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Multi Drug Resistant Gram Negative Pathogens in Long Term Care Facilities: A Steadily Arising Problem

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Abstract

Multidrug resistant bacteria are currently considered as an emergent global disease and a major public health problem. Since the elderly population increases along with people with other disabilities, long term care facilities (LTCFs) is becoming a need. The arising incidence of infections in LTCFs especially from multidrug resistant bacteria is attributed to the transfer of patients from the hospitals to LTCFs and from the LTCFs to the hospitals or the community as well. Recognizing the fact that LTCFs are considered as a reservoir of bacterial resistance, identification of patients at risk and strict implementation of infection control measures must be implemented.

Introduction

The emerging threat of multidrug resistant negative bacteria (MDR-GNB) in all healthcare settings is a well-recognized problem. Since the populations of developed countries are becoming increasingly elderly, the frequency of chronic diseases and disabilities necessitate special institutional care. The rate of infections in long term care facilities (LTCFs), reaches that of acute care facilities. In various studies the prevalence rate of the infections in LTCFs ranged from 2.8% to 32.7% and incidence rates from 1.8 to 13.5 infections per 1000 resident days [1].

This is explained by the fact that infected or colonized patients from acute care facilities are transferred to LTCFs, or patients from LTCFs are transferred to hospitals or the community as well [2,3]. So resistant bacteria can be transported from LTCFs back to the acute care facilities or can find their way into the community. Inappropriate and excessive use of antibiotics lead to select pressure of bacteria and confers to antibiotic resistance [4]. Once endemic, the antibiotic resistance genes can be transferred from one patient to another and from one species or genus to another on mobile genetic elements [5].

Gram negative organisms especially the extended spectrum beta lactamases (ESBL) and carbapenemases producers, express a real threat in all healthcare settings and poses the need to identify patients at risk and intensify infection control practices.

Epidemiology of MDR-GNB in LCTFs

Extended spectrum beta lactamases (ESBL) are beta lactamases capable of conferring bacterial resistance to the penicillins, first, second and third generation cephalosporins and aztreonam (but not cephamycins and carbapenems) by hydrolysing these antibiotics. They are inhibited though by beta lactamase inhibitors such as clavulanic acid. Over 75 ESBL are currently recognized and most of them are derived from TEM-1, SHV-1 and OXA beta lactamases. The first two are the most common beta lactamases found in enteric bacilli. Horizontal transfer of beta lactamase resistance on plasmids in *E. colli* and *Klebsiella pneumoniae* can result in the dessimination of resistance genes in nursing facilities. These mobile genetic elements often carry resistant determinants against many antibiotics (eg. aminoglycosides, tetracyclines) [6].

The first reported outbreak in the United States of bacteria resistant to ceftazidime, occurred among residents in a chronic care facility in Massachusetts in late 1988 [7]. Ceftazidime resistance resulted from two distinct extended spectrum beta lactamases of the TEM type. Genes encoding these enzymes were present on different antibiotic resistant plasmids. Using agarose gel electrophoresis of extracts from clinical isolates, the authors proved that the outbreak arose from plasmid transmission among different strains of the family Enterobacteriaceae.

Another outbreak from ceftazidime resistant *Klebsiella pneumoniae* strains recovered at the Cleveland Department of Veterans Affairs Medical Center [8]. The highest rate of resistance occurred on wards where ceftazidime used more frequently. The findings from pulsed field gel electrophoresis (PFGE) showed that most of the isolates derived from the original clone.

In a study of ceftazidime resistant *E. coli* and *Klebsiella pneumoniae* in 8 nursing homes in Chicago, 31 of 35 patients harbored an ESBL-producing enteric pathogen [9]. All strains were resistant to ceftazidime, to gentamicin and tobramycin, 96% were resistant to trimethoprim-sulfamethoxazole and 41% to ciprofloxacin.

The in vitro susceptibilities of 52, 637 *Pseudomonas aeruginosa* isolates deriving from 29 laboratories in the United States, were evaluated. These strains derived from intensive care unit (ICU) and non-ICU patients, from outpatients and from nursing home residents [10]. The authors found that the multidrug resistance rate was highest in isolates from patients in nursing homes (29.9%) and ICU (29.5%).

A study conducted by Erin O' Fallon at the Hebrew Rehabilitation Center in Boston, reveals the arising problem of MDR in LTCF. For a two year period the authors collected clinical isolates from residents of a 750 bed LTCF and analyzed them for MRSA, VRE and MDR-GNB. They concluded that MDR-GNB were isolated more frequently than methicillin resistance *Staphylococcus aureus* (MRSA) and vancomycin

resistant *Enterococcus* (VRE) with increasing prevalence from 7% in 2003 to 13% in 2005 (p=0.01). Additionally, more than 80% of MDR-GNB isolates were resistant to ciprofloxacin, trimethoprim-sulfamethoxazole and ampicillin/sulbactam [11].

