DEBATE 03

SUPERBUGS: A MYTH OR A REALITY

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INTRODUCTION

Superbugs are microorganisms that have acquired resistance against antibiotics. These can be bacteria, viruses, fungi and parasites

The problems associated with resistance are mostly caused by bacteria, according to WHO (world health organization) the bacteria that causes most problems are

·Acinetobacter baumannii

·Pseudomonas aeruginosa

·Methicillin resistant Staph. Aureus (MRSA)

·Mycobacterium tuberculosis (MDR and XDR)

·Streptococcus pneumonia

·Enterobacteriaceae

·Enterococcus

·E.coli H30-Rx

These and many other have become resistant to commonly used broad-spectrum antibiotics suchas Carbapenem, Methicillin, Doxycycline, Minocycline, Aminoglycosides (except for streptomycin), Ampicillin, Amoxicillin/clavulanic acid (Augmentin), Azithromycin, Carbapenems (e.g. imipenem)[1,2,3]

But The term "SUPERBUGS" is a media construct to scare the general public and not a reality. The problem associated with these microbes is termed as AMR (antimicrobial resistance)

•Resistance is a natural process developed by microbes over time to defend themselves from the antimicrobials produced by other microbes.

•Bacteria are the pioneer organisms on this planet earth and so they have got good survival skills.

•Therefore, to deal this issue, along with the discovery of new antibiotics, WHO has made it a priority to develop novel treatments and alternate solutions. which are:

Beta lactamase inhibitors

Inactivation of efflux mechanisms

Maximizing the concentration of antimicrobial agents. [4,5]

ACINETOBACTER BAUMANNII

Acinetobacter baummanni is an oppurtunistic pathogen. A.baumannii has a high incidence among immunocompromised individuals, particularly those who have experienced a prolonged (> 90 d) hospital stay.

It is now resistant to the antibiotic carbapenem that was being used to treat it. According to WHO The carbapenem resistant Acinetobacter (CRAB) is a top priority pathogen for the investment of new drugs.

Current treatment available for carbapenem resistant acinetobactor baumannii(CRAB) are:

Siderophore cephalosporins: Most commonly cefiderocol, that has shown activity against highly resistant CRAB isolates through various invivo and invitro studies performed.

•GSK-3342830, Fimsbactin, and a flouroquniolone derivative from tetracycline family

•Other siderophores: Including "Eravacycline" has also shown wider range of activity against Carbapenem resistant A.baumannii spp. [6]

These treatments are currently clinically being applied.

PSEUDOMONAS AERUGINOSA

According to WHO report Pseudomonas aeruginosa is the most opportunistic, gram negative and non-fermenting pathogen, which is able to adapt and survive in various clinical and artificial setting and is difficult to treat with conventional antibiotics. It became MDR pathogen and contributing to high mortality rate because of its presence of its innate resistance to many antibiotics like group of beta-lactams eg monobectams,cephlosporins and carbapenems. And its ability to acquire resistance against the multiple class of antibiotics including aminoglycosides and flouroquinolons. [7]

According to Medscape article "P.aeruginosa infections and medications" authorized by "Micheal staurt Bronze" and "Shahab Qureshi" in the year 2020 that P.aeruginosa infections are being treated with combination of carbapenem and antipseudomonal quinolones used in conjugation with aminoglycosides

Ceftazidime/avibactum is a combination of drug approved by FDA in Feb 2015

The treatment that is currently being used clinically for the treatment of pseudomonas infections is ceftalozane/tazobactum. [8]

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MRSA

Methicillin-resistant Staphylococcus aureus (MRSA) is a bacterium that causes infections in different parts of the body. It's tougher to treat than most strains of staphylococcus aureus because it is resistant to some commonly used antibiotics.

Staphylococcus aureus is natural microbiota of the body and found normally on skin and oral cavity.

A surveillance by WHO said that about 2 million people get infected with MRSA and about 23000 die every year because of it.

A few decades ago MRSA emerged resistant to most beta lactum antibiotics such as Methicillin, Amoxicillin, Penicillin and Oxacillin. [9]

Some of the resistive mechanisms of MRSA are

- *Transformation of resistive genes*
- *Altered PBP protiens*
- *Enzyme catalyze modification.*

Chemmedchem reported in 2021 that 80% of bacterimia are caused by MRSA biofilms.

