Analysis of the Local Resistance Patterns of *Acinetobacter baumannii* in Relation to Empirical Therapeutic Regimens in Patients with Pneumonia

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**ABSTRACT**

The aim of the study was to analyze the different types of pneumonia (HCAP and HAP) caused by *Acinetobacter baumannii* in patients hospitalized in pulmonology and internal ward of Masovian Specialist Hospital in Radom (MSS) in 2012 to 2016. The incidence and drug sensitivity of these non-fermenting rods were evaluated and the compliance of anti-microbial procedure with the algorithm of the guidelines in applicable recommendations estimated. This should result in determining the local patterns of resistance and verifying therapeutic procedures in accordance with the assumptions of hospital antibiotic policy. In addition, the study examined the effectiveness of empiric and target therapy according to the clinical condition of the patient. We also compared the effectiveness of the eradication of *A. baumannii* with the aggravating factors of the patient condition.

**Key words:** *Acinetobacter baumannii*, antibiotic resistance, multi-resistant strains (MDR XDR).

**INTRODUCTION**

*Acinetobacter baumannii* as the etiological agent of infection has become one of the most troublesome pathogens for health care centers around the world. The clinical significance of this non-fermenting rod has grown over the last several years.

A key strategy of *A. baumannii* in hospital environment, like of other organisms is to acquire resistance to commonly used antibiotics. Moreover, minimum nutritional requirements allow *A. baumannii* to survive long in hospital environment. Its natural resistance to many chemotherapy agents as well as weakly expressed pathogenic abilities (opportunistic micro-organism) cause the bacteria to target mostly at patients with immune disorders and other risk factors for infection. In addition, elderly patients who are generally more susceptible to infection were reported to be admitted to hospital more often. According to data from the literature, major infections caused by this *A. baumannii* is pneumonia, bacteriemia, infection of skin, soft tissues and bones, urinary tract infection and late meningitis (Zhao et al., 2015; Hartzell et al., 2007; Poirel et al., 2006).

Currently, the biggest problem caused by *A. baumannii* infection is the presence of numerous multidrug-resistant (MDR) strains in hospital environment, which are often insensitive to carbapenems and responding only to colistin (XDR) (Tripathi et al., 2014; Mastoraki et al., 2008). Hence, there is a growing problem of lack of drugs which would struggle effectively against these micro-organisms, because strains resistant even to colistin (PDR) have been isolated from clinical material. In this study, all *A. baumannii* strains were sensitive to colistin.

Symptoms of pneumonia caused by *A. baumannii* do not differ from those caused by other bacteria, but the problem is that the antibiotics usually applied in pneumonia do not include in its spectrum *A. baumannii* infections. Another problem is the co-infection with other bacteria.
In order to standardize the criteria for diagnosing, monitoring and empirical antibiotics treatment, we present the definitions of pulmonary infections associated with health care:

- Health care-acquired pneumonia (HCAP) concerns patients who had contact with the hospital environment during the 90 days before the diagnosis of pneumonia, patients in nursing homes and hospices as well as those on dialysis, who in the last 30 days were treated with intravenous antibiotics, those who received chemotherapy were treated for wound infection or underwent any other regular medical treatments;

- Hospital acquired pneumonia (HAP), which develops within forty-eight hours of hospitalization, excluding pre-incubating infection. These infections are ranked as severe, with high mortality rate (Qi et al., 2015; Torres et al., 2010; Romanelli et al., 2009).

**Treatment**

According to the prepared "Guidelines on diagnosis, therapy and antibiotic prophylaxis of hospital infections" (Hryniewicz et al., 2015), the strategy should take into account the etiology of infection and risk factors that is, the overall condition of the patient, liver or renal failure and other health disorders which are of great importance to the choice and dosage of antibiotics.

The patients were admitted to two different wards depending on the severity of the disease and aggravating factors. The patients admitted to the pulmonology ward had more severe pneumonia, suffered from respiratory failure and some of them required mechanical ventilation, whereas qualification for the internal department was based on the assessment of the severity of concomitant diseases.

In all cases you should consider the risk of infection with multi-resistant micro-organisms which increases with the time of hospitalization, previous antibiotic therapy and when a patient undergoes invasive therapeutic procedures or stayed in an Intensive Care Unit (ICU). In these patients, treatment options drawn from the recommendations should be adjusted according to the knowledge of the local resistance to antibiotics.

