Review

Emerging of bacterial resistance: an ongoing threat during and after the Syrian crisis

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Abstract

The rapid emergence of bacterial resistance worldwide is a serious problem, leading to many therapeutic failures and rendering inactive effective antibiotics currently used . This problem has recently been accelerated by conflicts and its related migration. The antibiotic resistance phenomenon is diffused in Syria with a high rate of multi drug resistance cases in gram negative and gram positive organisms during and after the Syrian crisis as a result of misprescribing and overprescribing of antibiotics. The inappropriate use of antibiotic plays an important role in resistance generation. Hence, big efforts are urgently needed by using phenotypic and genetic analysis of bacterial strains against antibiotics to increase characterization and identification of mutant resistant strains and find new strategies to control the spread of antimicrobial resistance infections. This review highlights the antibacterial resistance problem in Syria, showing its negative impact and presenting a sum of efforts that are urgently needed to overcome this problem.

Key words: Antibiotics; global problem; bacterial resistance; threat; Syria.

Introduction

The antimicrobial resistance has become a serious problem worldwide, confronts the antibiotics recently being used. This increasingly emerging problem appeared to be dangerous especially in the nosocomial setting where around 15% of hospitalized patients suffer from nosocomial infections according to the WHO estimates, which accounts for 7% in developed and 10% in developing countries [1]. Many types of bacteria can be the main reason for resistance problems: some gram negative bacteria like *Klebsiella pneumoniae*, *Escherichia coli*, *Acinetobacter baumanii*, *Salmonella typhi*, *Neisseria gonorrhoeae* or gram positive bacteria like methicillin resistant *Staphylococcus aureus* (MRSA) and also *Mycobacterium tuberculosis*, have developed a different mechanism of resistance and became a threat to the global health care. This problem has alerted us about the need to develop new drugs and study new mechanisms of bacterial resistance with more understanding on bacterial defence mechanisms against antibiotics in order to control the spread of bacterial infection not only in developing countries but also in developed countries such as Europe and United States. Despite all efforts to decrease the spread of infections, 30,000 blood infections are still occurring in the intensive care units (ICU) each year in USA [2] with an increase in the incidence of Extended –Spectrum beta lactamase (ESBL) infections estimated around 53,3% among hospitalizations in US between 2012 and 2017 [3]. Also in Europe the infections caused by multi drug resistant bacteria have been increasing since 2012 and an increase of resistance cases against one or more antibiotics especially for *Escherichia coli* and *Klebsiella pneumoniae* isolates over the last four year in European countries has been reported [4]. Recently, the war in the Middle East caused an economical problem affecting the health system, whith several people suffering from serious deadly infections as a results of the lack of drugs like antibiotics in many regions and inability to use new and more developed methods of diagnosis to control this widely spread problem. Furthermore, the inappropriate use of antibiotics led to increase of antibiotic resistance especially in Syria being a war zone with a lot of cases of nosocomial infection caused by aerobic and anaerobic microorganisms. Furthermore, in the major Syrian hospitals the antibiotic sensitivity is rarely investigated by physicians, who usually use new generation wide spectrum antibiotics with high doses to

rapidly control infections, without considering the consequences of developing bacterial resistance caused by inappropriate use of antibiotics or insufficient methods for resistance identification and further resistant strains isolation to choose the right antibiotic. Furthermore, in Damascus 87% of pharmacists sell antibiotics without prescription and only 3% refused to give antibiotic without doctor prescription [5] which lead to increase of antibiotic resistance in Syria and decrease of susceptibility of the most common pathogens to effective antibiotics compared to the pre-conflict period [6]. It is well known that antibiotic resistance could be transferred and spread to other countries especially by travelling or migration from war zones to Europe and this might develop a new resistance and might play a role of new multi drug resistant (MDR) strains emerging in European countries and also in other countries [7].

Bacterial resistance migration

Many factors contributed to the spread of bacterial resistance and MDR cases worldwide. Migration and international travelling could play an important role in resistance circulation [8]. Recently, the increased migration to Europe was correlated with increased incidence of resistance. The preliminary reports indicated a high rate of MDR pathogens among immigrants [9]. Also, a high number of gram negative multi drug resistant (60.8%) and methicillin-resistant *Staphylococcus aureus* (MRSA) (5.6%) was observed among immigrants in a refugee centre in Germany [10]. Some other resistant bacterial strains were transferred from one country to another, such as New Delhi metalllo-β lactamase 1 (NDM-1) producing *Acinetobacter baumannii* was isolated in migrants from Syria in Turkey and might have also been transported to other neighbouring countries transmitting the resistance [11].

