.7 The purpose of the study**

This study aims to shed light on the danger resulting from the (repeated, indiscriminate, or inappropriate) use of the antibiotic methicillin and the resulting infection of many serious infections that may lead to death in the end because of its resistance by the bacteria Staphylococcus aureus and became It is called methicillin-resistant Staphylococcus aureus.

**2 - previous studies**

**1.2- Arab countries**

A study was conducted in Palestine, where the prevalence of methicillin-resistant S. aureus among MRSA isolates was 8.7% among 28 isolates. The resistance rates to other antibiotics were as follows (82.1% resistant to erythromycin, 67.9% to clindamycin, 64.3% to gentamicin, 32.1% to ciprofloxacin, as no vancomycin-resistant isolates were identified in this study, where methicillin resistance was higher among 42.8% of the isolates of S. 

An exclusionary study was conducted at Khawla Hospital in Muscat, Sultanate of Oman of infection patterns in 168 patients who were admitted during 1995 and 1996 of the burn unit in the hospital, where the study showed that of 819 isolates positive for pathogenic bacterial culture, 326 (39.8%) isolates were positive for infection with methicillin-resistant bacteria MRSA. The incidence was slightly higher than that of Pseudomonas aeruginose, the
proportion of patients at one time or during burn stay increased from 1 to 112 days from 48% in 1995 to 52.7% in 1996, and no advanced tests were performed to determine the MRSA strain. However, the study of antibiotics showed that each of the positive isolates showed a very similar sensitivity to MRSA towards different antibiotics, as Vancomycin was the antibiotic that showed sensitivity to MRSA (26).

Another study was conducted in Tunisia in which 221 strains of nosocomial infection (Oxacillin resistant Staphylococcus aureus) were isolated from 1985 to 1989 in a medical intensive care unit. To beta-lactams, aminoglycosides and macrolides for epidemiological study, meningococcal infection was mainly septicemia (31%) and peritonitis (12%) these isolates were resistant to oxacillin at a high level, these phenomena associated with the spread of multidrug-resistant strains were responsible for the outbreak of infection Hospitals, where strains with the same resistance pattern were isolated among the medical staff and the environment (8).

- A typical study was conducted in Al Kabeer Hospital for Tertiary Care in Ismailia, Egypt, where samples of respiratory, urine, wound, burns and blood were collected from 350 patients admitted to different units, 10 strains (2.9%) of A. Abumannii were isolated, all isolates showed resistance for more than 3 classes of antibiotics. Along the isolates, 6 wasolates were carpenemase-producing, 2 were Amp C and none were β-lactamase-producing metallic isolates, despite the low prevalence of A (Naguib et al., 2014).

2.2 Countries of the world

A survey of 22 Malaysian hospitals revealed that staphylococcus was isolated from about 40% of positive blood cultures. A more detailed analysis of such cases in the hospital showed that approximately 70% of staphylococcus aureus and about 16% of coagulase negative staphylococci isolate S.aureus has been associated with disease of clinical significance. S.aureus has been observed mainly in neonatal sepsis, skin and soft tissue infections, pneumonia, arthritis, osteoarthritis, endocarditis and postoperative sepsis. Multidose bacteria were encountered in all hospitals studied, penicillin resistance rates ranged from 40% to approximately 100%, while methicillin resistance rates of up to 52% have been reported in several hospitals (26).

Research in New Zealand demonstrated that during a 17-month period from March 1985 to July 1986, 30 patients and four staff members were infected with S. aureus or colonized
with one strain of MRSA during disease onset at Wellington Hospital. Initially, disinfection occurred through the ICU but infected or colonized patients were distributed to 14 hospital wards and to five other hospitals in New Zealand, where septicemia contributed to the death of two patients (22).

