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Editorial Perspective

The Crisis of Resistant Gram-Negative Bacterial Infections: Is there any Hope for ESKAPE?

Morad Hassani*

Division of Infectious Diseases, Albert Einstein College of Medicine, USA

Corresponding author

Morad Hassani, Department of Medicine, Division of Infectious Diseases, Albert Einstein College of Medicine, 1301 Morris Park Avenue, Price Center 569, Bronx, NY 10461, USA, Tel: 301-852-3145; E.mail: morad.hassani@einstein.yu.edu

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EDITORIAL PERSPECTIVE

Bacterial infections involving antibiotic-resistant gram-negative bacilli (GNB) have emerged as major threats to human communities worldwide. Very few antibacterial agents with activity against resistant GNB have been successfully developed in recent decades [1]. The emergence of multi-drug resistant (MDR) GNB, as well as new mechanisms of resistance, among these pathogens in recent years is worsening the situation [2,3]. Currently, some GNB (e.g., the carbapenemase-producing *Klebsiella pneuminiae*, as well as many strains of *Pseudomonas* and *Acinetobacter*) show extreme or complete resistance to all first line antibiotics as well as 2nd line drugs (e.g., Polymyxin) that are available for the treatment of gram-negative bacterial infections [4]. These GNB are referred to as extreme- or extensively drug resistant (XDR) pathogens [4].

The pneumonic, ESKAPE, was originally described by Rice [5] to designate the most challenging nosocomial pathogens with significant antibacterial resistance. It included the gram-positive pathogens, *Enterococcus faecium* and *Staphylococcus aureus*, as well as the gram-negative pathogens, *Klebsiella pneumonia, Acinetobacter baumanii, Pseudomonas aeruginosa,* and *Enterobacter* species [5].

Enterococcus faecium is currently one of the most common causes of nosocomial bloodstream infections (BSI) [6]. More than 50% of *E. faecium* isolates are resistant to the glycopeptide, vancomycin, and serious infections involving vancomycin-resistant enterococci (VRE), are difficult to treat with few therapeutic options [1,6].

Staphylococcus aureus is a highly invasive gram-positive pathogen and methicillin-resistant *S. aureus* (MRSA) is not only arguably the most challenging nosocomial pathogen, but also emerging as a frequent cause of community-acquired infections and outbreaks in recent years [7].

Klebsiella pneumonia is an invasive GNB that has been a pioneer in developing novel resistance mechanisms in the antibiotic era. This bacterial pathogen has essentially evolved in parallel to beta-lactams, the most widely used class of antibiotics against GNB, which were recently elegantly reviewed by Rice [8]. Resistance to beta-lactams among GNB is primarily mediated by beta-lactamases, which enzymatically hydrolyze the beta-lactam ring and *K. pneumonia* was the first documented GNB to develop beta-lactamases, in the early 1960's few years after the initial use of ampicillin [8]. Later, other resistant GNB emerged, which expressed beta-lactamases exemplified by TEM-1 of *Escherichia coli* and SHV-1 of *K. pneumonia* [8]. Subsequently, newer classes of beta-lactams were developed (i.e., cephalosporins, aztreonam, and carbapenems) that were resistant to hydrolysis by TEM-1 and SHV-1 beta-lactamases. Then in the 1980's the first GNB with extended spectrum beta-lactamases (ESBL) were once again initially described among *K. pneumonia* isolates carrying point mutations in TEM-1 and SHV-1 type beta-lactamases that resulted in resistance to cephalosporins, although they were still sensitive to carbapenems [8]. This brought about the decreased use of cephalosporins and increased use of beta-lactam-beta-lactamase inhibitor combinations and carbapenems [8], which in turn resulted in the emergence of CTX-M family of beta-lactamases in different species of GNB in the early 1990's, including *K. pneumonia*, as well as the emergence of carbapenemases [8]. The former are natural cephalosporinases and are widespread among many pathogenic *E. coli* [8,9]. The latter, carbapenemases, have so far emerged as three main classes. The KPC class, which were again initially described in *K. pneumonia*, but are now widely spread among different GNB [10], the metalloenzymes that require a metal cofactor (usually zinc) and are exemplified by VIM-1, NDM-1 that are involved in many recent worldwide outbreaks [10], and the OXA-type enzymes that are primarily responsible for carbapenemase resistance in *Acinetobacter* species [11].

