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Zoran Gluvić[1,†], Bojan Mitrović[1], Biljana Radojević[2], Andrej Krasnjuk[3], Miloš Panić[4], Predrag Miličević[4], Miodrag Vukčević[5], Ratko Tomašević[6], Biljana Putniković[4], Aleksandar N. Nešković[4]

Initial respiratory specimen bacteriology and isolates susceptibility to antimicrobials in promptly intubated Chronic Obstructive Pulmonary Disease Adults – single-center two-year experience

Приказ иницијалне бактериологије узорака респираторног тракта и осетљивости бактеријских изолата према антимикробној терапији код ургентно интубираних адулта са хроничном опструктивном болешћу плућа – двогодишње искуство једног центра

[1]Clinic of Internal Medicine, Medicine ICU, Zemun Clinical Hospital Center, Belgrade, Serbia;
[2]Section for Clinical Pharmacology, Zemun Clinical Hospital Center, Belgrade, Serbia;
[3]Department of Laboratory Diagnostics, Microbiology Laboratory, Zemun Clinical Hospital Center, Belgrade, Serbia;
[4]Clinic of Internal Medicine, Department of Cardiology, Zemun Clinical Hospital Center, of Belgrade, Serbia;
[5]Clinic of Internal Medicine, Department of Chest Medicine, Zemun Clinical Hospital Center, Belgrade, Serbia;
[6]Clinic of Internal Medicine, Department of Gastroenterology, Zemun Clinical Hospital Center, Belgrade, Serbia

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†**Correspondence to:**
Zoran Marko GLUVIĆ
Clinic of Internal Medicine, Medicine ICU,
Zemun Clinical Hospital Center, Vukova 9, 11080 Zemun, Serbia;
E-mail: **zorangluvic@yahoo.com**

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SUMMARY

Introduction/Objective Chronic obstructive pulmonary disease (COPD) exacerbation is mostly triggered by infectious agents and seriously compromises the patient's quality of life and predicts a poor outcome of the disease as well. If the signs of the probable bacterial cause of COPD exacerbation are presented in an intubated patient, initial antimicrobial management must be launched. Depending on the results of the respiratory system sample cultures, the initial antimicrobials can be changed or continued.

The objective of this study is to present in-hospital suggestions regarding the use of the initial antimicrobial management of urgently intubated COPD adults with the probable bacterial cause of exacerbations, considering the source of bacterial acquisition (i.e. facility- or community-acquired bacteria).

Methods The cross-sectional study covered 51 patients urgently intubated on admission to the medical Intensive Care Unit of the Zemun Clinical Hospital Center during 2015/2016. The patients were divided into two groups: community-acquired (n = 26) and facility-acquired infection group (n = 25). The respiratory system samples were processed in the Microbiology Laboratory.

Results *Acinetobacter* and *Pseudomonas spp*. were the most frequently isolated bacteria in both groups, followed by *Staphylococcus aureus* and *Klebsiella spp.* as the third most frequent bacteria in the community- and facility-acquired group, respectively. The parallel use of tigecycline and aminoglycosides proved to cover a sensitive microbial spectrum in 52% of examinees of the community-acquired and 32% of examinees of the facility-acquired group.

Conclusion The present study suggests the initial management of intubated adults with probable bacterial infection-induced COPD exacerbation by the parallel use of tigecycline and aminoglycosides.

Keywords: COPD; Mechanical Ventilation; Anti-Bacterial Agents

САЖЕТАК

Увод/Циљ Погоршање хроничне опструктивне болести плућа (ХОБП) је најчешће узроковано инфективним агенсима, значајно компромитује квалитет живота оболелих и предиктује лош исход болести. Када постоје клиничко-лабораторијски знаци вероватне бактеријске инфекције као узрока погоршања, неопходно је код интубираног болесника одмах започети иницијални антимикробни третман. У зависности од резултата култура респираторних узорака, иницијални антибиотски третман може бити промењен или настављен. Циљ овог рада је представљање локалног водича за примену иницијалног антимикробног третмана промптно интубираног болесника са погоршањем ХОБП које је вероватно бактеријског порекла, узимајући у обзир болничко или ванболничко окружење.

