The emergence of antibiotic resistance in Lebanon: Reality check and call for action

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The discovery of Penicillin G by Alexander Fleming during the twentieth century is considered one of the most important breakthroughs in modern medicine. The discovery of penicillin has paved the way for the development of additional antimicrobial agents and classes (Neomycin, Streptomycin, cephalosporin, Gramicidin). These antimicrobial agents helped cure patients with various infectious diseases, conditions that would have been otherwise fatal. Unfortunately, not too long after the discovery of penicillin, resistance among staphylococci emerged. Newer antibiotics with enhanced activity were developed to overcome bacterial resistance. A race between the development of newer antimicrobial agents and bacterial resistance ensued. The medical community felt too confident about winning this war on infectious diseases and antimicrobial resistance. Since the early 1990’s, the number of antimicrobials in development dwindled, coupled with an epidemic of antimicrobial misuse that has led to the emergence of multidrug resistant organisms such as vancomycin resistant staphylococci (VRE) and carbapenem resistant Enterobacteriaceae.

Among gram-positive cocci (GPC), methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE) species are responsible for most of the burden of healthcare-associated infections due to multidrug-resistant bacteria [1-2].

The rate of Staphylococcus aureus (SA) infections in hospitalized patients has significantly increased in the past 20 years. Furthermore, the emergence of community-acquired MRSA in the late 1990’s has resulted into serious skin and soft tissue infections and deep-seated infections (pneumonia, bacteremia, osteo-articular infections). In the United States of America (USA), more than 63% of all SA isolates recovered from critically ill patients are methicillin resistant [3]; nearly 60% of skin and soft tissue infections in patients presenting to emergency departments are due to MRSA [4]; and MRSA infections kill ~19,000 hospitalized patients annually [5].

The development of vancomycin resistance among Enterococcus species was first observed in 1985. The resistance to vancomycin was mediated by acquiring vanA and less commonly vanB or other genes (vanD, vanE, vanG, vanL, vanC). Ampicillin resistance seemed to be a prerequisite for the dissemination of vancomycin resistance. Vancomycin resistance is frequently seen in Enterococcus faecium but it is much less common in Enterococcus faecalis. It is estimated that around one-third of enterococcal nosocomial infections are due to VRE (76% of Enterococcus faecium isolates; 6.5% of Enterococcus faecalis isolates) [6]. In Europe, the prevalence of VRE in 2007 varied significantly among countries, ranging from <1% in the Netherlands to 45% in Greece [7]. Since the introduction of daptomycin and linezolid as first choice treatment for VRE, several centers have reported on the emergence of resistant strains to these agents.

Multiple surveillance programs reported on the emergence of Streptococcus pneumoniae resistance to multiple antibiotics worldwide. In Europe, 7% of Streptococcus pneumoniae isolates were resistant to penicillin and 21% were intermediately susceptible. Fluoroquinolone-resistance was documented in Italy with 5.6% resistance rate to levofloxacin.

In 2012, Araj et al. reported in the Lebanese Medical Journal on the rates of antimicrobial resistance observed at the American University of Beirut Medical Center (AUB-MC) during the past decade (2000-2010) [8]. After a significant increase in MRSA rates between 1971 to 1999 (3% to 38%), Araj et al. are now reporting a decrease in the rate of MRSA to around 20% in the last decade. Fortunately, no VISA or VRSA strains were reported during the study period. It is reassuring to see that the rates of VRE reported in this study are very low. However, it should be noted that all seven reported VRE isolates occurred at the end of the study period. The rates of penicillin resistance among Streptococcus pneumoniae are very high (60-72%) compared to other countries. In previous studies, penicillin resistance among Streptococcus pneumoniae correlated with penicillin usage at the country level.

Antibiotic resistance among gram-negative bacilli (GNB) is rapidly spreading around the world and continues to evolve. Enterobacteriaceae (Escherichia coli, Klebsiella species, Enterobacter species, Proteus species, Serratia species) and non-fermenters (Pseudomonas species, Acinetobacter species) may develop antimicrobial resistance via a variety of complex mechanisms such as the production of multiple ß-lactamase types, outer membrane impermeability, up-regulated efflux pumps, and target-site mutations. Resistance started to occur when chromosomal AmpC ß-lactamases were acquired by Enterobacter spe-
cies, Serratia species, and Citrobacter freundii. Plasmid-mediated extended-spectrum β-lactamases (ESBL) are typically seen in E. coli and Klebsiella species. The rates of ESBL-positive E. coli and Klebsiella species worldwide range from ≥ 80% in India, ≥ 60% in China, ≥ 30% in East and Southeast Asia, Latin America, and Southern Europe, and 5-10% in Australia, Northern Europe, and North America. Many ESBL-producing bacteria are also resistant to non-β-lactam antibiotics such as fluoroquinolones and aminoglycosides. Carbapenems are commonly used to treat ESBL- and AmpC-producing Enterobacteriaceae. Resistance to carbapenems may occur via porin loss in presence of AmpC or ESBL, or via the production of carbapenemases (KPC enzymes, metallo-carbapenemases – including the famous NDM-1 metallo-carbapenemase, or OXA-48) [9].

Pseudomonas aeruginosa strains develop resistance through mutations allowing restriction of drug entry, derepression of chromosomal AmpC, and up-regulation of efflux. In other instances, resistance results from acquiring ESBLs or metallo-β-lactamases. Acinetobacter baumannii relies mainly on up-regulation of chromosomal AmpC and carbapenemase genes. According to the European Centre for Disease Prevention and Control, P. aeruginosa resistance rates to aminoglycosides, carbapenems, cephalosporins, and fluoroquinolones are lowest in the Northwest (< 10%) and highest (25-50%) in the Southeast, mainly Greece. Resistance rates are high in Latin America and Southeast Asia, and intermediate in the USA [10]. The prevalence of carbapenem-resistant Acinetobacter baumannii increases significantly as we move from northern Europe (4% in Sweden) to southern Europe (50-85% in Turkey, Greece, Italy) [11].

The study by Araj et al. [8] shows increasing resistance of E. coli to cephalosporins, fluoroquinolones, and gentamicin. The rates of ESBL-positive E. coli increased from 4% in 2000 to 30% in 2011. Furthermore, carbapenem-resistant E. coli emerged in the most recent years; however, those strains remain limited in numbers. Similar to E. coli, the prevalence of ESBL-producing Klebsiella pneumoniae increased during the study period from 12% in 2000 to 28% in 2011. The in vitro susceptibility to β-lactams remained steady or even improved (amoxicillin/clavulanate, ceftazidime, piperacillin/tazobactam) during the study period. The data presented regarding A. baumannii resistance profile observed at the end of the study period is alarming. P. aeruginosa has maintained a favorable pattern of susceptibility during the study period (80-90%).

The results of this study raise some intriguing questions regarding the discrepancy between the observed low rates of resistance among GPC and the high rates of resistance among GNB. For example, were there any infection control measures or other reasons that kept the VRE and MRSA rates low? The same horizontal infection control practices should have similar efficacy in limiting the spread of both GPC and GNR [8]. Could the implementation of specific vertical infection control strategies have explained the difference? The authors are commended for conducting this study that sheds light on the issue of antimicrobial resistance in Lebanon. This undertaking may lead to additional population-based studies that may improve infection control and antimicrobial stewardship programs and practices.

REFERENCES