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SUPERBUGS: A THREAT TO ANTIBIOTICS

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Abstract:

Antibiotic resistance has led to the development of so-called "superbugs" that no longer respond to the current treatment modalities. Multidrug-resistant (MDR) bacteria have become a severe threat to community wellbeing. Conventional antibiotics are getting progressively more ineffective as a consequence of resistance, making it imperative to realize improved antimicrobial options. This review emphasizes the microorganisms primarily reported of being resistance, has placed in their urgent category: Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, and Enterobacteriaceae accentuating their capacity to "escape" from routine antimicrobial regimens. The upcoming antimicrobial agents showing great potential and can serve as alternative therapeutic options were discussed.

Keywords: *Antibiotic resistance, superinfections, CDC surveillance, bacterial infections, antibiotics*

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INTRODUCTION:

Superbugs are strains of bacteria that are resistant to several types of antibiotics. Each year these drug-resistant bacteria infect more than 2 million people nationwide and kill at least 23,000, according to the U.S. Centers for Disease Control and Prevention (CDC). Antibiotic resistance has led to the development of so-called "superbugs" that no longer respond to the current treatment modalities [1]. The array of antibiotics available to treat these infections is dwindling with very few antibiotics in the pipeline. Drug-resistant forms of tuberculosis, gonorrhea, and staph infections are just a few of the dangers we now face. Antibiotics are effective against bacterial infections, such as Strep.throat and some types of pneumonia, diarrheal diseases, and ear infections. But these drugs do not work at all against viruses, such as those that cause colds or flu. And the overuse and misuse of antibiotics helps to create drug-resistant bacteria. Bacteria that are tough enough to survive the drug will have a chance to grow and quickly multiply. These drug-resistant strains may even spread to other people. Drugs may become less effective or not work at all against certain disease-causing bacteria.

A superbug is usually defined as a microorganism that is resistant to commonly used antibiotics, but not all superbugs are created equal. The number of different antibiotics to which it can be resistant determines the degree of the superbug. Some are resistant to one or two, but others can be resistant to multiple drugs. So, if a bug is resistant to every available antibiotic, it would be the superbug of all superbugs [2].

TYPES OF SUPERBUGS

The following types of bacteria have all been described antibiotic-resistant threats to patients in healthcare settings or have been referred as "superbugs":

- Carbapenem-resistant Enterobacteriaceae (CRE)
- Methicillin-resistant Staphylococcus aureus (MRSA)
- ESBL-producing Enterobacteriaceae (extended-spectrum β-lactamases)
- Vancomycin-resistant Enterococcus sp. (VRE)
- Multidrug-resistant Pseudomonas aeruginosa [3]
- Multidrug-resistant Acinetobacter [4]
- E.coli H30-Rx: The H30-Rx strain of antibiotic-resistant E. coli bacteria has become a main cause of bacterial infections in women and the elderly worldwide over the past decade.

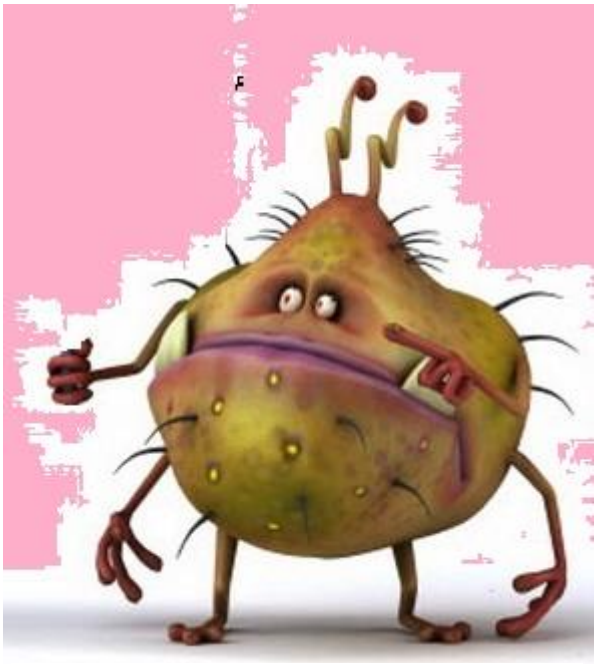

Fig. 1. An animated image of a Superbug

CRE(Carbapenem-resistant Enterobacteriaceae)

CRE, which stands for carbapenem-resistant enterobacteriaceae, are a family of germs that are difficult to treat because they have high levels of resistance to antibiotics. CRE bacteria develop when genetic material develops resistant mechanisms to antibiotics and is then transferred to other bacteria. CRE are an important emerging threat to public health [5].