Acinetobacter baumanii is a frequent cause of highly resistant nosocomial infections with increasing mortality [12]. It can survive routine disinfection efforts as it appears to be viable for relatively long periods on inanimate objects and surfaces including catheters, ventilator machines, respiratory tubes and devices [12]. *Acinetobacter* infections with pan-resistance are emerging in many regions worldwide and are frequently a challenging problem in long-term care facilities, burn units, and ICUs [12,13].

Pseudomonas aeruginosa is an inherently invasive and virulent GNB historically associated with pneumonias in cystic fibrosis patients and MDR nosocomial infections such as ventilator-associated pneumonia (VAP) in patients who remain

in ICUs for several days and BSI in immunocompromized hosts, including patients with hematologic malignancies. This pathogen exhibits an alarming high frequency of resistance in recent years to both fluoroquinolones and cabapenems and more recently to aminoglycosides and polymixins [14,15]. There are currently no antibiotics in the pharmaceutical pipeline with activity against MDR or metallo-carbapenemase producing *Pseudomonas* infections [16].

Enterobacter species are consistently common causes of MDR infections in hospitalized patients with high morbidity and mortality [17]. Like other Enterobacteriaceae, they frequently express ESBLs, cephalosporinases, and carbapenemases [18,19].

In addition to the involvement of the above ESKAPE pathogens in MDR nosocomial infections, there has been a dramatic increase in the incidence of MDR community-acquired infections (e.g., those due to MRSA) in recent years [7], and highly resistant bacterial infections involving GNB are no longer limited to hospital-acquired infections. In fact, the term ESKAPE, can now be easily used to represent an entirely gram-negative group of pathogens, as community acquired non-enteric *E. coli* and non-typhoidal *Salmonella* have recently emerged as major MDR pathogens [20,21]. The former is a frequent cause of urinary tract infections (UTI) worldwide and the spread of sequence type ST131 *E. coli* carrying both CTX-M and fluoroquinolone resistance in recent years has seriously complicated the treatment of community-acquired UTI, as there are no oral agents available for many infections caused by this pathogen [8,20]. The latter is now the most common cause of MDR bacterial BSI in both adults and children in sub-Saharan Africa with a high mortality rate [21]. Hence, the first E and S in ESKAPE can be underlined or bold-faced (**ES**KAPE) to add the emphasis for these two challenging GNB.

Several factors have contributed to the current state of the crisis which include: Inappropriate use of antibiotics in clinical practice and animal industry (e.g., antibiotics used to promote livestock growth despite no evidence in the practice [22]), poor infection control measures, poor sanitation and infrastructure, decreased access to clinical microbiology laboratory and data, lack of research in clinical infectious diseases especially controlled randomized trials, long courses of antibiotics, evolution of bugs and microbiomes, increased immunocompromised states (i.e., due to older population, HIV epidemic, new chemotherapeutics including immune-modulating agents), globalization, and increased travel among others.

There is an urgent need for new drugs against MDR and XDR GNB and the recent abandonment of antibacterial research and development by large pharmaceutical companies has further compromised the discovery and marketing of new agents especially in the U.S. In fact, in recent years antibacterial drug development is primarily performed by small biotech or pharmaceutical companies and some larger companies in Japan [23].

Since early 2000 IDSA has proposed legislative, regulatory and funding solutions to address this public health crisis [1,23,24]. In 2010, IDSA launched the "10 x '20 initiative" calling for development and regulatory approval of 10 new antibiotic agents by 2020 [25]. Since then and as of early 2013 only two new agents (i.e., Telavancin and Ceftaroline fosamil) have been approved, seven drugs are in clinical development for the treatment of infections caused by MDR GNB, and one drug had its development stopped due to adverse effects observed in its clinical trials [16].

