

ANTIBIOTIC TREATMENT AND RESISTANCE IN CHRONIC WOUNDS OF VASCULAR ORIGIN

VALENTINA TZANEVA¹, IRENA MLADENOVA², GALINA TODOROVA¹,
DIMITAR PETKOV¹

¹MHAT Trakia, Stara Zagora, Bulgaria

²Trakia University Stara Zagora, Bulgaria

Abstract

Background and aim. The problem of antibiotic resistance is worldwide and affects many types of pathogens. This phenomenon has been growing for decades and nowadays we are faced with a wide range of worrisome pathogens that are becoming resistant and many pathogens that may soon be untreatable. The aim of this study was to determine the resistance and antibiotic treatment in chronic wounds of vascular origin.

Methods. We performed a cross sectional study on a sample of patients with chronic vascular wounds, hospitalized between October 2014 and August 2015, in the Clinic of Vascular Surgery in Trakia Hospital Stara Zagora. The statistical analysis of data was descriptive, considering the p value of ≤ 0.05 , the threshold of statistical significance.

Results. In the group of 110 patients, the significantly most frequent chronic wound ($p < 0.001$) was peripheral arteriopathy (47.3%, CI95%: 38.19-56.54). Among 159 strains, 30% of patients having multiple etiology, the species most frequently isolated were *Staphylococcus aureus*, *E.coli*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* and *Proteus mirabilis* with a significant predominance ($p < 0.05$) of the Gram negative (55.1%). The spectrum of strains resistance included the Beta-lactams (36.4%, $p < 0.001$), Macrolides (20%), Tetracyclines (9.1%), Aminoglycosides (8.2%) and Fluoroquinolones (4.5%).

Conclusions. Gram negative microorganisms were the main isolates in patients with vascular chronic wound. Significantly predominant was the resistance to the beta-lactam antibiotics.

Keywords: vascular chronic wounds, antibiotic resistance, antibiotic treatment

Introduction

It is a worldwide problem that antimicrobial agents are some of the most widely and often injudiciously used therapeutic drugs and the consequence is the antibiotic resistance. This problem has been festering for decades and has finally reached the crisis point. There is a wide range of worrisome pathogens that are becoming resistant and many pathogens that may soon be untreatable. The decreasing effectiveness of antibiotics in treating common infections has quickened in recent years, and with the arrival of untreatable

strains of carbapenem resistant *Enterobacteriaceae*, we are at the dawn of a postantibiotic era [1,2,3].

The chronic wound bed houses a complex microenvironment that typically includes more than one bacterial species. With regard to antibiotic therapy in chronic wounds, there is a lack of evidence concerning its effectiveness, optimal regimens or clinical indications for treatment. Despite this lack of evidence, antibiotics are frequently a feature of the management of chronic wounds and these patients receive significantly more antibiotic prescriptions (both systemic and topical) than other age and gender matched patients. The physicians have to evaluate the role of microorganisms in the etiology and persistence

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Address for correspondence: vtzaneva@gmail.com

of chronic wounds, indications for antibiotic therapy and optimal treatment regimens. It is very important to understand and apply the principles of antimicrobial stewardship, which include the optimal selection, dosage and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance [4,5,6].

Important considerations when prescribing antimicrobial therapy include the knowledge when to consult infectious disease specialists for guidance and to be able to identify situations when antimicrobial therapy is not needed. By following these general principles physicians should be able to use antimicrobial agents in a responsible manner that benefits both the individual patient and the community [7,8].

In the particular case of chronic wounds contamination this is very easy, and the development of infection requires hospitalization. In health care facilities, person-to-person transmission of multidrug-resistant organisms by indirect and in some cases, direct contact constitutes the major route of transmission and dissemination. Health care workers may acquire these multidrug-resistant organisms on their hands or clothing while providing care to an infected or colonized patient. Without observing recommended precautions, staff members may then transfer bacteria acquired from these patients or their immediate environment to other patients, who then become colonized and at risk for infection and this process can replicate indefinitely [9,10,11,12].

The aim of the study was the description of the germs resistance and the antibiotic treatment in the particular case of the chronic wounds of vascular origin.

Methods

Between October 2014 – August 2015 we performed a cross sectional study in order to describe the etiology and the antibiotic treatment of infections in chronic wounds. The sampling was done by convenience, with the identification of the patients who were hospitalized in the Clinic of Vascular Surgery in Trakia Hospital Stara Zagora in the proposed period and met the inclusions criteria. In the study sample were included patients who had lesions due to Chronic Venous Disease, advanced peripheral arterial occlusive disease of the lower extremities and advanced diabetic microangiopathy with microbiological determinations from the local lesions and the germs sensitivity tested by antibiogram. Patients with cutaneous manifestations due to skin malignancies, histologically proven different types of vasculitis and those with Martorell ulcer were excluded.