Методе Студија пресека обухватила је 51 испитаника, који су по пријему у болницу одмах интубирани и механички вентилирани. Током 2015–2016 године сви испитаници су примљени у Јединицу интернистичке интензивне неге КБЦ Земун. Испитаници су подељени у две групе: групу 1 (26 испитаника), који су имали бактеријску егзацербацију из ванболничког, тј. групу 2 (25 испитаника) из болничког/домског окружења. Узорци респираторних течности (спутум, аспират) су обрађени у Микробиолошкој лабораторији.

Резултати У обе групе испитаника најчешће изоловане бактерије су *Acinetobacter* и *Pseudomonas spp.*, док је у групи 1 као трећа најчешћа изолована бактерија издваја *Staphylococcus aureus*, а у групи 2 *Klebsiella spp.* Комбинација тигециклин и аминогликозид покрива микробни спектар код 52% испитаника у групи 1, односно 32% испитаника у групи 2.

Закључак На основу спроведене студије, препоручује се иницијална антимикробна терапија истовременом применом тигециклина и аминогликозида код интубираних адулта са вероватном бактеријском инфекцијом као узроком егзацербације ХОБП.

Кључне речи: ХОБП; механичка вентилација; антибактеријски агенси

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic and progressive respiratory disease, frequently presented with different respiratory complaints, caused by airflow obstruction. Such an obstruction results from a damage to the airways, mainly due to an exposure to some harmful gasses and materials, infectious agents, etc. [1]. The stable course of COPD can be acutely disturbed (i.e. exacerbated), which requires additional management. The exacerbations that induce acute respiratory failure are considered serious. These serious exacerbations often require going to the Emergency or Chest Medicine Departments, or even to the medical Intensive Care Units (mICUs). When they persist, they occasionally require intubation and subsequent mechanical ventilation, described as invasive, which additionally aggravate patients' quality of life and predicts a poor outcome [2–5]. The most frequent causes of COPD exacerbations include mainly bacterial respiratory system infections [6].

A facility-acquired infection (FAI) is defined as a disease, which occurs up to 48 hours following hospital admission, but has not presented either during the incubation period or at the time of admission [7–10]. As far as COPD exacerbation is concerned, the 48-hour period is clinically very short for it to be defined as FAI for the purpose of this study, in order to distinguish it from bacterial colonization.

The management of the patient who experienced a highly suspicious COPD exacerbation of bacterial origin (according to the clinical and laboratory parameters) with antimicrobials is unequivocal. This is particularly true in cases requiring urgent intubation and mechanical ventilation. Initial antimicrobial management after proper and sometimes repeated sampling of respiratory system specimens is crucial for the outcome [11].

The purpose of this study is to determine the most frequent bacterial causes of serious COPD exacerbations and the susceptibility of facility- and community-acquired bacteria to the antimicrobial agents in patients admitted to mICU over the two-year period.

METHODS

This cross-sectional study included 51 patients, urgently intubated on admission to the mICU of the Zemun Clinical Hospital Center during 2015/2016. This study was done in accordance with standards of the institutional Committee on Ethics. The inclusion criteria were a medical record with the diagnosis of COPD, and an emergency indication for invasive mechanical ventilation (IMV). The exclusion criteria were the absence of the clinical and/or laboratory infection syndrome, negative bacterial findings of the respiratory system specimen cultures, COPD patients already covered by antimicrobial agents and a chest X-ray finding suggestive of pneumonia. The positive respiratory specimen (RS) culture conjoined with the presence of the clinical signs of infection (fever, an increase in the respiratory rate, progressive dyspnoea, purulent or changed sputum) and positive inflammatory markers (C-reactive protein, presepsin, procalcitonin, leucocytosis) were suggestive of infection. The colonization was defined as a positive RS culture with no clinical signs of infection and positive inflammatory markers [22]. The RS sampling procedures were conducted by experienced and well-trained mICU staff. After sampling, the material was forwarded to and duly managed by the Microbiology Laboratory staff. After detecting colony-forming units, the germs were identified, and, thereafter, the susceptibility to antimicrobials was tested. The examination of the germs' susceptibility to antimicrobial agents relies on the automated broth microdilution method and was conducted using the VITEK® 2 Compact (BioMerieux, France) device. The result is the precise measurement of the minimal inhibitory concentration (MIC) of the antimicrobial agents tested in the study. Using professional software, the device

