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ORIGINAL ARTICLE

THE EMPIRIC ANTIMICROBIAL THERAPY: THE COMPARISON OF INITIAL CHOICE WITH THE RESULTS OF MICROBIOLOGICAL INVESTIGATIONS. AN OBSERVATIONAL STUDY

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Introduction: Hospital infections are serious medical problem, causing deterioration in patients' outcome, prolonged hospital stay and increase costs of hospitalisation. Rapid administration of wide spectrum antimicrobial agents is a well known way to increase patient survival rate. Aim: To analyse the efficacy of initial empiric antimicrobial treatment in a large academic hospital.

Methods: In this retrospective cohort study, the initial choice of empiric therapy was compared with the results of the microbiological investigation and the susceptibility/resistance of isolated pathogens.

Results: Between February 1, 2018 and February 1, 2020, a total number of 267 samples were analysed. Amongst all 267 samples 163 (61%) were positive and 104 (39%) were negative. In those 163 samples 247 pathogens were isolated. In empirical therapy the most frequently administered antibiotic was meropenem (55/267, 20.6%), vancomycin (16/267, 6%), meropenem with vancomycin (14/267, 5.2%), ceftazidime (11/267, 4.1%), and imipenem/cilastatin (5/267, 1.9%).

The total number of samples where the empiric therapy corresponded with the results of microbiological tests was 166. There were forty-seven (28.3%) gram-positive bacteria, including 11 MRSA and 1 VRE, and 119 (71.7%) gram-negative pathogens, including 35 *K. pneumoniae* ESBL+, 12 *A. baumannii*, and 2 *E. coli* ESBL+.

Figures: 1 • **Tables:** 1 • **References:** 23 • **Full-text PDF:** http://www.pjambp.com • **Copyright** © 2023 Polish Aviation Medicine Society, ul. Krasińskiego 54/56, 01-755 Warsaw, license WIML • **Indexation:** Index Copernicus, Polish Ministry of Science and Higher Education

In 81 cases, the isolated pathogens were resistant to empirically administered drugs.

The empiric antimicrobial therapy complied with the results of microbiological analyses in 67.2% (166/247) of cases.

Conclusions: In our centre, meropenem and vancomycin seem to be a good choice in empiric therapy.

Keywords: nosocomial infections, anti-bacterial agents, drug therapy, combination

INTRODUCTION

Hospital infections comprise about half of all undesirable complications related to hospital treatment. Infections occur more frequently at high–level referral centres, especially in intensive care, haematological, and surgical units, where patients with severe medical conditions, comorbidities and immunosuppression are hospitalised, and where invasive procedures are performed [3,23].

According to the Wellcome Trust Report [10,18] about 10 million people die in 2050 because of infections caused by multidrug–resistant pathogens and this number will be higher than the number of deaths because of the oncologic reasons.

Antimicrobials are the main drugs against bacteria. However, its efficacy decreases, especially against multidrug-resistant Gram-negative pathogens.

For the most possible effectivity of antimicrobial agents, they should be administered both quickly and in optimal doses. Also, the therapeutic concentration of properly selected drugs should be achieved as soon as possible; as early as in 1913 Paul Ehrlich described this paradigm as „hit hard and fast" [9].

Nowadays the relation between delay in administration of antibiotics and increased mortality is well known. According to Kumar et al. the decrease in survival with inappropriate initial therapy may be up to 17.6-fold in cases of primary bacteraemia [15]. Such observations were confirmed by Keith et al. They found that the delay in administration of the antimicrobial in patients suffering from bloodstream infections caused by *Staphylococcus aureus* resulted in increased mortality of 1.3% per every hour of delay [6]. That is why proper empiric therapy is so important. Before the antimicrobial investigation will be completed, which may last up to 72 hours, a wide spectrum antimicrobials should be administered according to the type of infection, its origin, and the characteristics of the local pathogens.

The objective of this study is to analyse the comparison between the initial choice of empiric antimicrobial therapy and both the results of the microbiological identification and the susceptibility/resistance of isolated pathogens.

METHODS

Study design

A retrospective cohort study.