Moreover, it was reported that in Switzerland MRSA and ESBL strains prevailed more among refugees in refugee centres than in Swiss population and the MRSA rate was 15.7% in Syrian refugees and 23.7% were ESBL [12]. Thus, many cases of multidrug resistant pathogens among refugees from Syria have been reported by European centres [5]. Furthermore, the old threat represented by tuberculosis (TB) and MDR TB cases is higher among immigrants in Europe and most of cases were results of reactivation from latent tuberculosis infections (LTB) [13]. Another study in Germany found that the percentage of gram negative MDR cases among refugees was 60% in 2016 and such a high percentage needs to be urgently controlled [10].

Taking into consideration this emerging problem, the use of molecular screening methods was strongly recommended for immigrants as preliminary method that might help and play an important role to control bacterial resistance transmission and its spread worldwide [14].

Antimicrobial resistance during and after the Syrian crisis

Studies on antimicrobial resistance in Syria during and after the Syrian conflict are scarce and most of them were developed outside the country or in refugee centres. Many factors limited these data and the surveillance system is not very effective and available in all regions of the country compared to larger cities such as the capital Damascus. In addition, the low incomelimited the ability of the private sectors to adopt new methods of isolation including the specific identification of microorganism with antibiograms and the genetic analysis reports leading to the loss of a considerable amount if important data about the current situation. Many cases have been reported inside and outside the country. At molecular level, a phylogenetic analysis using whole genome sequencing (WGS) was performed on *Klebsiella pneumoniae* MDR strains isolated from a refugee centre in Italy which showed that the Syrian *Klebsiella pneumoniae* genome did not cluster with any Italian strains and closely related with the Greek sequences [14]. A pre-conflict study about *Acinetobacter baumanii* conducted on 206 patients showed a high level of antimicrobial resistance to Amikacin 78%, ciprofloxacin 81%, ceftazidime 80.6% and cefepime 84% [15]. A carbapenem resistant *Klebsiella pneumoniae* was isolated from 25 % of children with recurrent tonsillitis [16]. A study in Aleppo reported that 66% out of 123 ESBL *Escherichia coli* and *Klebsiella pneumoniae* isolates were phenotypically resistant to ciprofloxacin [17]. It was also observed in a study conducted in Syria that 63% of *Escherichia coli* isolates from positive urine samples were multi drug resistant and 61.33% of isolates were ESBL [18]. Other resistance cases were reported in Aleppo with 177 cases of *Pseudomonas aeruginosa* isolated from lower respiratory and urinary specimens that showed resistance to (piperacillin-tazobactam 46%, meropenem 41%, ceftazidime 37%) [19]. According to a study conducted in Damascus at Al Mouasat University hospital in 2015, a significant increase in *Escherichia coli* resistance to commonly used antibiotics (amikacin 74%, ceftriaxone10%, ciprofloxacin 21%, nalidixic acid 12%, tobramycin 23% and ceftazidime 25%) was observed when

compared with susceptibility patterns (amikacin 92.4%, ceftriaxone 35.7%, ciprofloxacin 43.7%, nalidixic acid 29.4%, tobramycin 53.7% and ceftazidime 34.7%) obtained from a study conducted in the same hospital in 2009, before the war. In addition, the study showed a significant reduction of sensitivity to *Staphylococcus aureus* to the following commonly used antibiotics:Erythromycin 33%, Gentamycin 51%, oxacillin 15% and cotrimoxazole 42%, compared with another study developed in the same hospital before the war in 2007 on the same antibiotics (Erythromycin 55%, Gentamycin 69%, oxacillin 31% and cotrimoxazole 67%) [6]. In a study conducted on medical staff in the main Syrian hospital, the MRSA rate was (9.4%) in nasal cavities [20]. The MRSA rate was also high in isolates obtained from diabetic foot ulcers in Syria where 61% of *Staphylococcus aureus* isolates that were MRSA [21]. A screening for multi drug resistant gram negative bacteria (MRGN) performed in a university children`s hospital in Germany on pediatric refugees, mostlyfrom Syria, showed that the majority of patients were colonized with MRGN and in 0.7% of hospitalized patients vancomycin resistant *Enterococcus faecium* (VRE) was detected [22]. Recently, unpublished data collected by the author of this review included observations about increase of MDR cases in Syria. The high rates of MDR cases, ESBL, MRSA and carabapenem resistant gram negative bacteria is a dangerous phenomenon still growing dramatically due to many factors such as the overuse of antibiotics, using antibiotics without prescription and lack of specific resistance identification to prescribe the appropriate antibiotics against the specific microorganism. The threat is hard to accept: it means that in the near future no effective antibiotics might be available for a lot of people, making even a small operation almost impossible to be performed.