In our practice, in order to optimize and assess the proper antibiotic therapy we perform routine microbiological screening for all hospitalized patient with wounds at the time of admission. This routine screening guides the antibiotic therapy but also provides information

about what additional infection prevention and control procedures and precaution recommendations should be applied in order to limit the transmission of infection from patient to patient.

All clinical, microbiological and treatment data were recorded in an Excel database. We analyzed for each patient the validity of the microbiological isolates, their resistance to antibiotics and the prescribed antibiotics. The statistical analysis was performed in Excel and the software OpenEpi Statistics for Public Health (www.OpenEpi.com), calculating percents, confidence interval for 95% level. To compare proportions in a large (at least 30 elements) sample, we used the z test, considering the level of significance for p value: ≤ 0.05 .

Results

For almost 1 year, in the period from October 2014 till August 2015, in the Clinic of Vascular Surgery of Trakia Hospital, 110 patients with chronic wounds of vascular origin who presented with signs of local inflammation had the microbiological determinations and analysis of antibiotic sensitivity of the isolates.

The patients who were in the range of our interest were aged between 41 to 84 years and their chronic wounds with vascular origin were due to Chronic Venous Disease (32 patients), advanced peripheral arterial occlusive disease of the lower extremities (52 patients) and advanced diabetic microangiopathy (26 patients) (figure 1). The significant ($p < 0.001$; $z = 4.196$), most frequent cause of the patient's local wounds was the arterial disease, without significant differences ($p > 0.10$; $z = 1.356$) between venous pathology and diabetic microangiopathy.

A total of 159 strains were isolated from 110 patients (table I). More than one isolate of bacterial species was detected in 33 (30%) of the patients. The most frequently isolated microorganisms were *Staphylococcus aureus*, *E.coli*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* and *Proteus mirabilis*.

Taking into account the Gram coloration characteristics from 158 bacterial isolates, the Gram negative (87 strains or 55.1%) significantly ($p < 0.05$; $z = 2.561$) predominate over Gram positive (71 strains or 44.9%) isolates.

Resistance was detected for 86 strains isolated from 54 (49%) patients, representing 54.4% from all 158 bacterial isolates. The isolated microorganisms were resistant to the 5 major classes of antibiotics: Beta-Lactams (Penicillins and Cephalosporins), Macrolides, Fluoroquinolones, Tetracyclines, Aminoglycosides (table II). The most frequent and highly significant ($p < 0.001$; $z = 4.291$) resistance was found to the Beta-Lactam antibiotics (36.4%, CI95%: 27.98-45.67).

The resistance to cephalosporine was present in Gram negatives and to macrolides in Gram positives (22 of the isolates) (table III). Among the *S. aureus* strains 3 of

them were resistant to all macrolides.

The patients, who were in the focus of our study, had undergone antibiotic treatment in different hospitals and the isolated microorganisms exhibited high level of resistance. The antibiotic treatment was administered after careful evaluation of the presence of clinical and laboratory signs of infection. The precise antibiotic choice was based on the microbiological result. Most of the patients

received Amoxicillin and clavulanic acid (41 patients) and Metronidazole (for 33 patients) as antibiotic treatment (figure 2). The duration of the antibiotic treatment was 5.7 days (4-9 days). Simultaneously with the antibiotic treatment all the patients received additional adequate treatment as vasoactive therapy, surgical interventions and endovascular procedures.

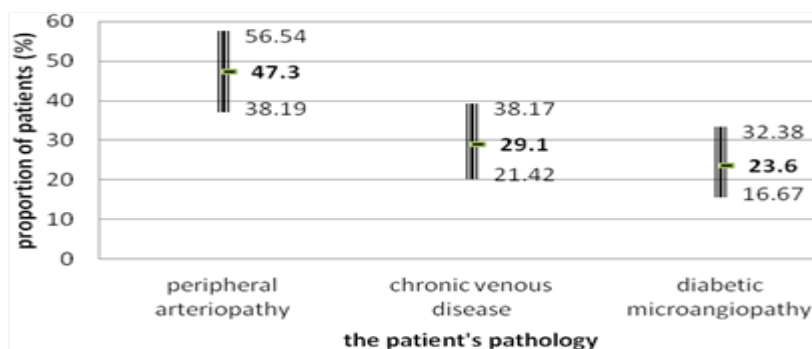


Figure 1. The origin of the chronic wound for the 110 analyzed patients. Legend: the middle numbers represent the proportion of cases and the lower and higher numbers represent the confidence interval for 95% of values.

