Innovative Systems Design and Engineering
ISSN 2222-1727 (Paper) ISSN 2222-2871 (Online)
Vol.6, No.2, 2015

A Review on Superbug: a Threat to Pharmaceutical Scientists

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Abstract:

The term "Superbug" is a nonspecific word that is used to describe any microorganism that is resistant to at least one or more commonly used antibiotics. Some authors restrict its use to microorganisms resistant to two or more antibiotics.

A super bug is a microbe, a virus or bacterium, that has resistance to the antibiotics and other drugs used to treat it. When the drugs become ineffective, viruses and bacteria are able to run their course. Then these microbes spread and diversify through the population and create havoc amidst people. Sometimes they create dangerous epidemics such as H1N1, etc.

This is often used for dangerous viruses as well as bacteria - bacteria that have resistance to antibiotics, or viruses that are difficult to control. These super bugs multiply rapidly creating dangerous outbreaks in the hospitals and cities, and are very difficult to kill with conventional antibiotics or drugs.

The bug has at this moment the potential to make all the present antibiotics redundant. These bacteria are resistant to the most powerful class of antibiotics called carbapenems, which are also called 'antibiotics of last resort', and turn into high resistance mode when exposed to them, which is really a cause to worry.

This bug can spread globally and can kill millions unless new antibiotics found. In addition worrying is that the gene was found on plasmids that can jump easily from one bacteria strain to another facilitating their transfer.

Key-Word:- Superbug, microorganism, H1N1, carbapenems.

1) Introduction

1.1) Bacteria:

Bacteria are single-celled, primitive cells with a simple nucleus without a membrane. Each bacterium contains about 1,000 genes.

1.2) Gram-negative bacteria:

These are the bacteria which stain red when Gram stained. Some of the Gram-negative Bacteria are:

1.2.1) Escherichia

1.2.2) Enterobacter

1.2.3) Klebsiella

1.2.4) Pseudomonas

1.3) Plasmids:

These are the segments or circles of DNA that are not part of the bacterial chromosome. The genetic material of a plasmid does not contain information necessary for the day to day functioning of the cell.

1.4) Antibiotics:

Antibiotics are biochemicals or drugs that are normally produced naturally by certain microbes/bacteria to kill or inhibit growth of other microbes/bacteria. Originally these were known as antibiosis which means against life. The first natural antibiotic, penicillin, was discovered by Alexander Fleming in 1928 which revolutionized the healthcare industry. At that time, penicillin was considered as the first choice drug for every disease.

2) Production of antibiotic resistance through bacteria:

2.1) Bacterial chromosomal mutation:

Bacteria divide and multiply through binary fission. During this fission process daughter/clone cells (exact copies of the parent cell) are reproduced in a large number. For example, Microbes such as Escherichia coli (E. coli) can increase their population from one to one million cells within 24 hours. Advantageous mutations produce more often during this reproduction. Occasionally when this cloning process/fission takes place, a mistake or mutation occurs and results in bacterium which is less susceptible to the action of antibiotics.

2.2) Horizontal gene transfer:

Bacteria can also develop antibiotic resistance through a genetic process. Bacteria have chromosomes which contain all the genetic information required to make and run the cell. This genetic information is passed to other bacteria through vertical gene transfer. They can also share genes with their neighbours through some bacteria. They have an extra bit of DNA called a plasmid. A plasmid contains 'bonus DNA' with information resulting in some type of survival advantage and sometimes antibiotic resistance. Bacteria can also share plasmids with each other thus increasing the chance of resistance to antibiotics.

2.3) Chance mutations :

The bacteria that developed a resistance to antibiotics were more likely to survive and reproduce, and therefore would eventually be present in larger numbers. The more we use antibiotics, the more is bacteria resistant to them.

3) **Superbug:**

The term "Superbug" is a nonspecific word that is used to describe any microorganism that is resistant to at least one or more commonly used antibiotics. Some authors restrict its use to microorganisms resistant to two or more antibiotics.A super bug is a microbe, a virus or bacterium, that has resistance to the antibiotics and other drugs used to treat it. When the drugs become ineffective, viruses and bacteria are able to run their course. Then these microbes spread and diversify through the population and create havoc amidst people. Sometimes they create dangerous epidemics such as H1N1, etc. The word "Super bug" is not defined by any research team or scientist. It is the creation of media. This is often used for dangerous viruses as well as bacteria - bacteria that have resistance to antibiotics, or viruses that are difficult to control.

