Hindawi Publishing Corporation
ISRN Infectious Diseases
Volume 2013, Article ID 759208, 6 pages
http://dx.doi.org/10.5402/2013/759208

Review Article

Resistance of Gram-Negative Bacilli in Lebanon

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Received 14 April 2012; Accepted 5 June 2012

Academic Editors: J.-M. Bart, C.-K. Fan, and A. P. Gibb

Several studies have reported the isolation of resistant Gram-Negative Bacilli in Lebanon. However, those studies are new and scarce as compared to worldwide data and mostly restricted to single center studies. In this review, we attempt to provide a reliable and comprehensive report describing the current situation and providing prospects for bacterial resistance in Lebanon. Several studies have shown that Extended Spectrum β-Lactamase-producing *E. coli* and *K. pneumoniae* strains are being increasingly reported. Moreover, 2.15% of *E. coli* and 7.84% of *K. pneumoniae* isolates have shown carbapenem resistance and up to 30% of isolated *E. coli* strains were found to be Multi-Drug Resistant. Molecular studies showed that the most widespread β-Lactamases in Lebanon are of the CTX-M-15 and SHV types. In addition, *K. pneumoniae* strains producing metallo-β-Lactamase and *Klebsiella pneumoniae* Carbapenemase have been reported. Resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* caused several nosocomial infections and some *Acinetobacter baumannii* strains were found to produce OXA-58 type ESBL. The few data addressing the rate of antibiotic consumption in Lebanon show a high rate of antibiotic misuse and abuse. In conclusion, there is a need for antibiotic stewardship programs and additional studies that go beyond the scope of single-center studies in Lebanon.

1. Introduction

Bacterial resistance is an issue that has cultivated major worldwide concern in clinicians and researchers alike [1]. Resistant bacterial strains are increasing in prevalence [2, 3] and their acquired ability to avoid the action of one or more antibacterial agents is causing a serious clinical threat [4]. Of the many resistant bacteria, Gram-Negative Bacilli (GNB) are increasingly isolated [5–7]. Two major families of GNB with considerable resistant strains are the Enterobacteriaceae and the nonfermenters [8].

One mechanism by which GNB acquire resistance is via the production of β-lactamases. These β-lactamases include, among others, the Extended Spectrum β-Lactamases (ESBLs), the Metallo β-Lactamases (MBLs), and the OXA β-lactamases [7]. Moreover, some organisms have acquired resistance to more than one antibacterial agent. These organisms are classified as Multidrug Resistant (MDR) if they are resistant to more than 3 classes of antibacterial agents, Extensive Drug Resistant (XDR) if they are resistant to all but 1 or 2 classes of antibacterial agents, and Pan-Drug Resistant (PDR) if they are resistant to all antibacterial agents [9].

Several studies show that the rate of antibiotic consumption is one factor that is directly correlated to the emergence of resistance in bacteria [10, 11]. Borg et al. [12] have shown that there is a high rate of wide spectrum antibiotic consumption in the Mediterranean region. More specifically, in Lebanon, alarming rates of misuse and abuse of antimicrobial agents have been reported [11, 13, 14]. This high rate of antibiotic consumption, coupled by a lack of judicious and rationale use, creates an environment for resistance to emerge. However, data regarding the spread of resistant GNB in Lebanon are relatively new and scarce when compared to worldwide data, and are mostly restricted to single-center studies [15–17].

In light of the significant clinical threat that resistant GNB are causing and the absence of a national surveillance center to provide reliable data, we intend to review the most important studies related to bacterial resistance in Enterobacteriaceae and nonfermenters in Lebanon. Our aim is to present a reliable and comprehensive report describing

the current situation and providing prospects for bacterial resistance in a country where antibiotics are easily accessible and widely abused.