Table I. The microbiological isolates, from local lesions of the patients with chronic wounds of vascular origin.

Isolated strain	Gram	Number of strains	Percent of patients [CI95%]
<i>Staphylococcus aureus</i>	positive	43	39.1% [30.49-48.43]
<i>Escherichia coli</i>	negative	21	19.1% [12.84-27.43]
<i>Enterococcus faecalis</i>	positive	18	16.4% [10.61-24.39]
<i>Pseudomonas aeruginosa</i>	negative	13	11.8% [7.04-19.17]
<i>Proteus mirabilis</i>	negative	11	10% [5.67-17]
<i>Proteus vulgaris</i>	negative	7	6.4% [3.12-12.56]
<i>Klebsiella pneumoniae</i>	negative	7	6.4% [3.12-12.56]
<i>Enterobacter cloacae</i>	negative	7	6.4% [3.12-12.56]
<i>Klebsiella oxytoca</i>	negative	6	5.5% [2.52-11.39]
<i>Streptococcus pyogenes</i>	positive	5	4.5% [1.96-10.2]
<i>Morganella morganii</i>	negative	3	2.7% [0.93-7.71]
<i>Aerococcus viridans</i>	positive	2	1.8% [0.5-6.38]
<i>Citrobacter diversus</i>	negative	2	1.8% [0.5-6.38]
<i>Streptococcus agalactiae</i>	positive	2	1.8% [0.5-6.38]
<i>Hafnia alvei</i>	negative	2	1.8% [0.5-6.38]
<i>Enterobacter gergoviae</i>	negative	1	0.9% [0.16-4.97]
<i>Enterobacter agglomerans</i>	negative	1	0.9% [0.16-4.97]
<i>Enterobacter spp.</i>	negative	1	0.9% [0.16-4.97]
<i>Enterobacter zakazakii</i>	negative	1	0.9% [0.16-4.97]
<i>Providencia stuartii</i>	negative	1	0.9% [0.16-4.97]
<i>Serratia rubidaea</i>	negative	1	0.9% [0.16-4.97]
<i>Serratia spp.</i>	negative	1	0.9% [0.16-4.97]
<i>Serratia odorifera</i>	negative	1	0.9% [0.16-4.97]
<i>Beta hemolytic streptococcus</i>	positive	1	0.9% [0.16-4.97]
<i>Candida albicans</i>	-	1	0.9% [0.16-4.97]
Total	-	159	-

Table II. Registered antibiotic resistance in the analyzed patients.

The class of antibiotics	Number of resistant strains	Percent of patients [CI95%]
Beta-Lactams	40	36.4% [27.98-45.67]
1. penicillins (<i>beta-lactam-beta-lactamase inhibitor combinations</i>)	20	18.2% [12.1-26.42]
2.cephalosporines	20	18% [12.1-26.42]
Macrolides	22	20%[13.6-28.43]
Tetracyclines	10	9.1% [5.01-15.93]
Aminoglycosides	9	8.2% [4.36-14.82]
Fluoroquinolones	5	4.5% [1.96-10.2]
Total	86	100%

Table III. The particular resistance of specified isolates to cephalosporins and macrolides.

The antibiotic class	The strains	The number of resistant isolates
2nd generation cephalosporins	<i>Enterobacter cloacae</i>	4
	<i>Pseudomonas aeruginosa</i>	2
	<i>Proteus vulgaris</i>	2
	<i>Serratia marcescens</i>	1
	<i>Providencia stuartii</i>	1
	<i>Hafnia alvei</i>	1
	<i>Klebsiella oxytoca</i>	1
	<i>Escherichia coli</i>	1
3rd generation cephalosporins	<i>Enterobacter agglomerans</i>	1
	<i>Proteus vulgaris</i>	1
all cephalosporins	<i>Klebsiella pneumonia</i>	1
macrolides	<i>S.aureus</i>	10*
	<i>Enterococcus faecalis</i>	9
	<i>Beta hemolytic streptococcus</i>	2
	<i>Aerococcus viridans</i>	1

*Among all *S. aureus* isolates, 3 strains were resistant to all macrolides.