4) Superbug metallo-beta -lactamase metallo-1:

A new health threat to humans has been discovered, a superbug called Metallo-beta- lactamase, in short M-1. It has been found that super bug M-1 is reacting negatively to antibiotics which normally cure such bugs. In short, antibiotics do not aid towards controlling the spread and total cure of this bug.

At present this superbug has been given the name of NDM-1, mainly because one of the first patients to have been diagnosed it with was treated at a hospital in New Delhi (ND) & is supposedly to have caught the infection there.

5) **History:**

Methicillin-resistant Staphylococcus aureus (MRSA) is a bacterium responsible for several difficult-to-treat infections in humans. It may also be called multidrug-resistant Staphylococcus aureus or oxacillin-resistant Staphylococcus aureus (ORSA).

MRSA is, by definition, any strain of Staphylococcus aureus bacteria that has developed resistance to beta-lactam antibiotics which include the penicillins (methicillin, dicloxacillin, nafcillin, oxacillin, etc.) and the cephalosporins .MRSA is especially troublesome in hospitals where patients with open wounds, invasive devices and weakened immune systems are at greater risk of infection than the general public.

6) MRSA Infection:

MRSA means methicillin-resistant Staphylococcus aureus bacteria.

The majority of MRSA infections are classified as CA-MRSA (community acquired) or HA-MRSA (hospital- or health-care-acquired).

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.

MRSA is sometimes sub-categorized as community-acquired MRSA (CA-MRSA) or healthcare-associated MRSA (HA-MRSA), although the distinction is complex.

7) Epidemiology of superbug:

In December 2009, after unsuccessful treatments in hospitals in New Delhi, a Swedish national was referred back to a Swedish hospital, where it was discovered that he had acquired an antibiotic-resistant bacterial infection during his stay in India. The Swede was infected with Klebsiella pneumonia (Gram-negative bacterium found in the normal flora of the mouth, skin, and intestines) infection. Since then the NDM-1 gene has been found in India, Pakistan, Bangladesh, Australia, Canada, the Netherlands, United States and UK.

In May 2010, a case of E. coli infected person expressing this bug was reported in UK. It is claimed that the bug has entered the UK and other countries via patients infected with it. These patients visit Asian countries for surgery (cosmetic, dental, complex heart surgeries, orthopedic procedures and even organ transplants) as it is cheaper than in the West. In August 2010, the first death due to NDM-1 bug was reported as a Belgian national who was treated in a hospital in Pakistan.

7.1) Escherichia coli bacterium:

Two types of Gram-negative bacteria are found which are host to NDM-1:

7.1.1. Escherichia coli (E. coli)

7.1.2. Klebsiella pneumoniae

8) Etiology of superbug infection:

Research studies have shown the primary cause of Metallo-1 is likely due to poor hygienic conditions.

Research studies claim that those who admit themselves to hospitals for undergoing cosmetic surgery are the most likely to catch the superbug Metallo-1.

On the pharmaceutical side, super bugs are also caused by the rampant abuse of antibiotics by doctors, who seem to prescribe them for everything under the sun including those things that are completely unaffected by antibiotics such as viral infections.

There are two major ways people become infected with MRSA. The first is physical contact with someone who is either infected or is a carrier (people who are not infected but are colonized with the bacteria on their body) of MRSA.

The second way is for people to physically contact MRSA on any objects such as door handles, floors, sinks, or towels that have been touched by a MRSA-infected person or carrier.

Normal skin tissue in people usually does not allow MRSA infection to develop; however, if there are cuts, abrasions, or other skin flaws such as psoriasis (a chronic inflammatory skin disease with dry patches, redness, and scaly skin).

9) Transmission of mrsa infection:

MRSA infections are transmitted from person to person by direct contact with the skin, clothing, or area (for example, sink, bench, bed, and utensil) that had recent physical contact with a MRSA-infected person.

The majority of CA-MRSA starts as skin infections; HA-MRSA can begin an infection of the skin, a wound (often a surgical site), or a location where medical devices are placed (catheters, IV lines, or other devices).

Cellulitis, abscess, or draining pus is often one of the first signs and symptoms of MRSA infections. Most MRSA infections are diagnosed by culture and antibiotic sensitivity testing of Staphylococcus aureus bacteria isolated from an infected site; a PCR test is also available.

Currently, MRSA bacteria are almost always found to be resistant to multiple antibiotics. All isolated MRSA strains need to have antibiotic susceptibility determined to choose the correct or appropriate antibiotic therapy.