1.1. Escherichia coli and Klebsiella pneumoniae. Strains of *E. coli* and *K. pneumoniae* with high rates of antibiotic resistance are increasingly reported worldwide [18, 19]. It has been shown that countries in the Eastern Mediterranean region have a higher prevalence of resistant strains when compared to several European countries [12]. In Lebanon, by the year 1994, as much as 65% of clinical isolates of *E. coli* were found to be resistant to ampicilin at the American University of Beirut Medical Center [20]. Around ten years later, this percentage had increased to 72% in the same institute [21]. Another study at the American University of Beirut Medical Center over a period of 4 years showed that the rate of ESBL producing *E. coli* increased from 3% to 5% whereas that of *K. pneumoniae* increased from 6.4% to 13% [22]. This high rate of increase in incidence is higher than that reported in other countries of the world, such as USA [23, 24]. The screening of 4399 clinical isolates of *E. coli* and 1248 isolates of *K. pneumoniae* from the Saint George Hospital, University Medical Center, in Beirut over a period of 5 years showed that 2% of the *E. coli* strains and 20% of the *K. pneumoniae* were ESBL producers [25]. Moreover, ESBL production in organisms isolated from Urinary Tract Infections (UTI) in that same hospital increased from 2.3% to 16.8% over a period of 9 years [6]. Another study investigating the intestinal carriage of ESBL producing *E. coli* and *K. pneumoniae* of hospitalized patients across 5 Lebanese tertiary care facilities reported that 80.5% of *E. coli* and 13.6% of *K. pneumoniae* were ESBL producers [14]. These studies show that the rate of ESBL production is increasing in both *E. coli* and *K. pneumoniae* isolates in this country and threatens to escalate if not dealt with promptly and appropriately.

E. coli isolated from prostate gland biopsies from the American University of Beirut Medical Center showed that 5 out of 8 organisms produced ESBL [26]. At that same hospital, 40% of *E. coli* and 33% of *K. pneumoniae* isolated from patients with ventilator-associated pneumonia were shown to be positive for ESBL production [27]. These rates of resistance are higher than those reported in other regions of the world [24, 28], but remain lower than those detected in other Mediterranean countries such as Egypt [29]. Nevertheless, these high rates warrant immediate attention due to the great risk they impose on hospitalized patients.

On the other hand, the production of statistical pamphlets by different Lebanese hospitals reporting the different susceptibility profiles of bacterial strains encountered throughout the year is becoming a general trend. These pamphlets are a valuable tool used mainly by clinical microbiologists, infection control personnel, and infectious disease clinicians for the monitoring of the patterns of resistance of different bacterial strains. The lack of a national surveillance center in Lebanon gives an even greater value for these pamphlets and encourages more and more hospitals to produce them. Although these pamphlets may lack specificity and might include nonstatistically significant data, or even may erroneously report duplicate strains (what would give a false increase or decrease in resistance), they remain a needed first step for the creation of a national surveillance center of studies.

Susceptibility testing of *E. coli* strains isolated from patients with hospital acquired Urinary Tract Infections (UTI) at the American University of Beirut Medical Center between January and December of 2001 showed that 64% of these isolates were resistant to Trimethoprim/Sulfomethoxazole (TM/SFX) and 46% were resistant to quinolones. However, only 1 isolate was found to produce ESBL [13]. At that same hospital, intestinal carriage of *E. coli* showed 100% susceptibility to ertapenem, 83% susceptibility to piperacillin/tazobactam, and 96% susceptibility to amikacin. In the same study, the susceptibility profile of *K. pneumoniae* strains in the intestines were 100% to ertapenem, 91% to piperacillin/tazobactam, 82% to amikacin, 72–75% to quinolones and 88% to cefepime [30]. In 2008, *E. coli* isolates were 100% susceptible to tigecycline, whereas 16% of *K. pneumoniae* strains were intermediately resistant and 3% were fully resistant to tigecycline in the same hospital [21]. A study by Borg et al. conducted at the Saint George Hospital, University Medical Center showed that 18.9% of clinical isolates of *E. coli* were resistant to third generation cephalosporins, 21% were resistant to quinolones, and 68% were resistant to aminopenicillin [12]. These reported profiles show that resistance in both intestinally carried and clinical isolates of *E. coli* and *K. pneumoniae* is evident; however, they were still reported to be susceptible to carbapenems. Nevertheless, 2.15% of *E. coli* and 7.84% of *K. pneumoniae* isolates were found to be resistant to carbapenems in a recent study [31]. Moreover, two other studies have reported that up to 30% of isolated *E. coli* strains were MDR [15, 32]. The observed resistance to carbapenems and tigecycline and the emergence of MDR strains impose a great threat that needs immediate attention and prompt action.