Setting

Analysis was performed from 01/02/2018 to 01/02/2020 in the Military Institute of Medicine in Warsaw, Poland. The Institute is a 1000-beds, multidisciplinary academic hospital and trauma centre. Every year, our Microbiological Department prepares microbiological maps for each of the hospital's ward. Such microbiological maps, as well as published clinical guidelines may be helpful in making of clinical decisions. Hospital procedures require that all decisions on empiric therapy with antimicrobials used in infections caused by multidrug resistant pathogens which were made in different hospital wards, except intensive care department, must be confirmed by the intensivists. Such list includes amoxicillin/clavulanate, ceftazidime, cefepime, ceftaroline, imipenem/cilastatin, ertapenem, meropenem, dalbavancin, teicoplanin, vancomycin, linezolid, colistin, and tigecycline. In our analysis the initial choice of empiric therapy was compared with the results of the microbiological investigation and the susceptibility/resistance of isolated pathogens. The decision on empirical therapy was assumed to be effective if pathogen isolated from the collected sample was susceptible to initially administered antimicrobial. Either when pathogen was not isolated or its resistance to antibiotics was confirmed, the decision on empiric therapy was recognized ineffective. Study design was approved by the Bioethical Committee, and was registered in Clinical Trials database (NCT number: 04448665). The research was conducted in accordance with the 1964 Helsinki Declaration and its later amendments.

Participants and study size

We analysed all decisions which were made in study period in our hospital wards other than critical care unit.

Data sources/measurement

Suspicion of the infection was based on clinical data, before the collected samples were analysed microbiologically, and the choice of antimicrobials as empiric therapy was made by the patient's attending physician, either by the specialist or the resident.

Microbiological methods

The accurate microbial identification was performed with automatic VITEK® 2 testing system (bioMérieux, France). The microbroth dilution method with VITEK® 2 AST Cards was used for antibiotic susceptibility testing of isolated pathogens.

The microbiological analyses between 2018 and 2020 were performed according to the regulations of the European Committee on Antimicrobial Susceptibility (EUCAST, Version 9.0, 2019) and the National Reference Centre for Susceptibility Testing (NRCST, Warsaw, Poland).

Control susceptibility tests included reference strains of *Escherichia coli ATCC 25922, Klebsiella pneumoniae* ATCC 700603, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213 and NTCT 12493 and *Enterococcus faecalis* ATCC 29212.

The analysis of mechanisms of bacterial resistance was performed according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance [8].

The confirmation of the bacterial growth was achieved after 24 hours. However, final results including analysis of bacterial susceptibility/resistance to antimicrobials were available up to 72 hours.

Statistical analysis

Nominal data are presented as numbers with percentage. All calculations were performed with the Microsoft Excel software.

RESULTS

In the study period totally 267 samples, withdrawn from 238 patients, were analysed. There were 29/238 (12.2%) patients from whom two (blood and urine) samples for microbiological samples were collected. There were 177 blood samples (66.3%), 63 samples from urine (23.6%), 19 from wounds (7.1%), eight (3%) were withdrawn from other locations; the majority of samples were from patients hospitalized in the departments of nephrology, neurology, gastroenterology, and surgery. Amongst all samples 163 (61%) of them were positive, and 104 (39%) were negative. In those 163 samples 247 pathogens were isolated. In empirical therapy the most frequently administered was meropenem (145/267, 54.3%), vancomycin (43/267, 16.1%), meropenem with vancomycin (37/267, 13.9%), ceftazidime (29/267, 10.9%), and imipenem/cilastatin (13/267, 4.9%). Antimicrobial agents in 230/267 (86.1%) cases were used as monotherapy and in 37/267 (13.9%) cases as combined therapy. Such relations were shown in Fig. 1.

The results of the study were presented in Table I. In 81 cases, the isolated pathogens were

