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SERVICES FOR SCIENCE AND EDUCATION

Priorities and Threats of Antibiotic Resistance

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Abstract

The history of the antibiotics would now be too long to be reported in detail. However, since the middle of the last century, after a first attempt made by sulfonamides, before, during and after the Second World War, it was precisely their discoverers who laid the foundations for the modalities of a therapeutic treatment which undoubtedly radically changed the life expectancy of most of the known infectious diseases, especially as regards the world of bacteria. Therefore, we report their formulas together with the great scholars who discovered them.

Keywords: AMR, antibiotics, ASM, DUSP6, GO775

INTRODUCTION

The former American Society of Microbiology (ASM) President Susan Sharp, Ph.D., joined world leaders at the United Nations General Assembly in New York (2016-9-21) in a historic meeting that has concentrated efforts to fight antimicrobial resistance (AMR). This is the fourth time in the history of the United Nations that a health topic is discussed in the General Assembly. (HIV, non-communicable diseases, Ebola).

AMR has become one of the obvious threats to global health and a growing concern for healthcare specialists. Around the world, many common infections are becoming resistant to the antimicrobial drugs used to treat them, resulting in increased mortality. Furthermore, there are not enough new antibiotics in development to replace older ineffective ones (1).

The ASM has established AMR as a top priority and is advocating for a concerted multi-sectoral approach to combat this problem. ASM Letter Issued to US Ambassador to the United Nations with Key Recommendation to Support the Strongest Possible United Nations Action Plan Against Antimicrobial Resistance.

METHODS

Other Initiatives to Fight AMR

New diagnostic tests to avoid unnecessary administration of antibiotics

a. Prompt diagnosis to resolve the type of viral or bacterial infection avoiding useless antibiotic prescriptions.
b. Identification of the most suitable antibiotics to eradicate a bacterial infection, thus limiting the appearance of resistant strains.
c. Ciprofloxacin or levofloxacin are drugs most involved in urinary, respiratory and bone infections resistant to other antibiotics.

Importance of Vaccines

Vaccines reduce the number of cases of infection and consequently the need for antibiotics. For example, we report what was claimed by Lord O'Neill who leads the Review on AMR (May 2016) <An anti-pneumococcal conjugate vaccine, which is already used in various parts of the world, could largely prevent the 800,000 annual deaths of children under five caused from Streptococcus pneumoniae and could also prevent over 11 million days of antibiotic use by these children, reducing the likelihood of resistance developing>.

Methicillin-Resistant Staphylococci (Nosocomial Infections)

These bacteria have a protein with poor affinity for antibiotics (beta-lactamases, such as penicillin and cephalosporin).

Vancomycin-Resistance of Enterococci

AMR is achieved with the production of other proteins that replace the target (the peptidoglycan of the bacterial wall) of Vancomycin, for the exposure of a transposon that codes for a protein that is located outside the bacterial cell and binds to Vancomincin inactivating it.

Procalcitonin

It has been demonstrated that the use of algorithms for the diagnosis of bacterial infections and the administration of antibiotic therapy (Antibiotic Stewardship) guided by procalcitonin (PCT) can significantly reduce exposure to antibiotics. It is therefore possible to suppose an indirect beneficiary in terms of reduction of antibiotic resistance deriving from the use of PCT

Use of Antibiotics in Food-Producing Animals as Growth Promoters

>70% of the antibiotics used in the USA are used to feed animals (chickens, pigs, cattle) in the absence of disease.

The use of antibiotics in food-producing animals has been associated with the emergence of antibiotic-resistant strains (Escherichia coli bacteria, Salmonella, Campylobacter, Enterococcus).

Both American and European studies suggest that these resistant bacteria can cause infections in humans that do not respond to commonly prescribed antibiotics.
In the agricultural sector it is now necessary to place restrictions on the use of antibiotics that do not have a therapeutic purpose.

Limits and Bans of Antibiotics in Food Production

Since the Swann report (1969) the use of antibiotics in animals has been restricted in Great Britain as a cause of AMR (1970).

The European Union has banned the use of antibiotics as growth promoting agents since 2003. Two US bills have been proposed to eliminate non-therapeutic antibiotics from animal food production.

RESULTS

We don't have to wait until 2050 to know more on bacterial infections as a cause of mortality and be aware that the hospital plumbing system must be considered as a reserve for AMR.

There is research on the role of hospital piping in the evolution and gene exchange of drug resistance, especially of gram-negative bacteria, and how these microorganisms evolve rapidly through DNA sharing. It is understandable how an antibiotic resistance gene can be exchanged between bacterial species in our hospital system where not tap water or drinking water is involved, but the so-called disposable water, that of bilges and toilets. Unfortunately, gram-negative microorganisms are at home in ambient water, especially disposable water, which is a good place to exchange antibiotic resistance and evolve. Recent genome research and recognition of the aquatic environment have represented how patients pick up antibiotic-resistant germs from water splashes and toilet splashes. On the other hand, the preventive intervention for these water dispersions has already halved the acquisition of infections from antibiotic-resistant microorganisms (2,3).

DISCUSSION

The pathogens Enterococcus faecium, Staphylococus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas areuginosa and Enterobacter species pose the most severe threat of developing antibiotic-resistant infections without treatment, particularly the gram-negative members of this group (Escherichia coli, K pneumoniae, P. auriginosa and A. baumannii) which pose a particular threat due to their double membrane which prevents many antibiotics from gaining access to their target. For 50 years, no new antibiotics have been approved for these pathogens.