classified the results into sensitive, intermediate, and resistant (SIR) categories for the tested antimicrobial agents that are presented on the card for every bacterial isolate. In the present study, the RS was initially examined after direct Gram staining using a microscope, then cultured on a proper growth medium (sheep blood agar plate, Mac Conkey agar plate, chocolate agar plate and Sabouraud agar plate) and incubated (24–48hrs at 37°C) in aerobic conditions, and in the presence of 5% CO2 for the Chocolate agar plate. For the purpose of rapid identification of bacterial isolates, Gram-positive (GP) and Gram negative (GN) device cards were used. As regards the antimicrobial susceptibility of the isolates, the device cards Antimicrobial Susceptibility Testing (AST) 76 and AST 240, and AST 580 and 592 were used in the cases of GN and GP isolates, respectively. Having determined MIC values, the device provided interpretation according to the standards of the Clinical and Laboratory Standards Institute and their recommendations for *cut-off* MIC values regularly updated by the relevant professional software.

The patients were divided into two groups depending on the incubation period (the time interval expressed in hours or days from the previous treatment episode in a Health/Care Facility to the current hospitalization). Group 1 – community-acquired infection (CAI Group) included 26 patients hospitalized for a COPD exacerbation probably caused by community-acquired bacteria, currently hospitalized from home, but beyond the incubation period. Group 2 included 25 patients hospitalized for a COPD exacerbation probably caused by facility-acquired bacteria (FAI Group), currently hospitalized from a healthcare facility or from home, but inside the incubation period.

For the purpose of this study, an arbitrary incubation period of two weeks was considered, despite the fact that it usually spanned 48 hours in literature [8]. The reason for extending the incubation period was to make a clear clinical distinction between colonization and FAI. This is of particular interest, because acutely deteriorated COPD patients are very

frequently hospitalized and almost never fully recovered due to the natural history of COPD and the presence of numerous co-morbidities. Thus, when satisfactory clinical improvement is achieved after in-hospital treatment, stabilized COPD patients are discharged home or referred to some other care facility outside the hospital.

Statistics

The data obtained was analyzed applying the methods of descriptive (relative numbers, arithmetic mean, standard deviation) and analytical statistics (t- test, $\chi^2$and Mann-Whitney test) by SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The level of statistical significance was 0.05.

RESULTS

The average study population age was 71 $\pm$ 10 (the 39–89 range) years. Of the 51 patients, 35 (69%) were males. There was no difference between groups in terms of age ($U = 246.00$; $p > 0.05$) and gender ($\chi^2 = 0.488$; $DF = 1$; $p > 0.05$). Table 1 shows the RS culture findings and Table 2 features the overall susceptibility of isolates to antimicrobial agents.

There was no difference in the bacteriology cultures findings ($\chi^2 = 10.295$; $DF = 8$; $p > 0.05$), and the overall isolates' susceptibility to antimicrobial agents between the groups ($\chi^2 = 13.729$; $DF = 9$; $p > 0.05$). Table 3 shows data classified per group. Table 4 shows the most frequent bacterial isolates in the groups, and antimicrobial agents, which they are susceptible to. The combination of tigecycline and aminoglycosides (i.e. amikacin) covered the microbial spectrum in 11 (52%) and seven (33%) patients in Group 1 and Group 2, respectively.

The mortality rates were 61% in CAI and 48% in the FAI group. The overall mortality rate of the study population was 55%. No difference was identified in the outcome of the COPD exacerbation episode between the groups ($\chi^2 = 0.943$; DF = 1; $p > 0.05$).

DISCUSSION

Our study revealed that the management with tigecycline and aminoglycosides (i.e. amikacin) covers the broadest possible microbial spectrum isolated from the RS of urgently intubated adults with an exacerbated COPD, regardless of the current habitat the patients are coming from. As these antimicrobial agents cover *Pseudomonas spp.*, they seem to be the appropriate initial antimicrobial combination, until the definite findings of RS culture are available to continue antimicrobial de-escalation. By repeated RS sampling (tracheobronchial aspirate and lavage), the findings of "negative" and sterile cultures, as well contaminated and colonizing germs, would be significantly reduced. That is why we have excluded all the patients with *Coagulase negative Staphylococci* with no signs of the infective/inflammation syndrome and no finding of *Coagulase negative Staphylococci* in repeated RS cultures.