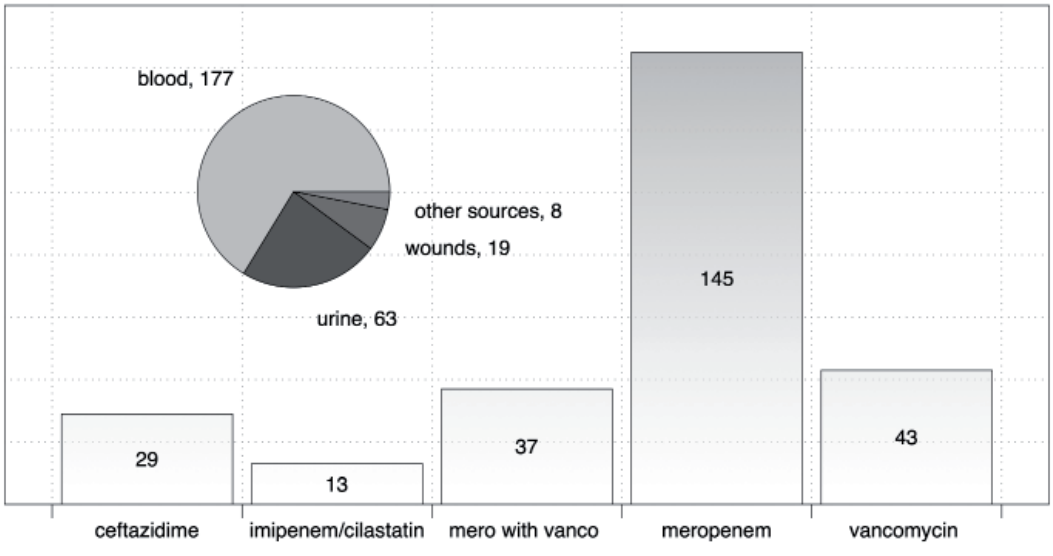

Fig. 1. Source of samples for microbiological investigations and antimicrobial agents chosen for empiric therapy.

resistant to empirically administered drugs. The ineffective therapy with meropenem was related to 38 isolates, including 12 gram-positive bacteria (MRSA, *Enterococcus faecium*), 19 gram-negative (*P. aeruginosa* and *A. baumannii*). There were seven fungal infections. Vancomycin was ineffective in 31 cases: in 27 specimens gram-negative bacteria, and in two – fungi were isolated. Ceftazidime was ineffective in eight samples, including three isolates of MRSA and two isolates of *Enterococcus*. Imipenem/cilastatin was ineffective against four isolates (three of *A. baumannii* and one – MRSA).

There was no pathogen resistant to vancomycin and only one isolate of *K. pneumoniae* resistant to meropenem amongst multidrug resistant pathogens.

The total number of isolates where the empiric therapy corresponded with the results of microbiological tests was 166. There were forty-seven (28.3%) gram-positive bacteria, including 11 MRSA and 1 VRE (25.5%), and 119 (71.7%) gram-negative pathogens, including 35 *K. pneumoniae* ESBL+, 12 *A. baumannii* (10.1%), and 2 *E. coli* ESBL+. In our material, empiric therapy was effective against 66.7% of alert pathogens.

The empiric antimicrobial therapy complied with the results of microbiological analyses in 62.2% of cases.

DISCUSSION

The necessity of administration of antimicrobials in the empiric therapy of severe infections and septic shock is well known [11,15,16] and was included in the recommendations of Surviving Sepsis Campaign [20].

Thomas et al. in their analysis of 660 empiric therapies found that in 50% of cases administration of antimicrobials was up to 72 hours [22]. Moreover, some data suggest that in 60% empiric therapy was extended up to 96 hours [1]. Every excessive extension of empiric treatment, especially when it will appear to be wrong, may result in increased bacterial resistance to antimicrobials and possible increase in patients' mortality [5]. Amongst 26,256 pathogens isolated between 2005 and 2012 in own material of our centre, 64% of species were gram-negative and 36% - gram-positive bacteria, 34.3% of them were multidrug resistant. *K. pneumoniae* ESBL (+) consisted of 11.2% of isolates from *Enterobacterales* order; methicillin-resistant *Staphylococci* were 25.6% of all isolated *Staphylococci*. In the last year of mentioned study (2012) we found no MRSA species resisted to vancomycin. Amongst 447 species producing ESBL mechanism of resistance, only two of them were resistant to meropenem [13]. The choice of carbapenems as a preferred antimicrobial in empiric therapy seems to be reasonable because of its pharmacologic

Tab. 1. Summary of the study results.

Patients: 238	Samples: 267	Negative: 104			Antimicrobial agents chosen for empirical treatment and the results of microbiological investigations	
		positive: 163	isolated pathogens: 247	resistant: 81	meropenem: 38	gram-positive: 12, incl. MRSA, *E. faecium*
						gram-negative: 19, incl. *A. baumannii, P. aeruginosa*
						Fungi: 7
					vancomycin: 31	gram-negative: 27
						Fungi: 2
						E. faecalis VRE: 1, *E. faecium* VRE: 1
					ceftazidime: 8	MRSA: 3
						Enterococci: 2
						E. coli ESBL: 2, *S. epidermidis:* 1
					imipenem/cilastatin: 4	*A. baumannii:* 3
						MRSA: 1
				susceptible: 166	meropenem: 99	gram-positive: 7
						gram-negative: 92, incl. *A. baumannii* 12, *K. pneumoniae* ESBL 33
					vancomycin: 37	gram-positive: 37, incl. MRSA 11
					ceftazidime: 21	gram-positive: 1
						gram-negative: 20, incl. *E. coli* ESBL 1
					imipenem/cilastatin: 9	gram-positive: 2
						gram-negative: 7, incl. *E. coli* ESBL 1, *K. pneumoniae* ESBL 2