When empiric treatment proves inefficient, the diagnosis and the aggravating factors should be verified and the method of treatment reconsidered, taking into account the results of microbiological test.

**Therapeutic regiment**

Schemes of antibiotic therapy in hospital acquired pneumonia (HAP) and healthcare acquired pneumonia (HCAP) are difficult to predict. For this reason, it is recommended to do microbiological tests before the application of an antibiotic. Diagnostic methods and treatment of both infections are similar (Falconet et al., 2015).

**Presumed bacterial etiological factor as the basis for recommendations for empiric therapy**

In the case of health care acquired pneumonia (HCAP) in patients residing in nursing homes, infections are more likely to be caused by Gram-negative rods than by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus* and in dialysis patients by *S. pneumoniae*, *P. aeruginosa*, *Klebsiella* spp and *H. influenzae*. The same applies to patients hospitalized less than a month.

Patients with low risk of infection with a bacterial multi-resistant strain should be treated with: ceftriaxone 1 g or ciprofloxacin 2 × 400 mg. Whereas those more exposed to multi-resistant strain infection should be given one of the following drugs: ceftazidime 3 × 2 g IV, piperacillin-tazobactam 4 × 4.5 g IV, imipenem 4 × 0.5 g IV or 3 to 4 × 1 g meropenem 3 × 1 g IV and cefepime 2 to 3 × 1 to 2 g IV. Therapeutic options are according to national guide (Hryniewicz et al., 2015).

**MATERIALS AND METHODS**

The subjects of microbiological and therapeutic analysis were patients whose etiological factor of infection was *A. baumannii* as the only micro-organism isolated or those with concomitant infection. Microbiological analyses were performed on 142 strains of *A. baumannii* derived from 142 patients and 45 isolates of other species which additionally accompanied 45 patients, as a second causative agent of the infection. All the subjects were treated in MSS between 2012 and 2016. Test materials were those routinely collected for diagnostics. These were the secretions from the lower respiratory tract (sputum, BAL – bronchoalveolar washings) obtained from patients from pulmonology and internal wards. For the analysis of *A. baumannii* strains, we applied the principle of one strain equal a patient.

In the case of severe course of inflammation of the lower respiratory tract (ILRT), severe sepsis or septic shock, microbiological diagnostics also included blood. Accordingly, 5 patients showed growth of *A. baumannii* in blood. The cultures were grown in an automatic system BacT / Alert 120 (bioMerieux). From test materials received from the hospital wards direct preparations stained with Gram method were made. For further diagnostics, the samples were qualified according to the amount of purulent secretions (> 25 leukocytes /
neutrophils <10 epithelial cells in the visual field of the microscope.

Microbiological diagnostics of ILRT takes into account quantitative culture secretions. To diagnose pneumonia, it was essential to assess the number and morphology of the bacteria in the direct preparation and the fact of incubating from bronchial secretions collected with BAL method in the quantitative plating > 104 CFU / ml of bacterial strains. In the case of sputum - colonies meeting the criterion of “dominating” growth are diagnostic indications for pneumonia. The material was cultured in accordance with general principles of microbiological diagnostics. Standard bacteriological media (bioMerieux) was used. They included Columbia Agar with 5% sheep blood, McConkey agar, Chapman Agar and Chocolate Agar selective for Haemophilus spp. Incubation was conducted in aerobic conditions in a CO2 enriched atmosphere at the temperature of 36°C ± 1°C and bacterial growth was evaluated after 18 to 24 h. Then, after determining the morphology of the cultured colony and microscopic observation, the species were identified by means of commercial kit including ID GN Cards and Vitek 2 Compact (bioMerieux).

Determination of antibiotic susceptibility of isolated non-fermenting rods was made by three methods: the disc diffusion (Kirby-Bauer), which uses discs (from Oxoid), gradient diffusion E-test and using an automatic camera Vitek 2 Compact, which uses cards with a set of antibiotics for Gram negative (bioMerieux).

A. baumannii isolates insensitive to carbapenems were examined with EDTA test for MBL (metallo-beta-lactamasases) presence and with test with boronic acid for KPC (Klebsiella pneumoniae carbapenemase).