Common enterobacteriaceae include *Klebsiella* species and *Escherichia coli (E.coli).* These germs are found in normal human intestines (gut). Sometimes these bacteria can spread outside the gut and cause serious infections, such as urinary tract infections, bloodstream infections, wound infections and pneumonia.

Carbapenems are a group of antibiotics that are usually reserved to treat serious infections, particularly when these infections are caused by germs that are highly resistant to antibiotics. Sometimes carbapenems are considered antibiotics of last resort for some infections. Some enterobacteriaceae can no longer be treated with carbapenems because they have developed resistance to these antibiotics (i.e. CRE), resistance makes the antibiotics ineffective in killing the resistant germ.[6] Resistance to Carbapenems can be due to a few different mechanisms. One of the more common ways that enterobacteriaceae become resistant to carbapenems is due to production of *Klebsiella*

pneumoniae carbapenemase (KPC). KPC is an enzyme that is produced by some CRE that was first identified in the United States around 2001. KPC breaks down carbapenems making them ineffective. Other enzymes, in addition to KPC, can breakdown carbapenems and leads to the development of CRE.

Symptoms of CRE infection [7,8]

- Urinary Tract Infection
- Cyanosis
- Sepsis
- Pneumonia
- Fever
- Septic Shock and low blood Pressure.

Mode of transmission of CRE infection

To get a CRE infection, a person must be exposed to CRE germs. CRE germs are usually spread person to person through contact with infected or colonized people, particularly contact with wounds or stool. CRE can cause infections when they enter the body, often through medical devices like ventilators, intravenous catheters, urinary catheters, or wounds caused by injury or surgery. It have been spread during ERCP (endoscopic retrograde cholangio pancreatography), a medical procedure that involves inserting a specialized endoscope commonly called a duodenoscope into the mouth and down to the intestine where the bile duct attaches.[9]

Preventive measures of CRE infection

- Washing hands with soap and water or an alcohol-based hand sanitizer before and after caring for a patient.
- Carefully cleaning and disinfecting rooms and medical equipment.
- Wearing gloves and a gown before entering the room of a CRE patient.[10]
- Keeping patients with CRE infections in a single room or sharing a room with someone else who has a CRE infection.
- Removing gloves and gown and washing hands before leaving the room of a CRE patient.
- Only prescribing antibiotics when necessary.
- Removing temporary medical devices as soon as possible.

Diagnosis of CRE infection

PCR (polymerase chain reaction) is a method to analyze a short sequence of DNA (or RNA) even in samples containing only minute quantities of DNA or RNA. PCR is used to reproduce (amplify) selected sections of DNA or RNA. Three major steps are involved in a PCR. These three steps are repeated for 30 or 40 cycles.[11] The cycles are done on an automated cycler, a device which rapidly heats and cools the test tubes containing the reaction mixture. Each step denaturation (alteration of structure), annealing (joining), and extension takes place at a different temperature.

To do PCR, the original DNA that one wishes to copy need not be pure or abundant. It can be pure but it also can be a minute part of a mixture of materials. So, PCR has found widespread and innumerable uses:

- To diagnose genetic diseases
- Do DNA fingerprinting, find bacteria and viruses, study human evolution, clone the DNA of an Egyptian mummy
- Establish paternity or biological relationships etc.
- Essential tool for biologists
- DNA forensics labs and many other laboratories that study genetic material.