ESBL – extended spectrum β-lactamases, MRSA – methicillin-resistant *Staphylococcus aureus*, VRE – vancomycin resistant *Enterococci*

properties. The comparison of efficacy of carbapenems with aminoglycosides and fluoroquinolones in empiric therapy showed no minority of the latter treatment. However, the number of analysed cases was relatively small [19]. Because of the design of our study, data from the patients hospitalised in the critical care unit were not analysed. It can be a source of possible bias. On the other hand, such hospital procedure meant that possible mismatching (32.7%) did not lead to as serious consequences as could it be observed in cases of septic shock. The incidence of inappropriate decisions was higher than observed by Cressman et al. [7]. This was mainly due to the fact that infections were caused by pathogens who were resistant, as a general rule, to antimicrobials which were administered. Moreover, the isolated species of *P. aeruginosa* and *A. baumannii* were resistant to carbapenems in 29% and 71%, respectively. Our previous in vitro analysis, with comparison of the carbapenems' MIC 50 and MIC 90 values showed that meropenem was the most effective, followed by imipenem and ertapenem against *Enterobacteriales* strains family [14].

Those 104 cases in which no pathogens were identified is a good example of harmfulness of empirically administered antimicrobials in the first 72 hours. It can be extremally important in patients treated with immune suppressive drugs. Analysis of 1615 patients suffering from febrile neutropenia found that overall mortality was higher in patients suffering from blood infections caused by gram-negative bacteria, who received inappropriate antimicrobial therapy (36% vs. 24%, p=0.004); it significantly pertained to the patients with infections caused by *P. aeruginosa* [17].

The increased hospital mortality is mainly due to infections caused by multidrug resistant gram-negative bacteria, especially producing extended spectrum beta-lactamases and carbapenemases. The drug of choice in therapy of invasive infections of β-lactamase producing pathogens are carbapenems [2,4,12]. The decisions in cases of infections caused by gram-negative bacilli producing metallocarbapenemases and *A. baumannii*, the drug of choice remains colistin. When *P. aeruginosa* is suspected as an etiologic agent of infection, some new antimicrobials, as ceftazidime/avibactam, meropenem/vaborbactam or new cephalosporin – ceftolozane/tazobactam may be administered. However, until now, there are no data regarding the use of those antimicrobials in empiric therapy.

In view of current literature, where the range of inappropriate clinical choice varies between 10 and 90% [8,21], the compliance of our initial empiric therapy with the results of microbiological investigations seems to be quite accurate.

Our analysis has some limitations. Due to study design, it is related to microbiological aspect only. We did not include the relations between the choice of antimicrobial therapy and the clinical outcome: such analyses affected patients hospitalised in fourteen hospital departments would be quite difficult to perform. The efficacy of empiric therapy may be increased by the in-depth analysis of both expected bacterial species and possible source of infection. Moreover, we analysed only the clinical decisions which were performed regarding selected group of antimicrobial agents. It could be another reason of possible bias. However, irrespective of the limitations of this study, the authors believe that its results may be interesting for physicians in making better clinical decisions regarding proper choice of empiric antimicrobial therapy to increase survival rate in cases of primary bacteraemia.

CONCLUSIONS

The empiric antimicrobial therapy, in our material, complied with the results of microbiological analyses in 67.3% of cases. Meropenem and vancomycin seems to be a good choice in empiric therapy of hospital infections.

ETHICS APPROVAL

Study design was approved by the Bioethical Committee of the Military Institute of Medicine, Warsaw, Poland.

AUTHORS' DECLARATION:

Study Design: Dariusz Tomaszewski, Aneta Guzek, Zbigniew Rybicki. **Data Collection:** Dariusz Tomaszewski, Aneta Guzek, Zbigniew Rybicki. **Manuscript Preparation:** Dariusz Tomaszewski, Aneta Guzek, Zbigniew Rybicki. The Authors declare that there is no conflict of interest.

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