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Perspective
Potential Strategies to Combat Antimicrobial Resistance

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Abstract

The increasing prevalence of antibiotic resistance and the lack of new antibiotic drug development have gradually reduced the treatment options for bacterial infections. To combat antimicrobial resistance, potential approaches were presented to prolong the useful therapeutic life of antimicrobials available at present: (1) To maintain heterogeneity (antimicrobial cycling or mixing) of antimicrobial agents, (2) To assure and ensure adequate serum drug concentrations by preventing patient self-medication and noncompliance with recommended treatments, (3) Repurposing of withdrawn and underused antimicrobial drugs (e.g., combinations between β-lactamase inhibitors and older β-lactams), (4) Combination therapy (e.g., broad-spectrum combination antimicrobial treatment between vancomycin, neomycin and metronidazole), (5) The right timing of prescription and (6) The development of appropriate educational programs targeted specifically to children and undergraduate students for prudent antibiotic use.

Key words: Antibiotic resistance, serum drug concentrations, repurposing of underused antibiotics, combination therapy, prudent antibiotic use

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INTRODUCTION

Antimicrobial agents have been greatly important cornerstones of clinical medicine since the second half of the 20th century and have saved a great number of people from life-threatening bacterial infections. However, the last decade of the 20th century and the first decade of the 21th century witnessed the emergence and spread of antibiotic resistance in pathogenic bacteria around the world and the consequent failure of antibiotic therapy, which has led to hundreds of thousands of deaths annually[1,2]. If antibiotic-resistant pathogens remain unchecked, it is estimated that by 2050 the global mortality attributed to antibiotic-resistant bacterial infections will soar to 10 million, at a cost of over $100 trillion (http://amr-review.org/). In 2013, the Centers for Disease Control and Prevention (CDC) named three microorganisms that pose an urgent threat to public health: Carbapenem-resistant *Enterobacteriaceae*, drug-resistant *Neisseria gonorrhoeae* and *Clostridium difficile*[3].

The increase in carbapenem or fluoroquinolone resistance will be a major threat in the future[4,5]. Recent reports showed that carbapenem-resistant *Escherichia coli* and *Salmonella enterica* are also isolated from food animals[6,7]. The hope of overcoming this threat by the development of new antibiotics is diminished both by the decline in novel antibiotic discovery, particularly in the Gram-negative spectrum[8-11] and by the possibility that pathogens will evolve resistance to novel antibiotics just as they adapt quickly to existing antibiotics[1,12,13]. Therefore, to address the problem of antibiotic resistance, potential strategies to combat antimicrobial resistance are required.

POTENTIAL STRATEGIES TO COMBAT ANTIMICROBIAL RESISTANCE

A recent study presented potential approaches to prolong the useful therapeutic life of antimicrobials available at present: (1) To maintain heterogeneity of antimicrobial agents, (2) To assure and ensure adequate serum drug concentrations, (3) Repurposing of withdrawn and underused antimicrobial drugs and (4) Combination therapy[14]. Here we draw attention to other important aspects overlooked by this study.

Heterogeneity (antimicrobial cycling or mixing) of antimicrobial agents: Maintaining prescribing diversity can be achieved through several methods (antimicrobial cycling or mixing)[14]. However, according to our report[1] antimicrobial heterogeneity (antimicrobial cycling or mixing) continues to be a debatable subject, although many investigators have studied its effects on antimicrobial resistance with the help of clinical investigations or theoretical models. It is noteworthy that antimicrobial mixing can carry the risk of inappropriate usage of antimicrobials because of the open formulary, whereas antimicrobial cycling can increase the duration of antimicrobial treatment[1]. Therefore, many more studies are required to demonstrate the effectiveness of antimicrobial heterogeneity.

Adequate serum drug concentrations: The optimization of dosage and guarantee of drug quality could reduce sub-therapeutic drug exposure and reduce this modifiable driver of resistance[14]. Unfortunately, suboptimal drug exposures have many causes: Use of poor quality drug, systematic under-dosing, inadequate drug absorption, unusual large apparent volume of distribution (pregnancy) or particularly rapid clearance. However, inadequate serum drug concentrations are also caused by some common types of human behavior (patient self-medication and noncompliance with recommended treatments)[15]. Self-medication almost always involves unnecessary, inadequate and ill-timed dosing. Noncompliance occurs when individuals forget to take medication, prematurely discontinue the medication as they begin to feel better[15]. The problems of self-medication and noncompliance are magnified in low-income and middle-income countries.

