ISSN No. 2394-3971

Original Research Article

THE INFECTIONS AND ANTIBIOTIC THERAPY IN PATIENTS WITH SOLID TUMORS IN PALLIATIVE CARE

Samir Husić[1], Dženan Halilović[2], Jasmina Smajić[3]

1 Center for Palliative Care, University Clinical Center Tuzla, Bosnia and Herzegovina
2 Clinic for Pulmonary disease, University Clinical Center Tuzla, Bosnia and Herzegovina
3 Clinic for Anesthesia and Reanimation, University Clinical Center Tuzla, Bosnia and Herzegovina

Submitted on: February 2018
Accepted on: April 2018
For Correspondence
Email ID:
drsamirhusic@gmail.com

Abstract

Background: Patients in the palliative stadium of cancer disease are frequently exposed to infections. Introducing the antibiotic therapy to those patients is a dilemma: what benefit do they have from antimicrobial therapy regarding their short lifespan and the resource consumption of these medicines.

Objectives: We researched the most common sites and causes of infections and estimated the price and the efficiency of antibiotic therapy with respect to difficulty reduction caused by infections.

Methods: The prospective study was performed on patients hospitalized at Palliative care department in the year 2015. The antibiotic therapy, whose efficiency was estimated by the loss of symptoms related to infection, is included to 78 patients who underwent laboratory testing (Le and CRP) because they had verified clinical signs of infection.

Results: 109 causes of infection were found. Most of them were Escherichia coli, Klebsiella pneumonia, Proteus mirabilis, Pseudomonas aeruginisa and Staphylococcus aureus. The most used antibiotics were gentamicin (21.1%), meropenem (20.2%), trimethoprim-sulfamethoxazole (11.9%), amikacin and Cefepime (11.1%). The success of antibiotic therapy was 61.5%. The mortality is registered at 16.7% patients during antibiotic treatment. For antibiotic treatment, 5329.69 € (68.33 €/ pat.) is spent. The parenteral antibiotic application was used in 75.2% of cases, and peroral in 24.7% of cases. Side-effects of anti-infective therapy were recorded in 3 (3.85%) of 78 patients treated with antibiotics.

Conclusion: Antibiotic therapy reduces the intensity of difficulties in patients with bacterial infections with rare side-effects. Therefore, the main principles of palliative treatment – reduce the suffering and not to harm patients, are satisfied.

Keywords: infections, antibiotic therapy, palliative care

Introduction

Patients in the palliative stadium of cancer disease are very sensitive to infections, which is directly or indirectly connected to elementary disease or its therapy. It is considered that infections of those patients are significantly connected with morbidity and mortality. Many studies are often contradictory and have very opposite results regarding the use of antibiotics in this stage of disease (1,2). There are many studies about antibiotic treatment of neutropenic patients with hematological malignancies (3), but only a few of them are about the use of antibiotics in patients with solid tumors in the palliative stage of disease (4). The autopsy study in 2007., lung infection was visible in 79% of cases and estimated as a leading cause of death in 44% cases (5). Still, the use of antibiotic therapy in an advanced stage of the disease shows big variations from 4% to 84% (6). Ford and Co. (7) state dilemmas regarding antibiotic therapy from a life prolongation and symptom improvement, necessity i.v.drug applications, increasing risks of resistance and increase of hospital treatment costs perspective. Similar ethical dilemmas are associated with blood transfusion (8), hemodialysis (9) or hydration/nutrition in patients with advanced stage of cancer disease. Considering the primary goal of palliative treatment, that is quality of life improvement, removing symptoms caused by infections is definitely very useful for these patients. Besides the subjective evaluation of patients, the improvement symptom evaluation would be related to the objective estimation of antibiotic therapy influence to symptom intensity decrease (for example, Edmonton Symptom Assessment Scale) (10). The absence of clear instructions and weight of making a hard-therapeutic decision represents very large stress for a clinician who works every day with critically ill patients. Additional problems are related to doctor's awareness about restricting effects of antimicrobial therapy in this stage of disease as well as financial costs related to its application (11). The symptom recognition directly related to infections represents a difficulty since many similar problems (fever, coughing, dyspnea, painful urination) can represent a consequence of advanced cancer disease or the current symptoms cannot be related to the current infection definition (12). The aim of the research is to establish the most common sites and causes of infection and to estimate the efficiency of antibiotic therapy in patients in palliative care.