Rapid methods for microbial identification, such as Polymerase Chain Reaction for *Pseudomonas spp.*, can largely contribute to the rational use of antimicrobial agents. Apart from that, the unnecessary expenses and the occurrence of hospital germ resistance might also be reduced. These methods ensure that clinicians must be swiftly informed of the presence of important isolates in the respiratory secretion of exacerbated COPD adults, such as *Pseudomonas spp.* [3, 7, 12–16]. Using such rapid *Pseudomonas spp.* identification, clinicians could additionally administer antipseudomonal cephalosporin to tigecycline and/or aminoglycosides [17–21], or meropenem in our study.

COPD exacerbations, especially those classified as frequent (≥ 2 exacerbations annually) or serious, significantly, compromise patients' quality of life and increase the

hospitalization rate and are considered a bad omen [6, 11]. Therefore, the mainstay of COPD exacerbation management is to minimize the effects of the current exacerbation and to prevent future ones [12]. In cases of the clinical and laboratory infection syndrome and an increased production of sputum, especially if it is purulent, the clinician must suspect a bacterial cause of the COPD exacerbation [6]. An inadequate gas exchange is the parameter that determines whether mechanical ventilation is to be added to symptomatic, supportive, and causative COPD exacerbation management. Non-invasive mechanical ventilation (NIMV) is usually the initial mode of mechanical ventilation, with a positive response in respiratory failure management in 80–85% of patients. Additionally, NIMV has an important role in reducing the intubation and mortality rate of COPD patients [4, 13]. However, when NIMV is unsuccessful in the management of respiratory failure, IMV must be applied. It is worth mentioning that IMV extends the length of hospital stay and may contribute to a progressive COPD course [14]. The COPD guidelines recommend antimicrobial management with the most sensitive antibiotic/s after the RS culture is found in patients with frequent and serious COPD exacerbations, especially when mechanical ventilation is obligatory [7, 16, 17, 18, 20, 21]. Therefore, initial antimicrobial management should be conducted in accordance with the local COPD guideline [19].

In comparison with other studies, the *Acinetobacter* frequency in RS of an acutely exacerbated COPD patient is significantly low, despite the fact that the frequency of *Acinetobacter* increases with the number of hospital admissions due to acute exacerbations of COPD, the duration of COPD and its treatment [22, 23]. A probable explanation for this lies in a different methodological approach. Nevertheless, the largest increase in the number of participants with the *Acinetobacter*-induced exacerbation of COPD was registered in critically ill patients. In this patient population, a serious resistance to antimicrobials and a significant increase in mortality rates [22, 23, 24] were detected. In addition, such an

increased frequency of *Acinetobacter* in RS reveals the inadequate use of empirical antimicrobials, especially in the "out-patient" environment, the insufficient treatment of previous COPD exacerbations, colonization with a new germ, irrational antimicrobial, and entire epidemiological management of hospital isolates. Many studies have shown a growing trend of *Acinetobacter* resistance to antimicrobials increase, including the culture of the "pan-drug-resistant" *Acinetobacter* strains or strains sensitive only to polymyxin [25–28]. In our study, we did not cover the cases of *Acinetobacter* resistance to tigecyclin, colistin, and carbapenems.

CONCLUSION

The results of our study point to the administration of tigecycline and aminoglycosides (i.e. amikacin) as the initial antimicrobial combination in urgently intubated adults with COPD exacerbations, irrespective of the incubation period of COPD exacerbation. It is of great importance to improve the quality of RS sampling, repeat tracheobronchial aspirate sampling, or perform parallel tracheobronchial aspirate and lavage samplings. In this manner, the findings of "negative" cultures, contaminates or colonizing germs could be reduced. The significant prevalence of *Acinetobacter* in RS of COPD adults is a serious cause for concern. Its RS detection is a bad omen concerning patient treatment, antimicrobials resistance and the outcome of COPD.