Arylomycins are a class of macrocyclic lipopeptides that inhibit bacterial signaling peptidase type 1 (SPase), an essential membrane-bound protease that uses an atypical serine-lysine pair to obtain signal sequences from pre-proteins before translocating across the cytoplasmic membrane (4). For 20 years, antibiotics that target these proteases have been studied to try to develop drugs with activity against gram-positive bacteria in which the active site of the enzyme is exposed on the surface of the cell. In gram negative bacteria the site of this enzyme is located in the periplasmic space between the membrane proper and the outer membrane thought that it was inaccessible to arylomycins because their molecular weight and tendency to lipophilicity precluded the penetration of the outer membrane. Over time, the systematic study of arylomycin analogues with increased affinity for the target and improved penetration of the outer membrane has begun. Thus, the molecule G0775 was finally discovered, a synthetic derivative of arylomycin, with powerful in vitro antibacterial activity against the gram-negative pathogens mentioned above (5).

CONCLUSION

The pathogenic microbes highly resistant to all known antibiotics are susceptible to the G0775 molecule with negligible de novo resistance. The potent in vitro activity of this molecule translates into strong in vivo efficacy in several infection models demonstrating the potential of these natural products to be targeted against the growing danger of antibiotic resistant gram-negative bacteria.

Finally, the broad spectrum and potent activity of G0775 together with the low spontaneous resistance capacity to antibiotics and the excellent preclinical efficacy suggest that arylomycin analogues could represent a new class of antibiotics against gram negatives, much needed. Such a new mechanism of this class of antibiotics has the potential to turn back the clock of current

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weapons against pathogenic bacteria and thus help to postpone the prospects of a return to the pre-antibiotic era to at least 2050 (6,7).

Acknowledgments

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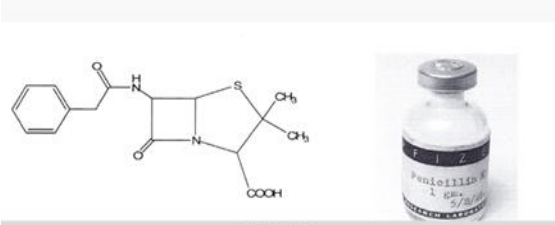
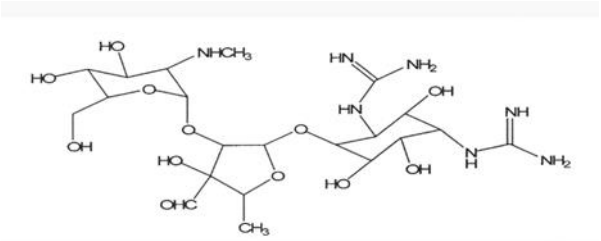
Figures

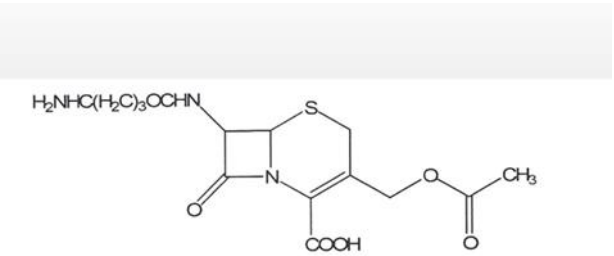


Penicilli

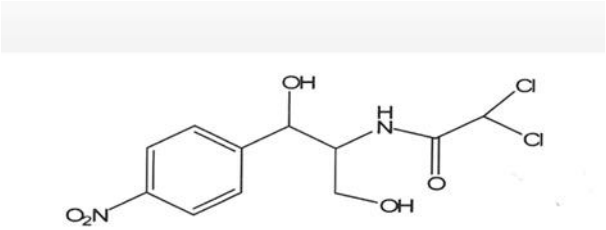
Sulfanilami



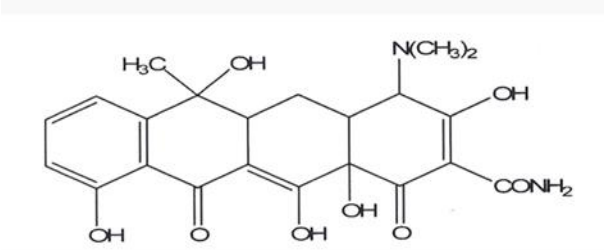
Streptomyc



Cephalospor



Chloramphenicol



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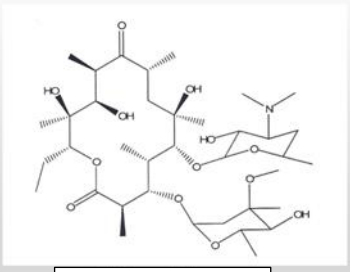
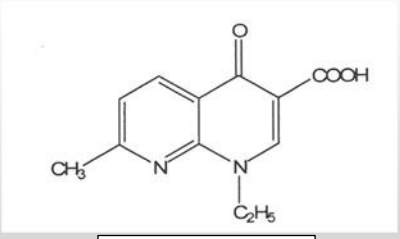


Erythromyc



Nalidixic