

Superbugs and antibiotics in the newborn

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From the womb to the adult

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Abstract

Antibiotic resistance has become an urgent and global issue, with 700,000 deaths attributable to multidrug-resistance occurring each year worldwide. The overuse of antibiotics, both in animal industry and in clinical settings, and the generated selective pressure, are the main factors implicated in the emergence of resistant strains. The Centers for Disease Control and Prevention (CDC) have pointed out that more than half of hospital patients receive an antibiotic during their stay, and nearly a third receive a broad-spectrum antibiotic. In neonatal units, previous antibiotic exposure to third-generation cephalosporin and carbapenem were identified as independent risk factors for infection caused by multi-drug resistant strains. While resistant 'superbugs' emerge, the arsenal to fight these microorganisms is progressively shrinking, as the number of newly discovered antibiotics approved by the Food and Drug administration each year is dropping. In face of global spread of antibiotic resistance and of the limited development of new drugs, policies and rules are under study by agencies (CDC, World Health Organization) and governments, in order to: i) facilitate and foster the discovery of new antibiotic compounds; ii) develop new, alternative therapies able to potentiate or modulate the host immune response or to abrogate the resistance and virulence factors in the microorganisms; and iii) prevent the emergence of resistance through antibiotic stewardship programs, educational programs,

and reduction of antibiotic use in livestock; the field of neonatal medicine will need its own, newborn-tailored, antibiotic stewardship programs to be implemented in the NICUs.

Keywords

Neonatal intensive care, infection, antibiotic, multi-drug resistant, carbapenemase, antibiotic stewardship.

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Introduction

Antibiotic resistance has become an urgent and global issue. Approximately two million people are infected each year by antibiotic-resistant bacteria in the US. Annual deaths attributable to antimicrobial resistance are estimated to be 23,000 in the US, 48,000 in the US and Europe, and 700,000 worldwide. Future projections estimate that, by 2050, 10 million people will die worldwide each year due to increasing antimicrobial resistance [1-3].

Data from the Centers for Disease Control and Prevention (CDC) show rapidly increasing rates of infection due to methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), and fluoroquinolone-resistant *P. aeruginosa*. Furthermore, multi- and even panantibiotic-resistant infections occur. Several highly resistant Gram-negative pathogens, namely *Acinetobacter spp.*, multidrug-resistant (MDR) *P. aeruginosa*, and MDR (extended spectrum β -lactamase – ESBL – and carbapenemase-producing) *Klebsiella spp.* and *E. coli* (carbapenem-resistant *Enterobacteriaceae*) have emerged as significant pathogens worldwide [4]. Altogether, antibiotic-resistant bacteria, including VRE, MRSA, ESBL- and carbapenemase-producing *K. pneumoniae*, *Acinetobacter baumannii*, *P. aeruginosa*, and *Enterobacter* species, have been referred to as “ESKAPE” pathogens [4, 5].

These MDR ‘superbugs’ are often isolated in nosocomial settings, from where they can easily spread in other hospitals of the same geographical region and worldwide. *Klebsiella* resistant to carbapenems, the powerful broad-spectrum antibiotics developed in the 1980s, exemplifies how pathogenic bacteria can spread globally.

A strain of *K. pneumoniae* carrying a gene called KPC, conferring resistance to carbapenems, was first discovered in 1996 from a North Carolina hospital. In the subsequent years, KPC-positive bacteria were found spreading rapidly through hospitals across New York City, then to several other countries including Israel, Italy, Colombia, the United Kingdom and Sweden [6]. In 2008, a new carbapenem resistance gene, New Delhi Metallo- β -Lactamase (NDM), originating in India, was found in Sweden [6] and NDM-producing *Klebsiella spp.* has been implicated in neonatal cases of infections caused by carbapenemase-resistant strains [7].

Datta et al. report the trend of carbapenem susceptibility in *Enterobacteriaceae* that caused septicemia in their neonatal intensive care unit (NICU) over a five-year period (2007-2011). One hundred and five *Enterobacteriaceae* including *E. coli* (n = 27), *K. pneumoniae* (n = 68) and *Enterobacter spp.* (n = 10) were isolated from blood of septicemic neonates. In their study, NDM-1 was the only carbapenemase identified, detected in 14% of the isolates. NDM-1 producing isolates were resistant to other broad-spectrum antibiotics and possessed other resistance molecules including ESBLs, AmpCs, 16S-rRNA methylases, AAC(69)-Ib-cr, bleomycin resistant gene and class 1 integron [7].

In another study, Cantey et al. report an outbreak caused by ESBL-producing *K. pneumoniae* in a III level NICU. The cohort consisted of 61 infants present in the NICU during the outbreak, from April 26, 2011, to May 16, 2011. The index case was an 18-day-old infant born at 25 weeks gestation who developed septicemia from ESBL-producing *K. pneumoniae*. A multidisciplinary team formulated a plan that allowed to control the outbreak and to eradicate the infecting strain. The study well exemplifies how quickly these microorganisms may spread in NICUs: despite the efforts, that limited the transmission of the microorganism and allowed quick eradication, eleven infants were either infected or colonized, and two infants, in the same room of the index case, developed sepsis from ESBL-producing *Klebsiella spp.* within 48 hours and both expired [8].