The method of determining drug sensitivity, resistance mechanisms and their interpretation were performed as recommended by EUCAST, the National Reference Centre for Antimicrobial drug-sensitivity Testing and according to the manufacturer’s instructions.

Methodology

The study was retrospective. The research was conducted from 2012 to 2016 at the selected departments of Mazovian Specialist Hospital in Radom. The study group included hospital patients with A. baumannii isolated from the lower respiratory tract and pneumonia symptoms. Detailed data on patient identification, the general condition of patients, risk factors for infection, diagnostic methods, diagnosed infections and a method of treatment were taken from the patients’ hospital records.

Pneumonia was diagnosed on the following basis: clinical manifestations observed in physical examination, laboratory results, microbial results, level of procalcitonin, leukocytosis or leukopenia, C-reactive protein concentration, a deterioration of gas exchange (of PaO2 / FiO2 ratio) and radiological tests chest X-ray and / or computer tomography. Non-fermenting Gram-negative rods were mostly isolated from MSS patients diagnosed using:

- Health care acquired pneumonia (HCAP);
- Hospital-acquired pneumonia (HAP).

RESULTS AND DISCUSSION

In the time and departments earlier mentioned, there were 4.655 inoculations done in 3.813 ILRT patients with suspected pneumonia. Most studies were performed for pulmonary unit – 4.310 (in 3.535 patients) and internal unit 345 (in 278 patients). The average number of days of hospitalization at pulmonology and internal departments is 27 and 18 days respectively.

There were 142 strains of A. baumannii isolated from 142 patients with clinically confirmed pneumonia. The percentage of patients with this etiological agent represented 3.7% of all patients with suspected ILRT. The test specimens were taken from 106 men and 36 women.

Comparative analysis of A. baumannii related pneumonia patients treated in pulmonary and internal unit was done due to the possible different origin and forms of infection (HAP and HCAP), different therapeutic regimens and different risk factors. The patients were admitted to pulmonology ward depending on the severity of pneumonia, the degree of respiratory failure and a probability of using mechanical ventilation. Qualification for the internal department was based on the assessment of the severity of concomitant diseases.

Most A. baumannii was detected in cultures from patients in the internal ward - 86 strains (2.3% of all patients with ILTR infection) and 56 isolates in pulmonology ward (1.5%). In five patients from pulmonology departments positive blood culture results were obtained. They showed increase in strains of A. baumannii. In these cases, the mortality rate was 100%.

Aggravating factors of the study group were analyzed. The average age was 71 years in pulmonology - 69 to 72 years in internal patients). In the vast majority of hospitalized patients (n = 124; 87%) respiratory failure was recorded on admission to hospital. 36 patients (25%) required artificial ventilation, including 15 patients in the first days of hospitalization. Circulatory failure occurred in 88 patients (62%) and renal failure in 20 patients (14%). In addition, 35 persons (25%) suffered from diabetes, 10 patients (7%) from obesity, 17 patients (12%) from cancer, 14 patients (10%) from alcohol addiction and 50 patients (35%) from nicotine addiction. Antibiotic treatment within 3 months before admission was confirmed by 30 patients (32%). All pulmonology patients (n = 56) and 59 out of 86
internal patients confirmed being hospitalized within 90 days before the subsequent admission to MSS.

**HCAP - analysis of the results**

HCAP was diagnosed in 56 out of 142 patients included in the study group (18 - pulmonology and 38 internal patients).

**Result analysis**

Eighteen HCAP patients were admitted to pulmonology ward, 11 had *A. baumannii* isolated in monoculture (61%) and 7 patients had *A. baumannii* and *S. aureus* MSSA (mecillin sensitive *S. aureus*) (n=3; 17%) as well as *Escherichia coli* (n=4; 22%), which represents 39% of coinfection.

In internal wards, HCAP was diagnosed in 38 patients. From clinical samples, 24 patients had *A. baumannii* grown in monoculture (63%) and 14 patients had a co-infection (37%) caused by MSSA (n = 3; 8%), *S. aureus* MRSA (Mecillin-resistant *S. aureus*) (n = 3; 8%), *S. marcescens* (n = 4; 10.5%) and *P. aeruginosa* (n = 4; 10.5%) (Figure 1).