In an article in Khyber medical university journal by Dr. Jawad et.al reported that MRSA is sensitive to imipenem but resistant to 1st and 3rd generation cephalosporins and amoxicillin. [10]

But recent studied and clinical trials have proved some drugs to be effective against MRSA infections.

These drugs include: [11]

- *Ceftaroline and ceftobifrole belonging to 5th generation of cephalosporins.*
- *Novel tetracycline derivatives inculding eravacycline and omadacycline.*
- *Fluoroquinolones such as delafloxacin, nemonoxacin.*

Groups of anti biotics that are highly effective against both gram+ and gram- bacteria including methicillin resistant Staphylococcus aureus(MRSA) and vancomycin resistance enterococcus (VRE) are [11]

- *Oxazolidinones (Tidizolid, Redazolid (second generation oxazolidinones)*
- *Lipo glycopeptides. (Telavancine, Dalbovancine, Oritavancine)*

These antibiotics are FDA approved and are being deployed in clinical settings to treat patients with MRSA infections.

Ceftaroline: 74% of 379 patients having serious MRSA infection and endocarditis etc were treated when this was used in combination with daptomycin, vincomycin and linezolid. [11]

This means that MRSA infections are treatable and MRSA is not a superbug because it is not resistant to all the available antibiotics.

MYCOBACTERIUM TUBERCULOSIS

Tuberculosis, caused by Mycobacterium tuberculosis is a leading cause of death with an estimated 1.7 million deaths in 2006. Global prospects of T.B control are challenged by the emergence of highly resistant strains specially those that are Multi-drug resistant (MDR) and extensively drug resistant (XDR).

Soon after anti-TB drugs became available in the 1940s came reports of drug resistance among patients undergoing treatment. With the advent of "short course chemotherapy" in the 1980s, the duration of treatment fell from 24 to six months, but even then full adherence to treatment regimens has been difficult to accomplish, due to the extensive length of therapy necessary to achieve cure. The prevalence of TB resistant to a single drug was continuously on the rise in several parts of the world, and eventually in the early 1990s, multiple converging factors led to an explosive emergence of MDR-TB, defined as resistance to the two most effective first-line anti-TB agents, isoniazid and rifampicin.

Since 2002, 45 countries have reported cases of XDR-TB, i.e., TB that is resistant not only to isoniazid and rifampicin but also to at least one fluoroquinolone and to any of the following injectable second-line drugs: kanamycin, amikacin, or capreomycin. Of the MDR isolates tested for second-line drugs, 0%–30 % were found to be XDR.

A large number of mutations have been identified that confer resistance, and these mutations account for most of the resistance found among clinical isolates. [12]

Treatment options of MDR and XDR T.B are still being explored.

There are prolonged treatments upto 18-24 months, currently available to treat MDR T.B.

The drugs are classified into 5 groups: [13]

- *First line oral agents (Isonazid, Rifampicin, Ethambutal, Pyrazinamide, Rifabutin, Rifopentine.)*
- *Injectable Anti T.B drugs, when resistance is high. these include Streptomycin,Kanamycin, amikacin or capreomycin.*
- *Group 3 include fluroquinolones for still resistant to group 2 drugs. These include levofloxacin, moxifloxacin and gatifloxacin.*
- *Group 4 includes oral bacteriostatic 2nd line anti T.B drugs; Ethionamide, Prothionamide, Cycloserine, Terizidone, Para-aminosalicylic acid.*
- *If the medication from group 1-4 is not working then group 5 anti T.B drugs are administered; Delamanid, Linezolid, Clofazimine, Meropenom, Clarithromycin, High dose isoniazid These are relatively new anti T.B drugs. [13]*

XDR-TB was first defined in 2006 and is estimated to occur in about 9.6% of MDR-TB patients While it occurs all over the world, it has been reported as a significant problem in a number of countries. Likelihood of cure has proven to be much lower than in other MDR-TB cases and deaths are higher, especially in HIV-infected patients. There is very limited data on the different clinical approaches to XDR-TB and a recent review of treatment outcomes of XDR-TB patients could not find any associations between any specific drug or regimen and success; however, the analysis did indicate that success in XDR-TB patients was highest if at least six drugs were used in the intensive phase and four in the continuation phase. [13]

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STREPTOCOCCUS PNEUMONIA

Streptococcus pneumoniaeis an important pathogen in many community-acquired respiratory infections in the United States and a leading cause of morbidity and mortality worldwide. Unfortunately,S. pneumonia is becoming increasingly resistant to a variety of antibiotics. Results of recent surveillance studies in the United States show that the prevalence of penicillin-nonsusceptible S. pneumoniae ranges from 25% to µ50%, and rates of macrolide resistance among pneumococci are reported to be as high as 31%. A high prevalence of resistance to other antimicrobial classes is found among penicillin-resistant strains. Newer quinolones (e.g., gatifloxacin, gemifloxacin, and moxifloxacin) that have better antipneumococcal activity in vitro are the most active agents and therefore are attractive options for treatment of adults with community-acquired respiratory infections. Efforts should be made to prevent pneumococcal infections in high-risk patients through vaccination.