The overuse of antibiotics, both in animal industry and in clinical settings, and the generated selective pressure, are the main factors implicated in the emergence of resistant strains [9-11].

The CDC have pointed out that more than half of hospital patients receive an antibiotic during their stay, and nearly a third receive a broad-spectrum antibiotic [1].

Specifically for the NICUs, Tsai et al. reported 1,106 bacteremia episodes in 8 years in their NICU; 35.5% were caused by Gram-negative organisms, and 18.6% by MDR strains. The most frequent mechanism of resistance was ESBL production (67.1%), mainly by *K. pneumoniae* (59.6%). Previous antibiotic exposure to third-generation cephalosporin ($p < 0.001$) and carbapenem ($p = 0.017$) were identified as independent risk factors [12].

Antibiotic prescribing practices vary widely in the European Union and European Economic Area. According to the European Centre for Disease Prevention and Control, Italy's consumption of antibiotics is high, ranked fifth after Greece, France, Luxemburg and Belgium. Between 2008 and 2010, antibiotic consumption has been 26-30 daily doses per 1,000 inhabitants in Italy, while the Netherlands, the country with the lowest consumption, only consumed 11-15 daily doses/1,000 inhabitants. This observation strongly highlights the need for standardized prescribing practices and policies to reduce the spread of resistant bacteria [13].

In addition, intense antibiotic use in animal farms and for agricultural purposes strongly contributes to the emergence of antibiotic resistance. It has been estimated that, in 2009, 80% of the antibiotics sold in the U.S. were used on farms [14]. In Europe, although the amount of used antibiotics varies widely from one European Union country to another, new policies have allowed to reduce the agricultural use of antibiotics from 2010 to 2011 in almost every country [9].

Together with the emergence and spread of the 'superbugs' resistant to most of the available compounds, the arsenal to fight these microorganisms is progressively shrinking, as showed by the dropping number of newly discovered antibiotics approved by the US Food and Drug administration each year. After granting 19 new drug applications in the years 1980-1984, that number dropped to 11 in the years 1985-1989, 1990-1994 and 1995-1999, to 4 in the years 2000-2004, to 3 in 2005-2009, and to only 1 during the years 2010-2012, showing a progressive and marked decrease in new antibiotic development [13].

Discovery of new antibiotics is challenging. Indeed, a new compound requires well selected pharmacokinetic (e.g. physicochemical properties that improve the likelihood of oral bioavailability) and pharmacodynamic properties (e.g. allowing the use of the compound at high concentrations, required for penetration of the drug into prokaryotic cells without causing toxicity); further difficulties are posed by drugs that target Gram-negative bacteria, as such drugs must be able to penetrate through the external outer membrane which is a barrier for most drugs [15]. In addition to technical reasons, the modest return on investment poses further challenges to antibiotic development: antibiotic therapy is typically short-term, lasting only several days, and resistance to any antibiotic will eventually develop, limiting its useful lifetime; on the contrary, therapies to control blood pressure or cholesterol last for years [15].

The fight to antibiotic resistance needs a coordinated international effort. In face of global spread of antibiotic resistance and of the limited development of new drugs, policies and rules are under study by agencies (CDC, World Health Organization) and governments.

New policies should facilitate the discovery of new tools to fight bacteria, including new antibiotics and innovative treatments.

It has been estimated that at least 200 molecules exist in bacteria that are essential for bacterial life and are highly conserved across species, and may be therefore new targets for novel antibiotics.

Ling et al. developed new methods to grow uncultured soil microorganism organisms by cultivation *in situ* or by using specific growth factors and discovered a new compound, teixobactin [16]. Remarkably, the researchers were unable to experimentally develop Gram-positive bacterial strains resistant to teixobactin. The relevance of this discovery relies on the isolation and characterization of the first compound of a new major class of antibiotics, but also, and more importantly, on the novel technology used by the investigators, that suggests a path towards developing new antibiotics that are likely to avoid development of resistance [16-18].

Additional methods, alternative to that of Ling et al., are under investigation to discover new antibiotic compounds and may help to discover additional antibiotic molecules from soil bacteria in the future [17].

Beyond discovery of antibiotics, new methods to fight resistant strains are on the horizon. The

novel, CRISPR-cas nuclease-based technology has been harnessed to revert bacterial resistance or virulence by targeting the resistance or virulence genes, respectively [19, 20]. Finally, the old concept of using inhibitors of resistance factors has been successfully applied to carbapenemase, with the development of inhibitors of carbapenemase offering hope to restore sensitivity to carbapenem used against resistant strains [21, 22].