**Drug - resistance of cultured strains**

In 56 isolates of *A. baumannii* cultured from HCAP patients in pulmonology ward (n=18) and internal ward (n=38), there was 80 to 90% resistance to piperacillin, tobramycin, levofloxacin, trimethoprim / sulfamethoxazole and to drugs recommended for empirical therapy in patients with HCAP, that is, piperacillin/ tazobactam, ceftazidime, cefepime and ciprofloxacin (Figure 2). Most alarming were HCAP patients
from pulmonary ward who within the first few days in hospital were diagnosed with *A. baumannii* 100% resistant to piperacillin, piperacillin/tazobactam, ceftazidime, cefepime, tobramycin, ciprofloxacin and levofloxacin.

Gentamicin resistance ranged from 40 to 42%, whereas amikacin showed even lower activity against *A. baumannii* with 64% resistance in internal ward patients. In pulmonary, the percentage of resistant strains to amikacin was similar to that of gentamicin, that is, 40%.

HCAP pulmonology patients showed the highest resistance to carbapenems, meropenem and imipenem (80%), whereas in HCAP internal patients these drugs showed higher activity, as resistance developed in 58%.

Analysis of ampicillin / sulbactam sensitivity showed that the drug proved to be ineffective in 40 to 42% of HCAP pulmonology and internal patients. Our study also aimed at determining the drug resistance of the remaining, other than *A. baumannii* strains isolated from HCAP patients to recommended antibiotics which should be used.

The strains causing co-infection in the study group with HCAP showed low resistance percent to the recommended empirical drugs.

All strains isolated from HCAP pulmonary patients had no resistance to piperacillin/tazobactam, cefotaxime, ceftazidime, cefepime, imipenem and meropenem, while 50% of the strains showed resistance to the ciprofloxacin, whereas strains isolated from HCAP internal patients displayed low percentage of resistance to cefotaxime, cefepime, imipenem, meropenem and ciprofloxacin and 50% were resistant to piperacillin/tazobactam and ceftazidime (Figure 3).

### Analysis of the applied empirical treatment

In pulmonary ward, empirical treatment was applied to all 18 patients with HCAP (Table 1). The drugs included amoxicillin with clavulanic acid \( (n = 7) \), ciprofloxacin + clindamycin \( (n = 7) \) and ciprofloxacin + cefuroxime \( (n = 4) \). However, these therapies proved ineffective to *A. bauma-
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Figure 4: Application of target therapy and clinical improvement in patients with HCAP. SAM: Ampicillin / Sulbactam, GE: Gentamicin, AN: Amikacin, COL: Colistin, CIP: Ciprofloxacin and MEM: Meropenem.

HAP - analysis of the results

There were 38 patients in pulmonology ward and 48 patients in internal ward diagnosed with HAP. A. baumannii was isolated from the monocultures of 63% of HAP patients (24 patients). At the same time, 14 A.baumannii positives patients had associated infection caused by E. cloacae (n = 4; 10.5%), E. coli (n = 4, 10.5%), K. pneumoniae (n = 4; 10.5%) and P. aeruginosa (n = 2; 5%), which accounted for 36% of co-infection in this group.

In the internal ward, A. baumannii as a single etiological factors accounted for 79% HAP (38 patients). Confection occurred in 21% of cases and was caused by A. baumannii and K. pneumoniae - 7 isolates (15%) or C. freundii - 3 isolates (6%) (Figure 5).

Drug sensitivity of cultured strains

In terms of drug resistance, 86 strains of A. baumannii extracted from HAP patients in pulmonology (n = 38) and internal ward (n = 48) were examined. It was found that the isolates had over 90% resistance to the following drugs: piperacillin, tobramycin, levofloxacin, trimethoprim / sulfamethoxazole and the drugs recommended for empiric therapy in patients with HAP mentioned piperacillin/tazobactam, ceftazidime, cefepime and ciprofloxacin. Yet, most alarming was the fact that HAP patients who stayed in internal ward for 3 or more days were detected with A. baumannii which was 100% resistant to piperacillin, piperacillin/tazobactam, ciprofloxacin,
trimethoprim / sulfamethoxazole and those in pulmonary ward – to ceftazidime. *A. baumannii* strains were resistant to gentamicin in 35% of HAP patients in pulmonology and 57% patients in the internal ward.

The second considerable aminoglycoside amikacin showed less activity against *A. baumannii*, as 64% all patients of both departments were found resistant to it.