MRSA is usually transmitted through direct contact with someone who has it. It can survive on surfaces for days, weeks and up to months depending on conditions such as humidity.

In theory, someone who carries MRSA could touch their nose (where MRSA usually lives), then touch a surface - anyone who comes along and touches that same surface and then touches their nose, mouth or an open wound could contract MRSA.

MRSA can cause pneumonia if given the opportunity - more commonly in hospitalized patients.

NDM-1 gene resides on plasmids and is resistant to almost all the antibiotics. The gene is found in Gram-negative bacteria for which the new antibiotics have not been developed.

10) **Diagnosis Of Superbug Infection:**

A skin sample, sample of pus from a wound, or blood, urine, or biopsy material (tissue sample) is sent to a microbiology lab and cultured for S. aureus. If S. aureus is isolated (grown on a Petri plate), the bacteria are then exposed to different antibiotics including methicillin. S. aureus that grows well when methicillin is in the culture are termed MRSA, and the patient is diagnosed as MRSA infected. The same procedure is done to determine if someone is an MRSA carrier (screening for a carrier), but sample skin or mucous membrane sites are only swabbed, not biopsied. These tests help distinguish MRSA infections from other skin changes that often appear initially similar to MRSA, such as spider bites and skin changes that occur with Lyme disease.

In 2008, the U.S. Food and Drug Administration (FDA) approved a rapid blood test (Staph SR Assay) that can detect the presence of MRSA genetic material in a blood sample in as little as two hours. The test is also able to determine whether the genetic material is from MRSA or from less dangerous forms of Staph bacteria. The test (PCR based) is not recommended for use in monitoring treatment of MRSA infections and should not be used as the only basis for the diagnosis of a MRSA infection.

11) Treatment of Superbug:

"First-line treatment for mild abscesses is incision and drainage."

"If antibiotic treatment is clinically indicated, it should be guided by the susceptibility profile of the organism."

When the tests are run to determine that the Staph bacteria isolated from a given patient are methicillin resistant, these tests also provide information about which antibiotics can successfully kill the bacteria (its susceptibility profile)."

Most MRSA can be treated by certain specific antibiotics (for example, vancomycin [Vancocin], linezolid [Zyvox], and others, often in combination with vancomycin). Most moderate to severe infections need to be treated by intravenous antibiotics, usually given in the hospital setting.

Some CA-MRSA strains are susceptible to trimethoprim-sulfamethoxazole (Bactrim) doxycycline (Vibramycin), and clindamycin (Cleocin); although reports suggest clindamycin resistance is increasing rapidly. In addition, some strains are now resistant to vancomycin.

A good medical practice is to determine, by microbiological techniques done in a lab, which antibiotic(s) can kill the MRSA and use it alone or, more often, in combination with additional antibiotics to treat the infected patient. Since resistance can change quickly, antibiotic treatments may need to change also. Many people think they are "cured" after a few antibiotic doses and stop taking the medicine. This is a bad decision because the MRSA may still be viable in or on the person and thus is capable of reinfecting the person.

MRSA may be exposed to low antibiotic doses when the medicine is stopped too soon; this low dose may allow MRSA enough time to become resistant to the medicine. Consequently, MRSA patients treated with appropriate antibiotics should take the entire course of the antibiotic as directed by their doctor.

12) Honey is 'cure' for killer bug :

A type of honey which destroys bacteria could be used to fight the deadly hospital superbug MRSA.

Research shows just a small amount of special brand Medihoney put on dressings can prevent MRSA spreading through open wounds.

Medihoney is fast proving its potential to provide a natural solution for the troubling, and increasing, problem of antibiotic-resistant infection.

Further, laboratory tests have proven that, as well as fighting the bugs that caused infection, there is no sign of the superbugs developing resistance to the honey-based treatment.

Treatment of HA-MRSA frequently involves the use of vancomycin, often in combination with other antibiotics given by IV; CA-MRSA can often be treated on an outpatient basis with specific oral or topical antibiotics.

13) Clinical Manifestations:

S. aureus most commonly colonizes the anterior nares (the nostrils), although the respiratory tract, opened wounds, intravenous catheters, and urinary tract are also potential sites for infection. Healthy individuals may carry MRSA asymptomatically for periods ranging from a few weeks to many years. Patients with compromised immune systems are at a significantly greater risk of symptomatic secondary infection.