MRSA (Methicillin-Resistant Staphylococcus Aureus) [12]

One common superbug increasingly seen outside hospitals is Methicillin-Resistant Staphylococcus Aureus (MRSA) that causes infections in different parts of the body. MRSA was first discovered in 1961. It's now resistant to Methicillin, Amoxicillin, Penicillin, Oxacillin, and many other common antibiotics. It's tougher to treat than most strains of Staphylococcus Aureus, because it's resistant to some commonly used antibiotics. MRSA can cause skin infections and, in more serious cases, pneumonia or bloodstream infections. The infection can spread through even a tiny cut or scrape that comes into contact with these bacteria. Many people recover from MRSA infections, but some cases can be life-threatening. The CDC estimates that more than 80,000 aggressive MRSA infections and 11,000 related deaths occur each year in the United States.

Mode of transmission of MRSA infection

MRSA infections are common among people who have weak immune systems and are in hospitals, nursing homes, and other health care centers. Infections can appear around surgical wounds or invasive devices, like catheters or implanted feeding tubes.

Signs and symptoms of MRSA infection

- Serious skin infections (small red bumps that resemble pimples, spider bites, or boils; they may be accompanied by fever and rashes)

- Infection in surgical wounds
- Infection in bloodstream, the lungs
- UTI

Diagnosis of MRSA infection

Diagnostic microbiology laboratories and reference laboratories are keys for identifying outbreaks of MRSA. Normally, the bacterium must be cultured from blood, urine, sputum, or other body-fluid samples. Still, because no quick and easy method exists to diagnose MRSA, techniques include quantitative PCR procedures, which are employed in clinical laboratories for quickly detecting and identifying MRSA strains. Another common laboratory test is a rapid latex agglutination test that detects the PBP2 a protein. PBP2a is a variant penicillin-binding protein that imparts the ability of S.aureus to be resistant to oxacillin.[13]

Preventive measures of MRSA infection

- Wash hands using soap and water or an alcohol-based sanitizer.
- Keep wounds clean and covered, avoid contact with other people's wounds
- To prevent the spread MRSA in the workplace, employers make available adequate facilities that encourage good hygiene.
- Surface and equipment sanitizing conforms to the environmental protection agency - registered disinfectants.
- Prevent the spread of MRSA in the home can be done by launder materials that have come into contact with infected person separately and with a dilute bleach solution.
- Reduce the bacterial load in your nose and on your skin.
- Clean those things in the house that people regularly touch like sinks, tubs, kitchen counters, cell phones, light switches, doorknobs, phones, toilets, and computer keyboards.
- Restricting antibiotic use like Glycopeptides, cephalosporins, and, in particular, quinolones are associated with an increased risk of colonisation of MRSA.
- Reducing use of antibiotic classes that promote MRSA colonisation, especially fluoroquinolones.

ESBL-producing Enterobacteriaceae (extended-spectrum β-lactamases) [14]

ESBLs are enzymes capable of hydrolyzing penicillins, broad-spectrum cephalosporins and monobactams, and are generally derived from TEM and SHV-type enzymes. ESBLs are often located on plasmids that are transferable from strain to strain and between bacterial species. 10–40% of strains of Escherichia coli and Klebsiella pneumoniae express ESBLs. In addition, there is an increasing association between ESBL production and fluoroquinolone resistance. Although in in vitro tests ESBLs are inhibited by β-lactamase inhibitors such as clavulanic acid, the activity of β-lactam/β-lactamase inhibitor combination agents is influenced by the bacterial inoculum, dose administration regimen and specific type of ESBL present. Currently, Carbapenems are regarded as the drugs of choice for treatment of infections caused by ESBL-producing organisms. Bacterial groups known to produce ESBLs includes Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, K. oxytoca, Proteus mirabilis, Salmonella enteric, Neisseria gonorrhoeae, Haemophilus influenza, Kluyvera species, Enterobacter aerogenes, Enterobacter cloacae.

Mode of transmission of ESBL infection

Anyone who has contact with a surface, object, animal, or another person that is infected with or has been exposed to ESBL-producing bacteria can spread the infection. Most ESBL infections, however, develop in healthcare settings and involve exposure to infected fecal matter.