In the case of carbapenems, both meropenem and imipenem showed higher resistance in HAP of pulmonary patients’ ward (45%) as compared with those of HAP / internal medicine ward (36%).

Ampicillin / sulbactam showed less efficacy in pulmonary HAP patients (64% resistant strains) than in internal patients (39% of resistant strains) (Figure 6). All strains tested showed 100% *in vitro* sensitivity to colistin. None of the examined isolates produced metallo-beta-lactamase (MBL) or carbapenemase type KPC. Same as in patients with HCAP, we also studied drug resistance of micro-organisms causing co-infection in patients with HAP to the antibiotics recommended for empirical therapy.

It was observed that the strains causing co-infection in HAP pulmonology patients had high resistance to the drugs recommended for empirical treatment. Resistance to ceftazidime and cefepime has not been reported but 25% of the culture was resistant to piperacillin/tazobactam, cefotaxime and ciprofloxacin.

The strain detected in HAP internal patients exhibited much higher resistance (67%) to piperacillin/tazobactam, cefotaxime, ceftazidime and cefepime and additionally 34% of cultures appeared resistant to fluoroquinolone – ciprofloxacin. Strains resistant to the carbapenems have not been found (Figure 7).
Analysis of the empirical treatment

In 38 pulmonology patients, combined antibiotic empirical therapy was used. It included amoxicillin with clavulanic acid associated with ciprofloxacin (n = 12) or metronidazole (n = 8), or trimethoprim / sulfamethoxazole with amikacin (n = 3), or amikacin with clarithromycin (n = 3), further cefuroxime and metronidazole (n = 3), ciprofloxacin combined with amikacin (n = 3) or cefuroxime (n = 3) and ceftazidime + imipenem + amikacin (n = 3).

47 internal patients were implemented antibiotic empirical therapy including amoxicillin / clavulanate (n = 4) or the combination of beta-lactam antibiotic ciprofloxacin (n = 20) or ciprofloxacin and clindamycin (n = 8), ciprofloxacin (n = 4) and ciprofloxacin + clindamycin (n = 11) (Table 2).

In five cases, ciprofloxacin showed activity against individual strains of *K. pneumoniae* and *C. freundii*, which caused their eradication: One patient had target therapy applied instead of empirical treatment (report on microbiological examination was delivered from another ward). In this case, they implemented colistin which eradicated *A. baumannii*.

In neither case, did empirical therapy lead to the improvement of the patient’s condition or the eradication of *A. baumannii* or accompanying micro-organisms.

The analysis of target therapy

In pulmonary ward, 25 HAP patients applied treatment in accordance with antibiogram, that is, meropenem (n = 3), meropenem combined with gentamicin (n = 3), imipenem

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**Table 2**: Empirical treatment applied in patients with HAP in pulmonology and internal department.

<table>
<thead>
<tr>
<th>Pulmonology</th>
<th>HAP (n=38)</th>
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<th>Internal</th>
<th>HAP (n=48)</th>
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<td>n=38-number of patients</td>
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<td>Applied empirical treatment</td>
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<tr>
<td>AMC+CIP</td>
<td>12</td>
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<td>AMC</td>
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<tr>
<td>AMC+MET</td>
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<td></td>
<td>AMC+CIP</td>
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<td></td>
<td>AMC+CIP+CC</td>
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<tr>
<td>AMC+AN+CLA</td>
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<td>CAZ+AN+IMP</td>
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**Figure 7**: Drug-resistance of co-infection inducing strains cultured from patients with HAP. TZP: Piperacillin / Tazobactam, CTX: Cefotaxime, CAZ: Ceftazidime, FEP: Cefepime, IMP: Imipenem, MEM: Meropenem, CIP: Ciprofloxacin and n: Number of patients.
Figure 8: Clinical improvement in patients with HAP who were applied target therapy. **GE:** Gentamicin, **MEM:** Meropenem, **IMP:** Imipenem, **CIP:** Ciprofloxacin, **SAM:** Ampicillin / Sulbactam, **COL:** Colistin and **n:** Number of patients.

with gentamycin (n = 3), ciprofloxacin (n = 3) and colistin (n = 13). The therapy proved successful in 14 patients, one patient required respirator and in 14 other cases the pathogens were eradicated with meropenem (n = 4), imipenem and gentamicin (n = 4), ciprofloxacin (n = 2) and colistin (n = 4). 13 patients died before empirical antibiotic therapy and the other seven died despite the application of target therapy (including 10 patients who required artificial ventilation).