Taken together, these technologies create opportunities to fight resistant strains, but will not be sufficient to prevent the spread of resistance. These drugs will be expensive, and may eventually lose their efficacy due to unexpected and unpredictable mechanisms of resistance. Antibiotic research and development will takeoff only if governments will invest in basic research and will issue new rules to facilitate industrial development of newly discovered drugs without promoting overuse and overprescribing. This will be possible only by delinking a drugmaker's profits from the drug's sales [2, 23].

Governments are moving in these directions. The US 2016 budget proposes nearly doubling the amount of federal funding to address the problem of antibiotic resistance; and in late March 2015 the White House announced a multiyear National Action Plan for combating antimicrobial resistance. The goals of the action plan include slowing the emergence of resistant bacteria and preventing the spread of resistant infections, improving surveillance, developing better diagnostic tools, accelerating research into new drugs, and improving global coordination [3].

In this perspective, surveillance organizations are promoting strategies that aim at preventing the emergence of resistance through antibiotic stewardship programs, educational programs, and reduction of antibiotic use in livestock.

Hand washing should be a priority in every hospital setting, in order to prevent, rather than treat, infection [24]. Once a MDR strain causes an outbreak in a NICU, infection control measures should be implemented, including staff reeducation on recommended infection prevention measures, auditing of hand hygiene and environmental services practices, contact precautions, cohorting of infants and staff, alleviation of overcrowding, and NICU-wide screening cultures [8, 25].

Among other interventions, the CDC recommends that each hospital build an antibiotic stewardship program, which should rely on infrastructures to provide physicians with the

information and tools they need to make the right decisions and on a surveillance program both during and after antibiotic prescription [1, 26]. One of the key elements of the stewardship should be the development of a checklist, allowing to reduce the inappropriate use of antibiotics through a systematic evaluation of all the steps of antibiotic treatment [1, 27].

A specific antibiotic stewardship program should be developed for the NICUs [28]. According to Cantey and Patel [29] specific issues of a neonatal antibiotic stewardship program include:

- diagnostic challenges, due to the often non-specific signs of sepsis and the frequent occurrence of culture-negative infections (clinical and laboratory signs of sepsis despite negative cultures);
- duration of treatment, that often varies among NICUs and even in the same unit, and that need standardization;
- management of infants born to mothers with chorioamnionitis, that may receive unnecessary yet often unavoidable antibiotics;
- difficulties in dosing and therapeutic drug monitoring;
- the optimal regimens for perioperative prophylaxis.

Key members of the NICU antibiotic stewardship team should include a neonatologist, an infectious diseases physician, a neonatal-trained pharmacist, infection preventionists, a bioinformatician, and a neonatal nurse; a neonatologist inside the NICU should be identified, and should work strictly with other institutional colleagues in a multidisciplinary effort to help determine which stewardship interventions are more likely to be accepted by his peers in the NICU and more likely to be implemented and be effective in reducing the use of antibiotics [29].

Key stewardship interventions include improvement in diagnostic techniques (appropriate blood cultures and use of laboratory tests), accurate measurement of antibiotic use and drug monitoring, rational selection of empiric therapy and avoidance of unnecessary broad spectrum therapy, and continual re-evaluation and discontinuation when appropriate [29, 30].

One essential aspect in the successful implementation of stewardship programs is the accurateness of diagnosis of infections. Indeed, with currently available diagnostic tests, antibiograms are only available days after an antibiotic treatment has been started, and, until they are available,

patients are often treated with broad-spectrum antibiotics, especially in intensive care units where resistance easily develops [31]. Polymerase chain reaction-based technology is available and could allow, if routinely implemented, the reduction of the time to diagnosis and sensitivity test to some hours and could better guide the choice of the right drug to use soon after onset of infection; furthermore, novel diagnostic tools are likely to enter clinical practice and especially neonatal units in the upcoming years, including, but not limited to, the powerful tool of metabolomics to obtain highly specific individual profiles and start individual-specific and infection-specific treatments [32-36].

Addressing antibiotic resistance will need both local and global efforts, and a multidisciplinary and multifaceted intervention that should rely on few, fundamental principles. Recognition by organizations (several organization have made antibiotic resistance the focus of highly visible reports, conferences, and actions), private-public partnership for antibiotic discovery, return and monetary reward to pharmaceutical companies, prevention of infections by vaccines and hygiene practices, access to antibiotics for all who need them, with conservation through prioritization of medical use (by limiting use for growth promotion in animals and plants), conservation through prescription-tailored to diagnosis (by developing quick and accurate diagnostic tools that allow distinction between viral and bacterial infections and providing the resistance pattern of the bacterium) and conservation through controlled access by instituting antibiotic stewardship programs, will be the key elements in the fight to preserve the unique and vulnerable resource of antibiotics [37].

Declaration of interest

The Authors have no conflicts of interest to disclose.

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