Signs and symptoms of ESBL infection

- Diarrhea includes:
  - having three or more loose stools in one day
  - bloody stool
  - gas and bloating
  - fever
  - stomach cramps
  - loss of appetite
- Skin infections
- Pneumonia
- Urinary tract infections
- Sepsis
  - fever and chills
  - nausea and vomiting
  - feeling disorientated and confused
  - difficulty breathing

Preventive measures of ESBL infection [15]

- Hand washing, should always be used in healthcare setting.
- Avoiding close contact with people or animals with bacterial infections.
- Wearing gloves in healthcare settings or around infected individuals.
- Avoiding touching the face and mouth.
- Wearing long-sleeved clothing when around

infected individuals.
- Washing hands before and after exposure to infected individuals.
- Washing all clothing and bedding that may have been exposed to infected individuals in hot water.
- Disinfecting surfaces, especially in bathrooms and kitchens.
- Disinfecting fixtures, such as doorknobs and faucets.
- Taking antibiotics exactly as directed.
- Telling a doctor if antibiotics are not improving symptoms of an infection.
- Talking with a doctor and taking extra hygiene precautions if several courses of antibiotics are necessary within a short time span.
- If an ESBL-involved infection is confirmed, avoiding exposure to others or being in public settings, especially crowded areas.

Treatment of ESBL infection

The first line of treatment for people who have been confirmed as having the infection is usually a class of drugs called Carbapenems. The treatment process may involve some degree of trial and error. It may take several courses of treatment and different medications to resolve a person's infection completely.

Commonly used medications to treat ESBL-involved infections include:
- Carbapenems (imipenem, meropenem, and doripenem)
- Cephamycins (cefoxitin and cefotetan)
- Fosfomycin
- Nitrofurantoin
- Beta-lactamase inhibitors (clavulanic acid, tazobactam, or sulbactam)
- Non-beta-lactamases
- Colistin, if all other medications have failed

VRE (Vancomycin-Resistant Enterococci) [16]

Enterococci are a group of gram-positive, round-shaped bacteria that commonly live in the gut, although they can cause infection anywhere in the body. They are resistant to several antibiotics, but in the past, physicians could rely on the drug vancomycin to effectively treat enterococcal infections. Vancomycin resistance is acquired when a sensitive Enterococcus acquires a special piece of DNA called a plasmid that permits the bacteria to become resistant to Vancomycin. The new strains are called Vancomycin-Resistant Enterococci (VRE). One concern is that VRE strains appear able to transfer vancomycin resistance to unrelate bacteria such as MRSA (Methicillin-resistant Staphylococcus aureus) and these strains are renamed VRSA. In recent decades, however, some enterococci have become resistant to Vancomycin. The two main species that cause problems are Vancomycin-resistant Enterococcus faecium and vancomycin-resistant Enterococcus faecalis. E. faecium is the most common species of VRE. These bacteria are not the same genus as other common fecal bacteria such as E. coli.

Signs and symptoms of VRE infection
- Blood pressure may fall
- Sepsis.
- Shock
- Urinary infections
  - experience burning or pain with urination
  - back pain,
  - difficulty urinating
  - frequent urination
  - fever
- Meningitis
- Endocarditis
- Infected wounds are inflamed, with red and warm skin, soreness, swelling, and contain pus or have pus drainage.
- Pneumonia causes fever, difficulty breathing, and cough.

Preventive measures of VRE infection
- Standard precautions including hand washing and gloving should be followed.
- Healthy household members are not at risk of VRE infection.
- Dishes and utensils can be washed in a dishwasher or with warm soapy water and rinsed.
- Bed linen and clothing can be washed in a washing machine using a standard detergent for clothing.
- When providing care in a private home, hospital or nursing home, health care workers should use disposable gloves and wash their hands with soap after caring for a person with VRE.
- A disposable gown should also be used if the type of care involves washing or turning the patient, or changing diapers.
- Routine cleaning of bed rails, toilets and commodes with a bleach solution or hospital-grade disinfectant is also important.
- In the hospital setting, equipment such as

rectal thermometers and blood pressure cuffs should be assigned solely to the infected patient.