MRSA can be detected by swabbing the nostrils of patients and isolating the bacteria found inside. MRSA may progress substantially within 24–48 hours of initial topical symptoms. After 72 hours, MRSA can take hold in human tissues and eventually become resistant to treatment. The initial presentation of MRSA is small red bumps that resemble pimples, spider bites, or boils that may be accompanied by fever and occasionally rashes. Within a few days the bumps become larger, more painful, and eventually open into deep, pus-filled boils. About 75 percent of community-associated (CA-) MRSA infections are localized to skin and soft tissue and usually can be treated effectively.

The most common manifestations of CA-MRSA are skin infections such as necrotizing fasciitis or pyomyositis (most commonly found in the tropics), necrotizing pneumonia, infective endocarditis (which affects the valves of the heart), or bone or joint infections. CA-MRSA often results in abscess formation that requires incision and drainage. Before the spread of MRSA into the community, abscesses were not considered contagious because it was assumed that infection required violation of skin integrity and the introduction of staphylococci from normal skin colonization. However, newly emerging CA-MRSA is transmissible (similar, but with very important differences) from Hospital-Associated MRSA. CA-MRSA is less likely than other forms of MRSA to cause cellulitis.

The symptoms of Delhi metallo-lactamase-1 (NDM-1) are the same as any other viral infection.

Most notably fever, weakness, body aches, stomach upset, and so on. There is nothing specific about this "super bug" and a regular flu or cold virus.

13.1) Most MRSA infections are skin infections that produce the following signs and symptoms:

13.1.1 Cellulitis (infection of the skin or the fat and tissues that lie immediately beneath the skin, usually starting as small red bumps in the skin).

13.1.2 Boils (pus-filled infections of hair follicles).

13.1.3 abscesses (collections of pus in or under the skin).

13.1.4 sty (an infection of an oil gland of the eyelid).

13.1.5 impetigo (a skin infection with pus-filled blisters).

13.1.6 rash (skin appears to be reddish or have red-colored areas).

14) Prevention of Superbug Infection:

Not making direct contact with skin, clothing, and any items that come in contact with either MRSA patients or MRSA carriers is the best way to avoid MRSA infection.In many instances, this situation is simply not practical because such infected individuals or carriers are not immediately identifiable.

What people can do is to treat and cover (for example, antiseptic cream and a Band-Aid) any skin breaks and use excellent hygiene practices (for example, hand washing with soap after personal contact or toilet use, washing clothes that potentially came in contact with MRSA patients or carriers, and using disposable items when treating MRSA patients). Also available at most stores are antiseptic solutions and wipes to both clean hands and surfaces that may contact MRSA. These measures help control the spread of MRSA.

Pregnant women need to consult with their doctors if they are infected or are carriers of MRSA. Although MRSA is not transmitted to infants by breastfeeding, there are a few reports that infants can be infected by their mothers who have MRSA, but this seems to be an infrequent situation.

In 2007, the first incidence of MRSA in a pet was recorded. Although relatively rare, MRSA can be transferred between pets and humans.

MRSA has been documented in dogs, cats, and horses but may be found in other animals in the future. Care and treatments are similar to those in humans, but a veterinarian should be consulted on all potential cases.

MRSA has been isolated from the environment (for example, beach sand and water), but there is no good documentation that people have become infected from these sources. Most authors suggest prevention methods should consist of a good soap and water

Prevention of MRSA is possible by excellent hygiene practices, avoiding skin contact with infected people or items they have touched and by wearing disposable gloves, gowns, and masks when treating or visiting hospitalized MRSA patients.

14.1) Tips to prevent spreading of mrsa infection:

14.1.1 Get medical care for your infection. Do not try to treat it yourself.

14.1.2 Cover your wounds. Keep wounds covered with clean, dry bandages until healed. Follow your healthcare provider's instructions on proper care of the wound. Pus from infected wounds can contain MRSA so keeping the infection covered will help prevent the spread to others. Bandages and tape can be thrown away with the regular trash.

14.1.3 Clean your hands often. You, your family, and others in close contact should wash their hands often with soap and water or use an alcohol-based hand rub, especially after changing the bandage or touching the infected wound.

14.1.4 Don’t demand a prescription of antibiotics from your doctor, unless he or she has diagnosed your affliction as a bacterial infection that requires it.

14.1.5 Take all of the antibiotics as prescribed, even if the symptoms subside.

15) Role of hospitals in prevention of superbug infection:

15. 1 Have better infection control.

15. 2 Strengthen laboratory facilities.