Twenty-eight patients underwent target therapy: meropenem (n = 4), meropenem with gentamicin (n = 4), imipenem and ampicillin / sulbactam (n = 4), ampicillin / sulbactam gentamicin (n = 1), colistin (n = 7) or a combination of the drug with meropenem (n = 5), or gentamicin (n = 3). The treatment was effective in 21 patients and in seven (7) other cases it ended up with death despite such active drugs as meropenem (n = 4), colistin (n = 3). 20 patients died before the introduction of target therapy. None of the patients in HAP study group (48 persons) was applied artificial ventilation (Figure 8).

**Conclusions**

The results obtained in this study showed that infections under study caused by **A. baumannii**, were caused mainly by multi-resistant strains and therefore it is necessary to draw up local scheme for empirical treatment when infection with these bacteria is suspected (Bassetti et al., 2016; Ren et al., 2016; Senok et al., 2015).

The differences between the degrees of resistance (> 80 to 90%) to most medications are insignificant. A significant discrepancy in activity was observed for carbapenems. In pulmonology patients with HCAP we observed high resistance (80%) to meropenem and imipenem as compared to patients with HAP (45%). However, internal ward patients with HCAP showed 58% resistance compared to 36% in HAP patients. Particular groups of patients showed different resistance to ampicillin/sulbactam. The highest level was noted in patients with HAP in pulmonology ward (64%).

Other patients showed lower resistance to the beta-lactam antibiotic: 39% (internal HAP patients) 40% (pulmonology HCAP patients) and 42% (internal HCAP patients).

These findings confirm the reports which indicate that patients whose condition was additionally deteriorated by old age, chronic respiratory disease, cardiovascular diseases, metabolic diseases, renal or liver failure and were hospitalized or previously treated with antibiotics, are more likely to have drug - resistant micro-organisms (Schiaroli et al., 2015; Ben et al., 2011).

Our study led to the conclusion that the incidence of infection caused by more than one bacterial factor ranged from 21% (patients with HAP internal) to 39% (patients with HCAP pulmonology). Other reports also indicate that the incidences of pneumonia caused by more than one bacterial species are very often. Their number is escalating especially in the case of patients with acute respiratory distress syndrome (ARDS) (Niederman et al., 2005).

In the case of suspected nosocomial pneumonia, empirical treatment is recommended. Before the therapy the patients should be tested for the most likely etiologic agent of infection. When choosing the right antibiotic and its dosage, certain risk factors affecting the patient's condition such as liver or kidney failure and other disorders should be taken into consideration (Bogomolova et al., 2014).

In the considered cases of pneumonia caused by co-infection with multi-drug-resistant, gram-negative strains
were usually associated with more severe and prolonged course of the disease.

It was noted that the recommendations for empirical treatment were not always respected. It should also be stressed that amoxicillin with clavulanic acid is often overused in the treatment of late nosocomial infections. Unfortunately, this type of beta-lactam antibiotic against hospital pathogenic bacteria which are usually multidrug resistant is not active. In addition, inadequate implementation of empiric therapy leads to the selection of resistant strains in the hospital environment as well as, in the physiological flora of the patient causing the destruction of the intestinal microflora, which might consequently lead to *C. difficile* induced infection.

It is noteworthy that, most empirical therapy showed no activity against the micro-organisms isolated from patients. Microbiological tests confirmed that *A. baumannii* strains selected from the lower respiratory tract were difficult to predict in terms of drug sensitivity, thus, the treatment should be done according to local susceptibility pattern.

For this reason, a target therapy against *A. baumannii* most often involved colistin or carbapenems (imipenem and meropenem). This procedure corresponds to the one already mentioned in the literature (Lee et al., 2016; Ali et al., 2015).

In our study group, in spite of the application of the target antibiotic therapy, some patients died due to severe condition caused by primary diseases which aggravated the patients' immunological system.

All strains tested showed sensitivity to colistin. This polymyxin belongs to the antibiotics of the last resort in infections triggered by multidrug-resistant *A. baumannii* strains and as such we should be extremely careful with its implementation as the strains resistant even to this drug have already emerged (Kuziemski et al., 2015; Okonomou et al., 2015).

REFERENCES