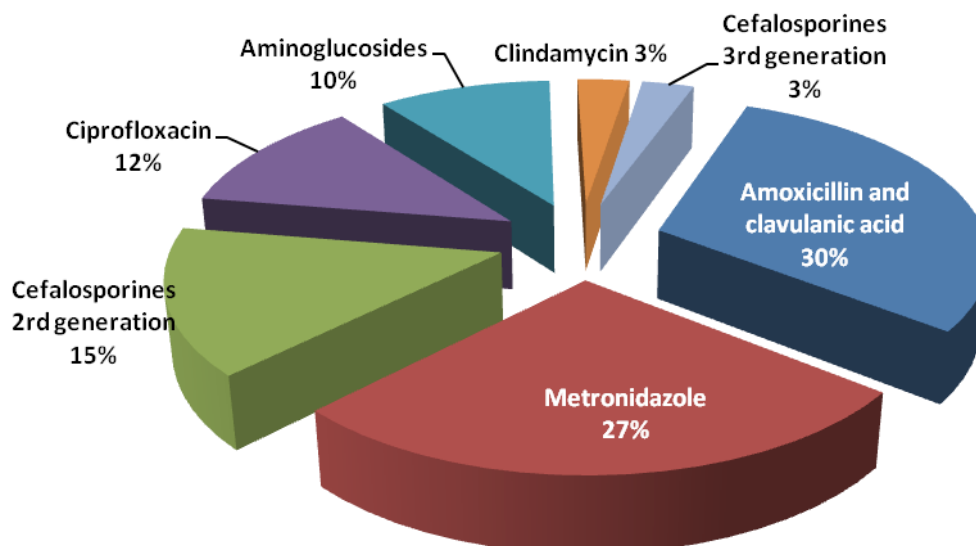


Figure 2. The antibiotic treatment for the infected wound in the 110 analyzed patients.

Discussion

Antibiotic resistance is one of the main problems of the team dealing with nosocomial infections [1,2,9].

Frequently the findings from the microbiological investigation in chronic wounds with vascular origin show presence of more than one bacterial species and the isolated bacteria exhibit antibiotic resistance. The measures in these patients should be focused on the active surveillance of antibiotic resistance of the local strains. The collaboration with the clinicians (vascular surgeons, microbiologists and epidemiologist) is important for obtaining early microbiological results before the initiation of antibiotic treatment and selecting the adequate antibiotic treatment.

The local data and statistics are of crucial value for empiric therapy since the incidence of resistance is highly variable.

The choice of the optimal antibiotic therapy in patients with vascular diseases is of great significance both for the treatment of the infection and for the prevention of the infection of the used implants - prosthesis and stents [8,13,14,15].

Tracking the resistance patterns is valuable for the administration of adequate antibiotics (as a mono therapy or combination of antibiotics), based on the results of the microbiological investigation.

In our study we found significant resistance to beta-lactam antibiotics, which are in many cases the antimicrobial agents of choice. The excess antibiotic use accelerated the emergence of resistance to beta-lactam-beta-lactamase inhibitor combinations. Their efficacy is significantly threatened by bacterial beta-lactamases which are now responsible for resistance to penicillins and cephalosporins. Beta-lactamase inhibitors (clavulanate, sulbactam, and tazobactam) overcome beta-lactamase-mediated resistance and enhance the efficacy of beta-lactams (amoxicillin, ampicillin, piperacillin, and ticarcillin) in the treatment of serious *Enterobacteriaceae* and penicillin resistant staphylococcal infections.

The choice for antibiotic treatment should be based on the answer to the following clinically evaluated questions: Is infection present? Are systemic antibiotics necessary? What antibiotic or combination of antibiotics should be used? What should be the duration of therapy? What special circumstances are present? Microbiological results and antimicrobial susceptibility tests are important to be taken into consideration in order to guide the antibiotic choice in combination with all these criteria.

In order to disrupt transmission of the multidrug-resistant organisms to other patients and staff members we performed and monitored the consistent use of hand hygiene, physical isolation, barriers, personal protective equipment, designated equipment and environmental measures. These infection control measures are of significant importance for preventing the spread of these microorganisms in the hospital environment and avoid the overuse of antibiotics

and development of resistance.

Conclusions

In our study the main observations were:

1. Obstructive arterial disease was the main cause for chronic wounds.
2. The most frequently isolated microorganisms were *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* and *Proteus mirabilis*, which are mainly Gram negative.
3. More than one isolate was detected in almost one third of the patients.
4. Resistance was detected in nearly half of the patients' isolates.
5. The most frequent resistance was found to the beta-lactam antibiotics.
6. The ability of the clinician to choose the most efficient antibiotic treatment must be developed and the proper choice for antibiotic treatment should be based on the answers of all clinically evaluated questions in combination with the microbiological results of each patient.
7. Permanent monitoring, committed leadership and efforts to achieve high levels of staff engagement in compliance with the multiple known interventions in this risk group reduce the need of antibiotic treatment and development of resistance.

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