In view of the significance of *Pseudomonas spp.* as the frequent causative germ of serious COPD exacerbations, and the fact that the concurrent use of tigecycline and aminoglycosides (i.e. amikacin) do not cover *Pseudomonas spp.*, the application of rapid methods for microbial identification, such as the Polymerase Chain Reaction, is strongly recommended. Moreover, this will contribute to the rational use of antimicrobial agents and lower drug resistance in healthcare facilities. After the definitive RS culture findings are

available, the clinician should correct or adjust COPD exacerbation management. Close cooperation between clinicians, microbiologists, and clinical pharmacologists is the key to successful antimicrobial management of urgently intubated COPD exacerbation adults on the IMV. We hope that the general recommendations for the introduction of reserve antimicrobials will favor positive results in keeping bacterial resistance to antimicrobials under control.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Table 1. Study population respiratory specimen isolates

Bacteria	n (%)
Acinetobacter	20 (39)
Coagulase negative Staphylococci	9 (18)
Staphylococcus aureus	6 (12)
Pseudomonas spp.	6 (12)
Klebsiella spp.	4 (8)
Escherichia coli	3 (6)
Enterococcus spp.	1 (2)
Staphylococcus sciuri	1 (2)
Citrobacter spp.	1 (2)

Table 2. An overview of isolates-susceptible antimicrobial agents

Antimicrobials	**n (%)**
Tigecycline	13 (25.5)
Meropenem	12 (23.5)
Amikacin	8 (16)
Colistin	5 (10)
Vancomycin	4 (8)
3rd/4th gen. of Cephalosporins	3 (6)
Levofloxacin	3 (6)
Piperacillin + tazobactam	1 (2)
Sensitive to more Antimicrobials	1 (2)
Resistant to more antimicrobial agents	1 (2)

Table 3. An overview of the overall study population data

Variable	Group 1 – CAI (n = 26)	Group 2 – FAI (n = 25)
Age [Mean ± SD (min–max)]	71 ± 11 (39–89)	69 ± 9 (56–85)
Gender [♂ (%)]	19 (73)	16 (64)
Bacteria [n (%)]	*Acinetobacter* – 9 (35)	*Acinetobacter* – 11 (44)
	Staphylococcus aureus – 5 (19)	*Klebsiella spp.*– 4 (16)
	Coagulase-negative Staphylococci – 5 (19)	*Coagulase-negative Staphylococci* – 4 (16)
	Pseudomonas spp.– 3 (11)	*Pseudomonas spp.* – 4 (16)
	Escherichia coli – 2 (8)	*Escherichia coli* – 1 (4)
	Staphylococcus sciuri – 1 (4)	*Staphylococcus aureus* – 1 (4)
	Citrobacter spp.– 1 (4)	*Enterococcus* – 1 (4)
Antimicrobial agents [n (%)]	Tigecycline – 7 (27)	Tigecycline –6 (24)
	Meropenem – 7 (27)	Meropenem – 5 (20)
	Amikacin – 6 (23)	Colistin – 5 (20)
	Vancomycin – 2 (8)	Levofloxacin – 3 (12)
	Others – 4 (15)	Amikacin – 2 (8)
		Others – 4 (16)

CAI – Community-acquired Infection; FAI – Facility-acquired Infection

Table 4. The group summary of the most frequent respiratory specimen isolates and susceptible antimicrobial agents

Isolates (n CAI/n FAI)	Group 1 – CAI	Group 2 – FAI
Acinetobacter (9/11)	Tigecycline – 7	Tigecycline – 5
	Amikacin – 1	Colistin – 5
	Piperacillin + tazobactam – 1	Levofloxacin – 1
Pseudomonas spp. (3/3)	Meropenem – 3	Meropenem – 2
		$3^{rd}/4^{th}$ gen. of Cephalosporins – 1
Staphylococcus aureus (5/-)	Amikacin – 3	
	Vancomycin – 2	
Klebsiella spp. (-/4)		Meropenem – 2
		Tigecycline – 1
		Amikacin – 1

CAI – Community-acquired Infection; FAI – Facility-acquired Infection