15. 3 Not use antibiotics unnecessarily.

15. 4 Teach medical students the right use of antibiotics.

15. 5 Stop treating trivial infections with new drugs.

15. 6 Expand admission screening to all admissions in wards where there is MRSA or a perceived risk e.g. neonatal unit or children’s hospital.

15. 7 Ensure improved compliance with admission swabbing.

15. 8 Ensure swabbing is accurately directed to the anterior nares.

15. 9 Ensure emergency delivery and processing of all admission screens.

16) Conclusion

In summary, NDM1 confers on its host bacteria almost all â lactic resistance and is accompanied byextensive antibiotic resistance. Two sites at Chennai and Haryana covering 3521 and 198 isolates respectively showed 1 and 13 percent prevalence of NDM1 carrying *Enterobacteriaceae*.

The Chennai isolates included different species whereas all the Haryana isolates were *K. pneumoniae*.

The sources of the isolates were community acquired urinary tract infections, pneumonia and blood stream infections. In the UK starting from 2008, isolates with NDM1 enzymes became the "dominant carbapenemase producing *Enterobacteriaceae*".

A number of isolates from nine locations in India, eight cities in Pakistan and Dhaka, Bangladesh have been confirmed to carry NDM1 (by PCR)6 indicating that the plasmid is perhaps quite widely distributed in the subcontinent. While this fact leads credence to the 'Indian' origin, it may not be necessarily so. multiple antibiotic resistant *Pseudomonas aeruginosa* speticaemia in a 34 yr old woman being prepared for bone marrow transplant, brings the issue to the fore9. Septicaemia caused by a bacterium carrying NDM-1 would be well nigh impossible to treat if it has the accompanying resistances. However, the mere presence of the organism in the environment would not translate to infection if control measures are in position, as they would be, in the major corporate hospitals that cater to medical tourism.

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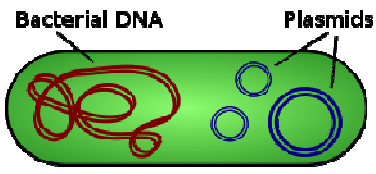

Figure:1 Bacteria

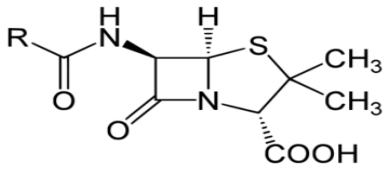

Figure: 2. Structure of Penicillin, the first natural antibiotic.

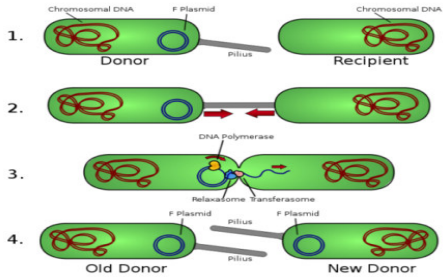

Figure:3 Bacteria mating or conjugation plasmid transfer.

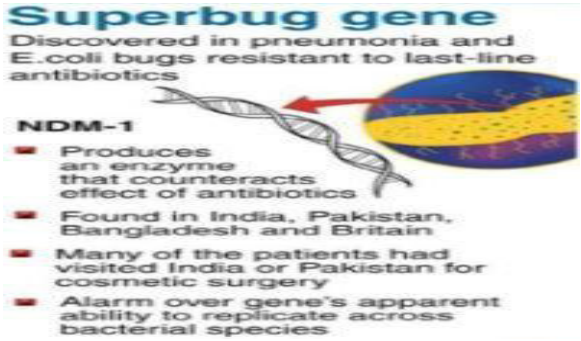

Figure:4 Superbug gene.

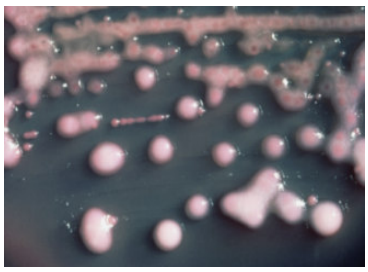

Figure:5 Klebsiella pneumoniae.

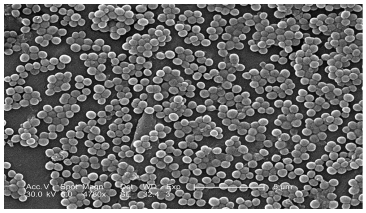

Figure: 6 Metallo-1

Figure: 7 Petri plate of Bacteria

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