There are some recent glimmers of hope. Regulatory agencies, including the FDA and the European Medicines Agency, have acknowledged the existence of the crisis and have initiated public-private collaborations and investments on relevant research [16]. In addition, the U.S. Congress has enacted new legislations and started new initiatives and incentives for antimicrobial development [16]. Furthermore, IDSA has consistently emphasized the need for strengthening antibiotic stewardships to maintain the efficacy of the currently available antibacterial agents, suggested new incentives, such as Research and Development (R & D) tax credits and new reimbursement models [26,27], and proposed novel pathways to approve antibiotics based on smaller clinical trials for the most serious bacterial infections [27]. Of note, the recent radical proposal by IDSA for the establishment of a Limited Population Antibacterial Drug (LPAD) approval addresses some of the main obstacles in antibacterial drug development for resistant bacteria, by allowing smaller, rapid, and less expensive clinical trials on specific pathogens and facilitating the approval of much needed antimicrobials. It is critical, however, that approved drugs through such a mechanism maintain their narrow indications (e.g., treatment of MDR and XDR pathogens) to prevent their overuse and loss of their efficacy, and are subsequently studied in larger trials to confirm and expand their safety.

The bottom line is that all of the involved stakeholders in this public health crisis need to do their part. NIH and NIAID need to increase their antibacterial research budget to adequately support innovative scientists and clinical researchers working on novel antimicrobial drug development as well as new approaches to address the prevention and treatment of infections involving highly resistant bacterial pathogens. At the same time the U.S. defense budget needs to decrease to adequately facilitate the latter budget adjustment. The pharmaceutical industry needs to show more responsibility and commitment to high priority drug development such as antibacterial agents for MDR and XDR infections, to stop developing more "me too" drugs, and to cut wasteful marketing costs, such as unnecessary advertising. Basic scientists and researchers need to think outside the box and utilize the recent knowledge (e.g., host immunology, human microbiome biology, and biofilm physiology), as well as the available databases (e.g., human and microbial pathogen genome sequences) and technologies (e.g., rapid genomic DNA sequencing, metabolomics, and nanotechnology) in their search for new antimicrobial agents and drug targets to combat highly resistant infections. Two recent examples of the successful use of the latter type of approach for antimicrobial research are the in vitro screen for anti-tubercular compounds against *Mycobacterium tuberculosis* biofilms, which identified a novel drug target and a new class of agents that are active against persistent and drug-resistant TB [28] and the recent demonstration of the in vivo activity of LpxC, a lipopolysaccharide synthesis inhibitor, against resistant *A. baumanii* infections, which apparently works not by

killing the pathogen but rather preventing disease in the host via modulating inflammation and enhancing phagocytosis [29]. Clinical and translational researchers need to work harder on developing efficacious and safe preventive and therapeutic vaccines for bacterial pathogens and to propose and set up controlled studies to answer the most relevant clinical questions regarding high priority bacterial infections (e.g., documentation of effective infection control measures, determination of optimal duration of therapy, and synergy of combined antibacterial regimens). Clinicians need to abide by established education guidelines (e.g., those provided and regularly updated by IDSA, DOH, CDC, as well as WHO), and stronger and more innovative infection control measures and antibiotic stewardship efforts, as proposed most recently by IDSA [30], to protect the public and to maintain the efficacy of our available weapons against resistant bacterial pathogens. Finally, Congress and the FDA need to allow much needed and effective legislations (e.g., LPAD and stopping the use of antibiotics in U.S. livestock to promote growth) and more appropriate incentives and disincentives to facilitate R & D of new antibacterial agents and therapeutic regimens for serious infections caused by drug-resistant GNB and other challenging pathogens.

We launch this new clinical journal with the hope that some of the necessary changes to deal with this public health crisis are realized in the near future.

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