Data from an Italian LTCF confirm the presence of high percentage (51.8%) of ESBL Enterobacteriaceae among catheterized inpatients with predominance of CTX-M type ESBL *E.coli*. [12] Another point-prevalence study which was conducted in four co-located LTCFs in Australia, [13] poses the emerging problem of MDR-GNB since their prevalence was 21% instead of MRSA and VRE which were 16% and 7% respectively. The high percentage of ESBL producers gram negative pathogens compared to MRSA and VRE, confirm the Frankfurt HALT plus MDRO project 2012 where the prevalence of ESBL in clinical isolates from residents in 8 LTCFs were 26.7% whereas the prevalence of MRSA was 9.2% and VRE 2.7% [14].

Similar results were published by March et al. [15]. The rates of colonization in residents of an Italian LTCF were 64% for ESBL produces gram negative pathogens and 38.7% for MRSA. Current prevalence of multidrug-resistant organisms in long-term care facilities in Rhine-Main district in Germany is remarkably high and exceeds the rate of 17.8% [16]. Concerning carbapenemase producers gram negative bacteria which have steadily increased worldwide, a few studies regarding the epidemiology in LTCFs have been published.

An outbreak from *Klebsiella pneumonia* producing KPC karbapenemase was described in a long term acute care hospital in South Florida [17]. Seven KPC strains were isolated from different patients isolated to a single Long Term Acute Care Hospital (LTACH) with a further three isolates recovered from patients at different hospitals. All KPC-*Klebsiella pneumoniae* isolates shared the same PFGE pattern and showed high resistance to carbapenems (MIC>32 mg/lL)

An epidemiological survey concerning antimicrobial resistance among gram negative organisms recovered from patients of LTCF, revealed imipenem resistance of 6% for *Klebsiella pneumoniae* species [18].

Twelve strains of *Klebsiella pneumonia* that exhibited non susceptibility to extended spectrum cephalosporins, collected from residents in LTCF for children and young adults in Ohio, were further analyzed. Reassessment of carbapenem MICs using recently revised breakpoints, uncovered carbapenems resistance. Genetic analysis revealed that a single sequence type not previously reported to contain bla kpc, had disseminated in Northeast Ohio in this LTCF [19].

On January 2011 in West Virginia, a cluster of carbapenem-resistant *Klebsiella pneumoniae* cases were detected in a local hospital. The outbreak was associated with admission from or prior stay at a LTCF [20]. *Acinetobacter baumannii* is an increasingly common pathogen in health care settings with an emerging resistant pattern during the past decade. *Acinetobacter* infections in LCTF and in older adults though, are not well described.

A study conducted in Community Hospitals and Nursing Homes in Ohio [21], showed that during a 6 year period *Acinetobacter* prevalence increased 25%. Although resistance was stable in community acquired isolates (resistance to a mean of 4.2 ± 2.2 antibiotic classes), resistance increased among nursing home-acquired and nosocomial-acquired isolates after adjustment for age, length of stay and origin, resistance to each additional antibiotic predicted a >20% increased risk for discharge to higher levels of care or death.

Acinetobacter baumannii isolates that collected from residents of an LTCF in Richmond California during a 2 year period, were all MDR. Their prevalence was significantly higher than that found among isolates from hospital patients [22].

There are two reports from Greece concerning the emergence of MDR-GNB in LTCFs. The first one took place at the University Hospital in Larissa in Central Greece. The authors studied ten *E. coli* carabapenemases producers (KPC-2), isolates derived from seven patients. Six of them had previously been treated for prolonged time period in a LTCF located in the same city [23].

The second study describes the epidemiology of bloodstream infections and sepsis in Greece for a 7 year period. Thirty one hospitals participated in this study including departments of internal medicine, general surgery and ICU as well. Using logistic regression analysis the authors found that residence in a LTCF is an independent risk factor for the occurrence of infections by multi-drug resistance pathogens [24].

Risk factors

Factors associated with the emergence of resistant pathogens in LTCFs are: Transfer of patients from a tertiary care institution who are colonized or infected with multi-resistant bacteria, excessive use of broad spectrum antibiotics that select for the emergence of resistant strains, gastrostomy feeding tubes, pressure ulcers, malnutrition, immunosuppression (age and medication-related), prior antibiotic use (Table 1) [25-27].