The negative impact of antibacterial resistance

Antibiotic resistance has a negative impact at different levels related both to public health and economics. The spread of bacterial resistance leads to increase of infection cases, limitations to therapeutic options and adds more complications during hospital surgery procedures. This negative impact could further worsen infections and even replace non resistant with resistant bacteria [23,24]. In addition, the percentage of mortality caused by bacterial resistance in the health care units such as hospital and intensive care units is more than twice higher in patients with resistant infection than patients with infections caused by non

resistant microorganisms [25]. Economy is also affected by the spread of bacterial resistance. The control of resistant bacterial infections costs 4-5 million USDper year according to an estimation conducted by the Institute of Medicine of the Washington National Academies in United States and the cost of treating such infections has increased to 2.2 billion USD annually [26,27]. Moreover, the total cost of treatments for antimicrobial resistant infections due to resistant infection by *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii* and *Pseudomonas aeruginosa* in USA is around 2.9 billion USD [28]. Moreover, the impact of antimicrobial resistance might further affect physicians by changing their treatment protocol to achieve an appropriate treatment and the patient will be overcharged with more than one antibiotic for treatment. The pharmaceutical industries also have to make more efforts for drug discovery and development of new generation of antibiotics by adopting new strategies in order to combat emerging bacterial resistance [26].

Efforts and strategies to control bacterial resistance

Controlling bacterial resistance is very difficult even impossible in some cases. Lack of new anti bacterial drugs makes the control of anti microbial resistance more difficult. In order to contain this emerging problem, many strategies have to be considered like developing new anti microbial drugs and building better educational programs combined with specific microorganism identification and resistance determination to minimize unnecessary or excessive antimicrobial exposure [29]. In 2017, WHO has listed many pathogens including *Mycobacterium tuberculosis* as the most resistant microorganism which became a threat to the global health [30]. Hence, novel antimicrobial agents and new combination of treatments are urgently needed, so different strategies have been taken in consideration like combination of two antibiotics to achieve different antimicrobial mechanisms or combinations between antibiotics and adjuvant inhibitors of drug efflux pump which are over expressed in the resistant strains [31]. Recently, the antimicrobial compounds incorporating oxazolidinone (protein inhibitor) and quinolone (DNA synthesis inhibitor) have been used to treat resistant *Clostridium difficile* strains [32,33]. Furthermore, new antimicrobial agents known as efflux pump inhibitors (EPI) that disrupt the pump activity to efflux antibiotics outside the bacterial cell, could modulate the resistance on some antibiotics [34,35]. It has been demonstrated that

the covalent bonding between ciprofloxacin and naringenin, a phenolic flavoniod with known EPI activity, increases the DNA gyrase inhibiting the ciprofloxacin activity by 23-fold [31,36]. Understanding the host-pathogen interaction and using the host directed therapy (HDR) to alter the host response is another important novel strategy to control the bacterial resistance and could be used as an alternative way to overcome resistant and multi drug resistant bacterial infections [37,38]. Moreover, using Toll-like receptor (TLR) ligands regulating the pattern recognition receptor like TLR might help in eradicating bacteria by modulating the inflammatory response. This strategy showed a significant reduction in the number of *Haemophilus influenzae* strains from nasopharynx when the monophosphoryl lipid A was used as TLR4 modulator [39,40]. The host directed therapy was also studied to treat the intracellular bacterial infection by using food and drug administration (FDA)-approved compounds targeting G-protein signalling (Trifluoperazine) and interfering with calcium transport (Lomerizine) to inhibit different microorganism such as *Coxiella burnetii*, *Legionella pneumophila*, *Brucella abortus*, and *Rickettsia conorii* or using sterol hemostasis (Mifepristone) which showed activity against *Coxiella burnetii* and *Legionella pneumophila* [41]. Furthermore, using therapy directed at stimulating autophagy increases the ability of the phagocyte to eradicate intracellular bacteria like *Mycobacterium tuberculosis* and different HDRs can help the host to control *Mycobacterium tuberculosis* and other intracellular bacteria by stimulating the autophagy with metformin to induce the maturation of the phagolysosome as an adjuvant therapy to control tuberculosis infection. Therefore, the combination of host directed therapy with anti TB drugs might improve the treatment in special cases such as in MDR *Mycobacterium tuberculosis* infections [42]. Several researchers are still studying how to increase the ability of human defences against resistant microorganisms by altering some host cell defence mechanisms to be resistant against bacterial infection.

Concluding remarks

Overuse and the inappropriate use of the antibiotics contribute in the spread of bacterial resistance worldwide in addition to many other factors including lack of efficient diagnosis. The antimicrobial resistance is an ongoing threat in Syria and the multidrug resistant strains are rapidly expanding. Therefore, there is an urgent need to improve diagnostic systems in order to isolate and specifically detect the antibiotic resistant and multidrug resistant strains, select the appropriate antibiotic to clear infections and stop MDR strains diffusion. This could be achieved by using efficient and more developed methods in microbiology diagnosis at molecular level. Finally, there are a lot of challenges that researchers are facing to overcome MDR and extensively drug resistance (XDR) strains due to many bacterial-related reasons such as the resistance mediated plasmid, impermeable outer membrane and efflux pump. Hence, creating new antibiotics with different modes of action and host directed therapy should be considered in the future.

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