At the molecular level, the analysis on 72 ESBL producing GNB (of which 77% were *E. coli*) showed that all CTX-M type ESBL producers (83% of total strains) harbored the $bla_{\text{CTX-M-15}}$ gene, while the SHV-type ESBL producers (18% of total strains) harbored the $bla_{\text{SHV-5a}}$ gene. All the isolates were found to carry the bla_{TEM} gene. 25 *E. coli* strains were also found to harbor the $bla_{\text{OXA-1}}$ gene and only one *E. coli* isolate harbored both the $bla_{\text{CTX-M-15}}$ and the $bla_{\text{SHV-5a}}$ genes at the same time [17]. A separate study at the American University of Beirut Medical Center showed that 96% of the ESBL producing *E. coli* had the $bla_{\text{CTX-M}}$ gene, 67% had the bla_{SHV}, and 57% had the bla_{TEM} genes. Analysis on *K. pneumoniae* strains showed that 40% of ESBL producing *K. pneumoniae* had the $bla_{\text{CTX-M}}$ gene, 82% had the bla_{TEM}, and 84% had the bla_{SHV} genes [33]. Taken together, these studies suggest that the most widespread β-lactamases in Lebanon are of the CTX-M-15 and the SHV type. Trans-continental comparison of the CTX-M-15 *E. coli* isolates in Lebanon revealed that these strains were genetically related to the O25: H4 clones found in France, Canada, and Portugal, suggesting a common ancestry [34].

In 2007, the first metallo-β-lactamase producing *K. pneumoniae* in Lebanon was isolated and found to harbor the

bla $_{\text{IMP-1}}$ and *bla* $_{\text{CTX-M}}$ genes [35]. Another carbapenem-resistant *K. pneumoniae* strain was isolated later on in 2008, mediated via the *bla* $_{\text{OXA-48}}$ gene [36]. This type of carbapenem resistance is consistent with findings from Turkey, Belgium, Egypt, and France [37]. Moreover, *Klebsiella pneumonia* carbapenemase (KPC) was detected in a single isolate [38]. These carbapenem-resistant strains greatly limit the choice of antibiotic treatment and therefore impose a huge threat to hospitalized patients.

In conclusion, resistance in *E. coli* and *K. pneumoniae* isolates is increasing in the Lebanese population, with the major types of β-lactamases produced in these isolates being CTX-M-15- and SHV- type ESBLs. The high rate reported is expected to increase even more if the current lack of control over antibiotic consumption persists. Moreover, the emergence of multidrug resistance and carbapenem resistance is a major threat because of these strains' ability to render a large number of antibiotics obsolete. Therefore, antibiotic stewardship programs are urgently needed in order to control antibiotic consumption and limit the wide-spread antibiotic abuse and misuse in the Lebanese population [12] and attempt to decrease the rate of emergence of resistant strains.

2. Other Enterobacteriaceae

Salmonella species have been isolated from Lebanese fast food [39] and incriminated in food poisoning outbreaks [40], suggesting therefore some degree of exposure of the community to this organism. ESBL production among *Salmonella* isolates has also been reported in Lebanon. The major type of ESBL found in *Salmonella* species in Lebanon is of the TEM and SHV type [23]. In 2003, Daoud et al. noted that all 49 *Salmonella* strains isolated at the Saint George Hospital were susceptible to ceftazidime and cefotaxime (Z. Daoud, personal communication). In January 2004, a CTX-M-15-type ESBL producing *Salmonella eneterica* was isolated from the stool of a 6-year-old child in Lebanon [41], reporting for the first time a detrimental change in the resistance profile of this organism. Molecular analysis revealed that this type of ESBL is similar to those reported in India and Turkey [42]. The relatively high prevalence of *Salmonella* in Lebanese fast food and its ability to produce ESBL makes it a public health issue that concerns the whole community.