Transfer of patients from an acute care institution who are colonized or infected with MDR-GNB
Use of broad spectrum antibiotics
Use of invasisve devices (urinary catheters, gastrostomy feeding tubes)
Pysical disability
Chronic obstructive pulmonary disease
Dementia
Fecal incontinence
Malnutrition

Table 1: Risk factors associated with MDR-GNB in LTCFs.

The importance of transferring patients colonized or infected with multiresistant pathogens from hospital to LTCF is described by Strausbaugh et al. [28]. The authors also point serious underlying conditions, poor functional status, wounds such as pressure ulcers, invasive device such as urinary catheters and prior antimicrobial therapy, as significant risk factors for acquisition of multiresistant pathogens. In a case control study Sandoval et al. [29] showed that exposure to any cephalosporin and log percentage of residents in a LTCF using gastrostomy tubes, were associated with clinical isolates resistant to third generation cephalosporins.

Risk factors for harboring MDR-GNB in a 750 bed LTCF followed for a 2 year period, include pressure ulcers, poor functional status, advance dementia and antimicrobial exposure [11] Age>85 years, antibiotic treatment in the previous 3 months, indwelling devices, chronic obstructive pulmonary disease, physical disability and

dementia, are defined as risk factors for MDR-GNB colonization in residents of a geriatric clinic [15].

In a point prevalence study in 4 separate wards at a 600-bed urban LTFC risk factors such as length of hospital stay of at least 4 years, fecal incontinence, and antibiotic exposure for at least 8 days, were independent risk factors associated with harboring MDR-GNB among the residents [30] Patients with decubitus ulcer had a higher risk of colonization by at least one resistant strain ($p<0.001$) in a study conducted by Arnoldo et al. [12]. Furthermore, patients undergoing antibiotic therapy and patients with decubitus ulcer, showed a higher risk ($p<0.005$) of colonization by beta-lactam resistant microorganisms.

In Germany, 288 patients from 2 geriatric clinics, 8 nursing homes and 2 ambulant care facilities as well as 64 staff members were screened for MDR bacteria. Risk factors were found to be immobility, urinary catheter, former hospitalization and decubitus ulcer [31] Wound management during the preceding three months before study enrolment, pressure ulcer, and prolonged antibiotic use (>14 days), are defined as significant risk factors in a study conducted by Ching Jou Lim in LTCFs (13).

The high level of care and the presence of chronic wounds are describing as independent risk factors for inguinal skin colonization with MDR pathogens among residents of elderly care facilities [32].

Infection Control Measures

To control the spread of MDR-GNB, numerous interventions must be applied (Table 2). It is well understood that hand hygiene is the mainstay of an infection control program. Person to person transmission via the hands of healthcare workers appears to be the most important means of spread [33]. Hand washing before and after touching the patient or the surrounding environment, seems to be the most important way to decrease the colonization and infection of staff and patients [34].

Source identification
Early recognition of patients colonized or infected with MDR pathogens
Stop transmission among patients
Apply standard and contact precautions (barrier precautions, use of gloves and gowns, dedicated equipment), emphasizing on hand hygiene
Control antibiotic use

Table 2: Control measures against MDR-GNB in LTCFs.

Identification of patients colonized or infected with MDR-GNB using appropriate detection method in the clinical microbiology laboratory, is mandatory [35,36]. Using rectal swabs plated into selective media helps to identify colonized patients [6].

Since the identification of patients completed, contact precautions measures must be implemented. This implies use of gloves and gowns when contacting with the patient. The compliance to these precautions must be high in order to maximize the effectiveness. Isolation rooms are also recommended for patients harboring carbapenemases positive and ESBL positive gram negative bacteria with the exception of *E. coli* ESBL(+) [37]. Since environmental source for MDR-GNB has occasionally been described such as ultrasonography coupling gel or blood pressure cuff, regular cleaning procedures using detergents or disinfectants must be applied [38,39]. When available, dedicated non critical medical items for use on individual patient infected or colonized with MDR-GNB, must be used [35].

The overuse and misuse of antibiotics was mentioned as one of the most important risk factors for acquiring MDR-GNB. Rice et al proved that restriction policy for ceftazidime decreased ceftazidime resistant organisms [7,8]. On the other hand, exposure to >7 days of quinolones and third generation cephalosporins, significantly increased the risk of ESBL producing bacteria in urinary tract infections [40]. Antibiotic stewardship programs and continuing education in medical and nursing staff concerning the infection control policies are also of great importance [41-43].

Conclusion

Multidrug resistant organisms represent an ever increasing share of causative agents of infection in LTCFs and their prevalence is now just as high as in acute care facilities, or even higher. Given the fact that LTCFs are now considered as a major reservoir of these bacteria, prompt identification of colonized or infected patients and implementation of strict infection control measures, are obviously mandatory.

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