Repurposing of withdrawn and underused antimicrobial drugs: Repurposing previously discovered (often FDA-approved) pharmacotherapies (e.g., the return of colistin and fosfomycin use for multidrug-resistant Gram-negative infections) might provide a potentially less economically risky pursuit than de-novo drug discovery[14]. Furthermore, purposing of combinations between β-lactamase inhibitors and older (underused) β-lactams[16], as well as repurposing of underused antimicrobials is important for the sustainable effectiveness of antimicrobials. Due to the emergence of class C (AmpC) extended-spectrum β-lactamases (ESBLs) with carbapenemase activity (cESBLs/carbapenemases) and no β-lactam-β-lactamase inhibitors (BLBLIs) available for class B carbapenemase producers[16], BLBLIs targeting cESBLs/carbapenemases and/or class B carbapenemases should be developed urgently for specific situations in, which no other drugs are available.

Combination therapy: This therapy is use of several antimicrobials to which the targeted organisms do not show cross-resistance, which relies on microbial populations

containing singly resistant mutants, but none that are resistant simultaneously to several drugs[14]. However, what are affected by antimicrobial treatment is not limited to bacteria, which are directly susceptible to antimicrobials. Recent many reports have shown antimicrobial-associated changes in host immunity: Reduced expression of REG3γ by broad-spectrum combination antimicrobial treatment (Vancomycin, neomycin and metronidazole), reduced expression of TLR2 and TLR4 in peritoneal macrophages by the treatment of streptomycin and cefotaxime and so on[1]. Therefore, in the context of combination therapy, further studies of how each antimicrobial affects not only the microbiome but also the host immune system are required.

Right timing of prescription: In addition to four strategies, as mentioned above[14], to combat antimicrobial resistance, timing of prescription is also important in the context of sustainable access of antimicrobials. All too often the latest new antimicrobial is left as the last-resort treatment, despite the causative pathogen being identified as multidrug-resistant bacteria[17]. The late use of effective antimicrobials can limit the efficacy of a new drug because the patient might be unable to mount a clinical response[17]. A better medical approach might be to use the so-called big new antimicrobials sooner rather than later[17].

Development of appropriate educational programs targeted specifically to children and undergraduate students for prudent antibiotic use: In addition to four strategies[14], continuous efforts to educate the public about prudent antibiotic use are very important. Up to now, most educational efforts have been targeted to medical professionals and to the adult public. However, because medical professionals and adults have already established their knowledge, attitudes and behaviours about antibiotic use, it is difficult to change their deeply established views and behaviours[18]. Thus, in the past few years, a variety of programs to educate children has been made. Programs directed to children education have been developed as follows: e-Bug in Europe, Do Bugs Need Drugs? in Canada and the Microbes en question in French[18]. The e-Bug, the European Commission-funded antibiotic teaching resource is a representative educational program for children[19]. Since, the launch in 2009, visits to the e-Bug web site (http://www.e-bug.eu) have increased annually and were recorded from more than 190 different countries. The number of available languages has also increased from 8-25 with extension outside the EU into Turkey and Saudi Arabia. Especially, educating parents through children is novel and interesting[19]. Through, e-Bug children and their parents increased their awareness of hygiene, the spread of infection, vaccination uptake and prudent antibiotic use[19]. Many studies showed that these educational efforts targeted to medical professionals, the adult public and children are fairly effective in improving serious misunderstandings about antibiotics and reducing its use[18]. However, novel antibiotics introduced in the market are still rare and pathogenic bacteria are adapting quickly to existing antibiotics, particularly to antibiotics acting on the Gram-negative bacteria[20]. Therefore, educational efforts to reduce antibiotic use must be expanded. The contents of teaching programs for prescribers and the public, training the trainer and evaluation of program effectiveness are very important. Efforts on a national level to improve current educational programs are required and it is necessary to develop appropriate educational programs targeted specifically to each group.

In addition, appropriate curricula to teach medical and nonmedical undergraduate students should be developed as soon as possible. Because the undergraduate training track is the time when knowledge, attitudes and behaviours of medical professionals are being shaped, educating them about prudent antibiotic prescribing will be significantly effective in reducing antibiotic use. On 18 August, 2015, the National Institute for Health and Care Excellence (NICE) in the UK released its first guideline on antimicrobial stewardship[21]. However, the NICE guideline does not show enough direction and clarity about education for judicious antibiotic use[22].

CONCLUSION

Antimicrobial agents have been greatly important cornerstones of clinical medicine since the second half of the 20th century. However, the last decade of the 20th century and the first decade of the 21th century witnessed the emergence and spread of antibiotic resistance in pathogenic bacteria around the world and the consequent failure of antibiotic therapy. To address the problem of antibiotic resistance, potential strategies to combat antimicrobial resistance are required and here six potential strategies were presented.

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