Mode of transmission of VRE infection

VRE is transmitted from person to person most commonly by healthcare workers whose hands have inadvertently become contaminated, either from feces, urine, or blood of a person carrying the organism. It can also be spread indirectly via hand contact with open wounds or by touching contaminated environmental surfaces, where the bacterium can survive for weeks. VRE is not transmitted through the air. Of more than a dozen forms of enterococci bacteria, two are the primary concern for human disease: E. faecium and E. faecalis. E. faecium is the most frequent species of VRE found in hospitals.

Treatment of VRE infection

VRE are resistant to a wide array of antibiotics. Linezolid, daptomycin, tigecycline, oritavancin, telavancin, quinupristin-dalfopristin and teicoplanin (not available in the U.S.) are antimicrobials that have been used with success against various VRE strains.

Multidrug-Resistant Pseudomonas aeruginosa Infection [17]

Pseudomonas aeruginosa (*P. aeruginosa*) is an aerobic, gram-negative bacilli that can be found ubiquitously in soil, plants, and hospital reservoirs of water, including showers, sinks, and toilet water. A recent report from the National Healthcare Safety Network, summarizing the health care-associated infections from 4515 US hospitals from 2011 to 2014, reported to be the sixth most common nosocomial pathogen overall.

Signs and symptoms of Multidrug-Resistant Pseudomonas aeruginosa Infection

- Bloodstream infections
  - Fever and chills
  - Body aches
  - Light-headedness
  - Rapid pulse and breathing
  - Nausea and vomiting
  - Diarrhea
  - Decreased urination
- Pneumonia
  - Fever and chills
  - Difficulty breathing
  - Cough, sometimes with yellow, green, or bloody mucus
- **Urinary tract infections**
  - Strong urge to urinate frequently
  - Painful urination
  - Unpleasant odor in urine
  - Cloudy or bloody urine
- Wound infections
  - Inflamed wound site
  - Fluid leakage from wound
- **Ear infections**
  - Ear pain
  - Hearing loss
  - Dizziness and disorientation

Preventive measures of Multidrug-Resistant Pseudomonas aeruginosa *I*nfection

- Preventing transmission through medical equipment like catheters is an important way to prevent Pseudomonas infections.
- Aseptic techniques and sterile environments are important to prevent the spread of *P. aeruginosa*.
- Proper hygiene regarding medical devices like catheters is important to prevent opportunistic infection in a patient as well.
- Prophylactic use of antibiotics is not recommended to prevent the evolution of antibiotic-resistant strains of bacteria.
- Severe burn victims should be put into strict isolation to prevent unnecessary contact with potential pathogens.
- Care should be taken to seek help when there might be potential infection, such as with corneal scratches due to contact lenses [18].

Mode of transmission of Multidrug-Resistant Pseudomonas aeruginosa *I*nfection

Pseudomonas aeruginosa is a common inhabitant of soil, water, vegetation, and animals. It is found on the skin of some healthy persons and has been isolated from the throat (5 percent) and stool (3 percent) of non-hospitalized patients. In some studies, gastrointestinal carriage rates increased in hospitalized patients to 20 percent within 72 hours of admission. *P. aeruginosa* finds numerous reservoirs in a hospital setting such as disinfectants, respiratory equipment, food, sinks, taps, toilets, showers and mops. Because of its ubiquity, it is constantly reintroduced into the hospital environment on food, visitors, and patients transferred from other facilities. Transmission occurs from patient to patient on the hands of healthcare workers, by patient contact with contaminated reservoirs, and by the ingestion of contaminated materials.

Diagnosis of Multidrug-Resistant Pseudomonas aeruginosa Infection

A complete blood count (CBC) is often performed to look for a rise in white blood cell count with a shift towards more immature leukocytes circulating in the blood. Blood cultures are often performed as well, both aerobic and anaerobic, to look for bacteremia. If endocarditis is suspected, echocardiography should be considered to verify diagnosis. UTIs are most often diagnosed through urinalysis and possibly a urine culture. Sputum and respiratory secretions are cultured in the diagnosis of pneumonia, but more accurate quantitative cultures are being performed more often to get a more accurate picture of the potential Pseudomonas infection. Blood gas analysis and chest radiography are also performed in cases of pneumonia. Wound and burn cultures in addition to cultures from other body fluids are important in accurate diagnosis and understanding of the scope of the infection. A bacterial count of greater than 100,000 organisms per gram of tissue is diagnostic of burn wound infection. If meningitis is suspected, a Gram stain and culture of cerebrospinal fluid should be performed, and in cases of suspected brain abscess, a CT scan or MRI is most often used. A triple-phase bone scan or MRI should be used to diagnose a suspected skeletal infection. Fluorescein staining and slit-lamp examination of the cornea is used to diagnose infections of the eye.