Resistance of S. pneumonia to the macrolides and azalides (e.g., clarithromycin, erythromycin, and azithromycin) has been increasing since the late 1980s. In the United States, 0.2% of S. pneumonia were resistant to macrolides in 1988. This increased to 6.4% in 1992, 10.6% in 1995, 13.9% in 1996, and 20.4% in 1999. In recent US surveillance studies, rates of macrolide resistance among the pneumococci have been reported to be as high as 31%. There also have been recent reports of clinical failure of macrolide treatment for infections caused by S. pneumonia. [14]

A variety of novel antibiotics are being investigated that acts on different targets of bacteria i. e

- *Bacterial topoisomerase II inhibitors are used for quinolone resistant infections and its classes includes Gepotidicin, pyrrolamides, tetrahydropyrans, tricyclics, pyrimidines.*
- *Thymidylate kinase inhibitors*
- *Pyridopyrimidines and naphtyridines are used as NAD dependent DNA ligase inhibitors*
- *Teixobacten is used for inhibition of cell wall synthesis*
- *Pantothenamides are used for inhibition of coenzyme A pathways*
- *Robenidine acts as cell membrane potential disruptors. [15]*

Based on current levels of resistance to penicillin and cephalosporin, most patients with mild/moderate pneumococcal pneumonia may respond to oral amoxicillin, and most with severe pneumonia may be successfully treated with intravenous ceftriaxone, cefotaxime, or amoxicillin-clavulanic acid. It is of concern that patients infected with erythromycin-resistant pneumococci may not respond to therapy with a macrolide. In our opinion, except for well-selected patients, imipenem and vancomycin should not be widely used for the treatment of pneumococcal pneumonia. Some new drugs such as the new quinolones may play an important role in the management of pneumonia in the near future.

CONCLUSION

In conclusion; Resistant bacteria are a serious problem world wide and cause many deaths.

A study has been published recently conducted states 'that most of the pathogens show high resistance to commonly used antibiotics.

According to (Kang CI, Song JH. 2013) AMR is a serious issue worldwide, especially in less developed countries. South-Asia is deliberated to be the central region for antibiotic-resistant bacteria.

It is anticipated that 70% of antibiotic resistance is ascending in the Asia region, making it county-wide and worldwide hazard.

According to the CDC recent report 2.8 million people get an antibiotic-resistant infection and more than 35000 people die each year in US.

According to Natural Resources Defence Council (NRDC) SUPERBUGS are the 4rth largest cause of deaths in US.

But are they really "Superbugs" ?

As in the previous topics most common resistant bacterial infections have been discussed in detail and their treatment that are currently being applied in clinical settings are also mentioned.

So if they were superbugs, they should've been resistant to all the available drugs but evidence shows otherwise.

Resistant bacteria exist but they are not superbugs, resistance is a natural phenomenon that occurs in nature because these microbes needed to survive. So as naturally should be expected they developed processes to better survive against stresses such as antimicrobial agents.

By the misuse of antibiotics over the years, we only helped select the resistant bacteria as opposed to non resistant bacteria from nature.

Alexander Flemming, the person who discovered the first antibiotic, knew about the process of resistance in bacteria. He was aware of these better surviving bacteria and he warned us about them as well, in an interview with NewYork TIMES in 1945.

AMR is a serious problem but we do have solutions for it. All around the world researches are being carried out to tackle AMR. Along with discovery of novel drugs, reseachers are developing alternate methods as well such as CRISPR gene editing and nanoparticles.

CRISPR can selectively remove the specific genes responsible for resistance in bacteria and other microbes. These processes are still under development and will be available in the future.

A hadith in Sahih Bukhari, Narrated by Abu Huraira R.A says that the Prophet Muhammad (peace be upon him) said that:

"There is no disease that Allah(swt) has created, except that He also created its treatment."

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