A study conducted at the University of Kyoto, Japan, confirmed that noncompliance with washing hands causes at least 75% of hospital infections. The World Health Organization launched a global campaign bearing the slogan “We save our patients by washing our hands.” The study showed that only about 44% of doctors and medical staff are committed to washing hands periodically and regularly, while infection control bodies in hospitals and the World Health Organization recommend that at least 95% of cadres working in health institutions commit to washing hands on a permanent basis (27).

Another study was conducted at Henry Ford Hospital in Detroit, where 211 samples were included for patients with skin rash infection. The infection rates were in 6 patients (2.8%), 7 patients (3.5%) and 3 patients (1.4%) respectively, and it was observed Clinical success in 86 (68.3%) of the 126 patients included in the efficacy population. The monotherapy and combination subgroups had similar proportions of patients with success (69.7%, 64.9%, respectively), where the treatment period was 2 days (quadruple range of 1.5 to 4 days) for monotherapy, in 3 days (Quadruple range from 1.5 to 5 days) for combination therapy, where the results showed that cefazolin is effective for monotherapy or combination therapy (25,26).

A study was conducted at Shenzhen Hospital (China), where 1834 mothers and newborns were included in this study. The prevalence of isolated transmission among mothers was as follows: Staphylococcus aureus (nasal 25.8%, vaginal 7.3%, nasal and vaginal 3.3%) and MRSA (nose 5.7%, vagina 1.7%, nose and vagina 0.5%). The incidences of S.aureus and MRSA carriage between the two parents were 3.3% and 0.8%, respectively. Among the 21 pairs of mothers and newborns using the S.aureus carriage, 14 pairs matched with the same phenotypic and molecular characteristics (28).

3 Conclusions and recommendations

3.1 Conclusions:
We conclude from this study that the uncontrolled use of the antibiotic methicillin results in resistance to this antibiotic, causing a prolonged recovery period for people infected with
MRSA and an increased risk of death. For example, the risk of death for people infected with methicillin-resistant Staphylococcus aureus (MRSA) increases by 64% Compared to people with non-drug-resistant infections, drug resistance increases the cost of health care due to prolonged hospitalization and the increased need for intensive care.

3.2 Recommendations:
1. The patient should not insist on the treating doctor or pharmacist to dispense the antibiotic because antibiotics are only used in the case of bacterial infections only, and their frequent use has severe damage to the patient’s health, which could lead to the emergence of stubborn bacteria that are resistant to many antibiotics, such as bacteria Methicillin-resistant Staphylococcus aureus is the cause of many chronic infections.
2. The patient must complete the specified period of treatment, and this antibiotic should not be stopped when the health condition improves, because this leads to the re-emergence of bacteria and it may acquire immunity from the antibody so that it will not be affected by it in the future, which leads to the difficulty of treatment.
3. It is not permissible to use tetracycline, penicillin, or any other multi-active antibiotic against inflammation that can be eliminated by antibiotics with specific efficacy, such as penicillin or others. Multiactive antibiotics attack many types of bacteria (including bacteria that are beneficial to the body), unlike antibiotics with specified efficacy.
4. Antibiotic treatment should not be started without ensuring the presence of disease-causing bacteria, because antibiotic treatment in cases that do not require this leads to the formation of stubborn bacteria in the child’s throat that do not respond to antibiotics, and in the event that the child needs antibiotics in the future, he will not respond properly to them properly.
5. When it is confirmed that there is a bacterial infection, the appropriate antibiotic must be chosen. In this case, the best option to start with is penicillin, and choosing stronger antibiotics in the beginning may not be in the interest of the patient.
6. During the period of antibiotic use, it is useful to eat yogurt (or curdled milk) because it helps compensate for beneficial bacteria in the body that are killed by antibiotics such as ampicillin and others. It also helps restore the natural balance

Acknowledgment
High gratitude to the collaboration and assistance of everyone in the department of Clinical Pharmacy Al Karkh Health Department Baghdad, for their support.

**Disclaimer:** None

**Conflicts of interest:** None.

**Source of support:** This research did not receive a specific grant from any funding agency in the public, commercial or non-profit sectors.

**See also reference 29**

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