Treatment of Multidrug-Resistant Pseudomonas aeruginosa *I*nfection

Often a two-drug therapy is used. Sometimes, steroids are used in conjunction with these antibiotics. The specific drugs used often depend on the site of the infection and, therefore, their ability to reach the site of infection in the highest percentages possible. Sometimes, surgery is required, such as in the case of malignant otitis or retinal detachment due to eye infection. Hydration is important in addition to antibiotics in GI infections. Surgical debridement of necrotic tissue is necessary to treat soft tissue infections as well.

Multidrug-resistant Acinetobacter

Definitions of multidrug-resistant *Acinetobacter* species vary when referring to a wide array of genotypes and phenotypes. Different terms like 'multidrug resistant (MDR)', 'extensive drug resistant (XDR),' and 'pandrug resistant (PDR)' have been used with varied definitions to describe the extent of antimicrobial resistance among *Acinetobacter* spp. In the current review 'MDR *Acinetobacter* sp.' shall be defined as the isolate resistant to at least three classes of antimicrobial agents all penicillins and cephalosporins (including inhibitor combinations), fluroquinolones, and aminoglycosides. 'XDR *Acinetobacter* sp.' shall be the *Acinetobacter* sp. isolate that is resistant to the three classes of antimicrobials described above (MDR) and shall also be resistant to carbapenems. Finally, 'PDR *Acinetobacter* spp.' shall be the XDR *Acinetobacter* sp. that is resistant to polymyxins and tigecycline.

Signs and symptoms of Multidrug-Resistant Acinetobacter

Acinetobacter is an opportunistic bacterium that causes a variety of different diseases with different symptoms.Types of possible A. baumannii infections include:

- Pneumonia
- Bloodstream infections (bacteremia and sepsis)
- Meningitis (an infection or inflammation of the meninges, the membranes covering the brain and spinal cord)
- Wound and surgical site infections, including the "flesh-eating" bacterium necrotizing fasciitis
- Urinary tract infections (UTI)

Mode of transmission of Multidrug-resistant Acinetobacter

- Hands of the hospital staff
- Respiratory therapy equipment
- Food (including hospital food)
- Tap water
- Infusion pumps
- Mattresses, pillows, bed curtains and blankets in vicinity of infected patients
- Soap dispensers
- Fomites like bed rails, stainless steel trolleys, door handles, telephone handles, tabletops
- Hospital sink traps
- Hospital floor

CONCLUSION:

Superbug resistance is escalating within the clinical setting and community at large. Innovative antibiotic strategies are still lacking within the pharmaceutical industry to keep pace with the growing resistance, with a glaring absence of any novel class of antibacterial drug in the United States for decades. Most new antibiotics are chemical modifications of existing drugs and are quickly outsmarted by the bacteria in the environment. Clinicians are challenged by some strains of bacteria which are resistant to essentially all available antimicrobial agents. New antibiotics must be used with precision after the

infectious organism is identified by culture and sensitivity testing. Using the exact antibiotic which specifically targets the identified organism is a key strategy to limit bacterial resistance.

FUTURE ASPECTS

Traditional infection-prevention efforts must be buttressed by new technologies that can more effectively disinfect environmental surfaces, people, and food. It also needs technology that enables intensive health care without requiring the implantation of foreign materials such as plastic or metal (e.g., improved drug delivery by means of the gut, skin, or respiratory mucosa to replace intravenous therapy and regenerative-tissue technology that obviates the need for prosthetic implants). Improvements in population health and health care delivery systems can reduce admissions to hospitals and skilled nursing facilities, thereby reducing infections. Finally, new vaccines hold great promise for preventing antibiotic-resistant infections.

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