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Antibiotic Resistance - A Gathering Storm

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Throughout history, man has been in continual battle with microbes and until relatively recently could only depend on the innate and acquired immune systems as defense systems. Malaria, tuberculosis, polio, measles, syphilis and bubonic plaque are examples of infections that plagued mankind and resulted in significant morbidity and mortality. It is relatively recently that the development of vaccines and antibiotics has made an impact on viral and bacterial infections.

The development of penicillin in the early 1940's was the start of the antibiotic era. Almost immediately, bacteria developed mechanisms of resistance. The pharmaceutical industry responded by developing newer agents and for the most part we have stayed ahead of bacteria and their ability to develop resistance. The cost and time to developing new antibiotics and maneuvering through the labyrinth of the F.D.A. approval process is limiting the delivery of new agents. The practice of using antibiotics even when bacterial infection has not necessarily been demonstrated and pressure exerted on physicians by their patients for antibiotic treatment has influenced the emergence of resistance. All of have come to view antibiotics as "cure alls".

Antibiotic Mechanism of Action

Interference with cell wall synthesis	β-lactams - penicillin, cephalosporins, glycopeptides - vancomycin
Interference with protein synthesis	Macrolides, chloramphenicol, linezolid, aminoglycosides, tetracyclines, mupirocin
Interference with nucleic acid synthesis	Fluoroquinolones, rifampin
Interference of metabolism	sulfonamides, folic acid analogues

Mechanism of Resistance

Bacteria become resistant through mutation and selection or by acquiring from other bacteria the genetic information encoding resistance.

1) innate resistance
2) acquisition of genes encoding enzymes that destroy the antibiotic e.g. β-lactamases that destroy penicillins and cephalosporins
3) Efflux pumps e.g. fluoroquinolones in *S. aureus*
4) acquisition of genes for a metabolic pathway or mutations that limit access to the intracellular site.

Antibiotic Resistance in Gram-Positive Bacteria

Gram positive bacteria such as Staphylococcus aureus and Enterococcus species particularly *E. faecium* are important pathogens in hospital environments.

Vancomycin resistant enterococci (VRE) occurred first in intensive care units and then throughout hospitals in the 1990's and now nearly 30% of all isolates from patients infected in ICU's are resistant to vancomycin. This resistance is caused by 2 classes of related gene clusters which alter the cell wall target by changing D-alanine-D-alanine to D-alanine-D-lactate.

The development of VRE appears to have been influenced by the use of antibiotics which enhanced colonization and persistence of colonization already established.

S. aureus is a major pathogen for both cutaneous and systemic infections. The initial euphoria following development of penicillin was dampened by the evolution of β-lactamase production. These resistant strains first appeared in hospital settings but over time spread to the community and today virtually all strains of *S. aureus* are resistant to natural penicillins, aminopenicillins and antipseudomonal penicillins. Methicillin came along just in time, 1959 in Europe and 1961 in America. Almost immediately scattered resistant isolates were reported, followed by periodic outbreaks of MRSA in the 1970's and by the 1980's, MRSA became a significant problem in hospitals. By 2001, more than half of *S. aureus* infections in hospital settings were MRSA. Nosocomial MRSA has been shown to be clonal in nature and infection control lapses by healthcare workers have helped the spread of these strains. In general, these strains are multi-drug resistant and contain gene encoding for a low affinity penicillin-binding protein. For many years vancomycin was the only effective treatment of MRSA. In recent years, 4 new agents have been introduced just as vancomycin resistance is emerging. These resistant strains are associated with cell wall thickening limiting access to the cytoplasmic membranes where the functional targets of vancomycin are located. Horizontal transfer of genes from VRE have been shown to play a role particularly in high level resistance.

As is the case in other examples of resistance, MRSA has now spread to the community. CA-MRSA was first described in illegal drug users or those with serious underlying disease or previous hospitalization. It is now apparent that CA-MRSA occurs in those without risk factors and is becoming more prevalent particularly in children. Skin and soft tissue infections (particularly furuncles) are the most common manifestation of CA-MRSA. A high percentage of CA-MRSA carry genes for a leukocidin that causes destruction of leucocytes and also causes tissue destruction. CA-MRSA contains different genetic material conferring resistance than HA-MRSA. As a consequence, CA-MRSA does not show multiple drug resistance. CA-MRSA strains are more susceptible to other antibiotics than HA-MRSA and tend to be susceptible to sulfonamides and tetracycline.

P. acnes Resistance

Propionibacterium acnes is a gram positive anaerobic bacterium which proliferates in sebaceous follicles of acne patients. Antibiotic therapy has been a major factor in treating the multi-factored pathophysiology of acne and antibiotics work primarily by suppressing *P. acnes* viability although there is evidence for non-antimicrobial, anti-inflammatory effects as well.

P. acnes wild strains are very sensitive to a wide range of antibiotic classes with tetracyclines, macrolides such as erythromycin, the chemically related clindamycin, the agents most widely used. *P. acnes* sensitivity remained unchanged despite widespread use of systemic antibiotics until the early 1980's. Following the introduction of topical erythromycin and clindamycin, less sensitive strains *of P. acnes* were found and patients carrying these strains had poorer clinical outcomes. In the past 20 years, decreasing sensitivity particularly to erythromycin and clindamycin has been found worldwide and is associated with poor clinical response. Specific point mutations in genes encoding 23S (erythromycin and clindamycin) and 16S rRNA (tetracycline) have been identified worldwide. In addition, resistant strains have been isolated in which mutations could not be identified suggesting as yet uncharacterized resistance mechanism have evolved.

Antibiotic Resistance in Gram-Negative Bacteria

Gram-negative bacteria of the Enterobacteriaceae family are important causes of urinary tract infections, blood stream infections, pneumonia and intra-abdominal infections. Resistance related to production of extended spectrum β-lactamase (ESBLs) is a major cause of resistance although other mechanisms are emerging leading to multidrug resistance. The genes that encode ESBLs are frequently found on the same plasmids as genes that encode resistance to aminoglycosides, sulfonamides and quinolones.

To date, the vast majority of Enterbacteriaceae remain susceptible to carbapenems although resistance to these agents is beginning to occur due to carbapenemases.

Studies indicate that as many as 50% or more of antibiotic use is unnecessary or even inappropriate. The pharmaceutical pipeline of new antibiotics has been curtailed because of the cost and long regulatory process for approval. It may be 10 years or more before new antibiotics to treat emerging resistant bacteria are available. Antibiotic stewardship is essential. We all need to do our part whether we are prescribers or patients.

References

Excellent Review Papers.

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