A study at the American University of Beirut reported that 60% of isolated *Shigella* species were resistant to ampicilin, chloramphenicol, and co-trimoxazole [20]. In 2005, three individually unique ESBL producing *Shigella sonnei* species were isolated [43]. These isolates were resistant to amoxicillin, cefotaxime, ceftazidime, aztreonam, trimethoprim/sulfamethoxazole, gentamycin, and kanamycin. Two of these isolates harbored the *bla*$_{\text{TEM1}}$ gene and all three isolates harbored the plasmid-encoded *bla* $_{\text{CTX-M}}$ gene [43]. Moreover, in 2009, 4 ESBL producing *Shigella sonnei* species harboring the *bla* $_{\text{CTX-M-15}}$ gene were isolated from the stool of patients in a single tertiary care center. This finding suggests that the transfer of resistant genes occurred via horizontal plasmid transfer [44]. In addition, it has been noted that Lebanese immigrants living in Sweden had high incidence rates of traveler-associated shigellosis after visiting Lebanon, suggesting that *Shigella* species are highly prevalent in Lebanon [45] and making resistance in this organism a very serious problem.

2.1. Pseudomonas aeruginosa and Acinetobacter baumannii. Pseudomonas aeruginosa is a bacterium that poses a threat to immunocompromised patients [46] due to its high prevalence in tap water, medical equipment, hospital personnel, and hospital patients [47]. A study in 2003 showed that out of 38 bacterial species isolated from patients with ventilator-associated pneumonia, 8 where *Pseudomonas aeruginosa* [27]. In 2005, a single *Pseudomonas aeruginosa* clone of genotype 1 was found to be responsible for 18% of nosocomial infections in various medical units at the American University of Beirut Medical Center [48]. This finding shows the potential of *Pseudomonas aeuroginosa* of causing serious nosocomial infection outbreaks. However, deeper investigation into the spread of virulent *Pseudomonas aeruginosa* strains across multiple tertiary care centers in Lebanon is needed.

Acinetobacter baumannii has caused several outbreaks throughout the Mediterranean area [49]. In Lebanon, a single *Acinetobacter baumannii* strain was responsible for an outbreak in a major tertiary care center in Beirut. Analysis on this strain showed that it produced the OXA-58 type ESBL [50]. A multidrug resistant *Acinetobacter baumannii* harboring the *bla* $_{\text{OXA-58}}$ gene caused another outbreak at the Saint George Hospital of Beirut between the years 2004 and 2005 [51]. Even though the *Acinetobacter baumannii* strains causing these outbreaks were found to be multidrug resistant, they were still fully susceptible to tigecycline [21]. Nevertheless, the heavy dependence of several patients on multiple antibiotics in the ICU [52] may result in increased emergence of resistance among *Acinetobacter baumannii* strains.

3. Antimicrobial Consumption and Conclusion

Very few data is available regarding antibiotic consumption in Lebanon. A study by the ARMed group has shown that broad spectrum antibiotics (such as 3rd generation cephalosporins and quinolones) are extensively consumed in this country, where more than 15% of the total national consumption consists of quinolones [12]. A high rate of consumption of 3rd generation cephalospirins has been shown to be a major risk factor for the development of resistance [11]. Therefore, the high rates detected in Lebanon poses a great threat, where resistant strains will keep on increasing and making treatment progressively harder [53]. Moreover, the haphazard distribution, easy availability of antibiotics, lack of stewardship programs, and proper record keeping in Lebanese hospitals aggravates this problem even more [16]. One step towards limiting the emergence of resistant bacterial strains would be to encourage the hospitals to calculate their consumption of antibiotics and study its possible correlation with bacterial resistance. Many softwares and applications

such as "ABCcalc" and "WHOnet" are made available for this purpose. These programs are easily installed and allow hospitals to track the antibiotic consumption and the emergence of resistant strains throughout the year. This information may prove to be extremely valuable in the constant struggle to decrease the emergence of resistance in Lebanon.

In conclusion, the widespread antibiotic abuse and misuse has been a major driving factor for the high rate of resistance found in Gram-Negative Bacilli isolated in Lebanon [16, 24]. Antibiotic stewardship programs are urgently needed since their continued absence would only result in sustaining the increasing rates of resistance and an ever increasing difficulty in their treatment. Several additional studies that stretch beyond the scope of single-center studies are needed as well in order to shed light on the prevalence of resistance across the country. Nevertheless, few novel studies targeting endogenous plants are being conducted in Lebanon in an attempt to discover new molecules that exert antibiotic activity [54, 55]. Whether these attempts would be successful and helpful in the ongoing effort to combat resistant strains remains to be unveiled.

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