Patients and Methods

265 patients hospitalized in Palliative care Centre, in University Clinical Center Tuzla, in Bosnia and Herzegovina, during 2015, were observed.

Of 78 patients who had verified clinical signs of infection of [a) skin (1. fever, 2. local temperature and redness, 3. wound secretion), b) respiratory tract (1. fever 2. coughing 3. dyspnea) or c) urinary tract (1. fever, 2. frequent, painful urination 3. change of urine color)], the laboratory (Le- Leukocytes and CRP – C reactive protein) and microbiologic (MB) tests were performed, and antibiotic as well as symptomatic therapy is prescribed. 187 patients, without clinically noticed signs of infection, were treated only with symptomatic therapy. (Table 1.)

Table 1. Signs and efficiency evaluation of antibiotic therapy

EFFICIENCY SIGNS OF AB THERAPY		EFFICIENCY EVALUATION OF AB THERAPY	
1.	Fall of fever;	EVALUATION (from 1 - 4)	CONDITION
2.	Decreasing number of Le (over 20%)	(1) Successful evaluation	Improvement of at least 4 signs of therapy efficiency
3.	Decrease of CRP value (over 20%);	(2) Partially successful evaluation	Improvement of 2-3 signs of therapy efficiency
4.	Withdrawal of clinical signs of infection	(3) Unsuccessful evaluation	Improvement of at 1 or none signs of therapy efficiency
5.	Karnofski score (before and after the antibiotic therapy in patients who finished their treatment)	(4) Success of therapy is not possible to evaluate	Exitus letalis or sterile MB result (without AB treatment)

Results

During the year 2015, in Palliative care Centre, 486 patients were hospitalized with an average age of 64.33 ± 11.32 (31 to 93 years old) /, of which 248 (50.82%) were males and 239 (49.18%) were females. The average duration of hospitalization was 8.21 ± 6.14 days (1 to 41 days) which is represented in Table 2.

Table 2. Duration and result in hospitalized patients

DURATION AND RESULT OF HOSPITALIZATION (Total 486 patients)					
RELEASED FROM HOSPITAL–home treatment		DEATH RESULT DURING HOSPITALIZATION			
Total: 223 (45.88%)		Total: 263 (54.12%)			
Duration of hospitalization until release from hospital		Duration of hospitalization before death (days)			
days	patients	≤ 2*	3 - 5	6 - 9	More than 10
1 - 9	105 (47.08%)	78 (29.7%)	90(33.5%)	53(20.4%)	42(16.4%)
10 – 19	89 (39.91%)	*previous hospitalization	*First time	56 (71.79%)	
> 20	29 (13.01%)		*Multiple times	22 (28.21%)	
*Death during 48 hours ≤ 2 days after hospitalization					

Out of a total number of patients (265) who were included in this study, 187 did not have clinical signs of infection, which is significantly more when compared to patients who had verified signs of infection (78). There is no statistically bigger difference in the outcome of the treatment (released from hospital vs exitus letalis) when comparing those two groups (p = 0.953) (Table 3).

Table 3. Characteristics of patients included in the study

		(1) With clinical signs of infection		(2) Without clinical signs of infection	
Number of patients (265)		78 (29.43%)		187 (70.57%)	
Age		61.59±11.45		63.17±11.65	
Gender	F (%)	46 (58.97)		109 (58.29)	
	M (%)	32 (41.03)		78 (41.71)	
Result of treatment		Released from hospital	Exitus letalis	Released from hospital	Exitus letalis
		65 (83.3)	13 (16.7)	158 (84.5)	29 (15.5)

Location of tumor in 265 patients is represented in Figure 1.

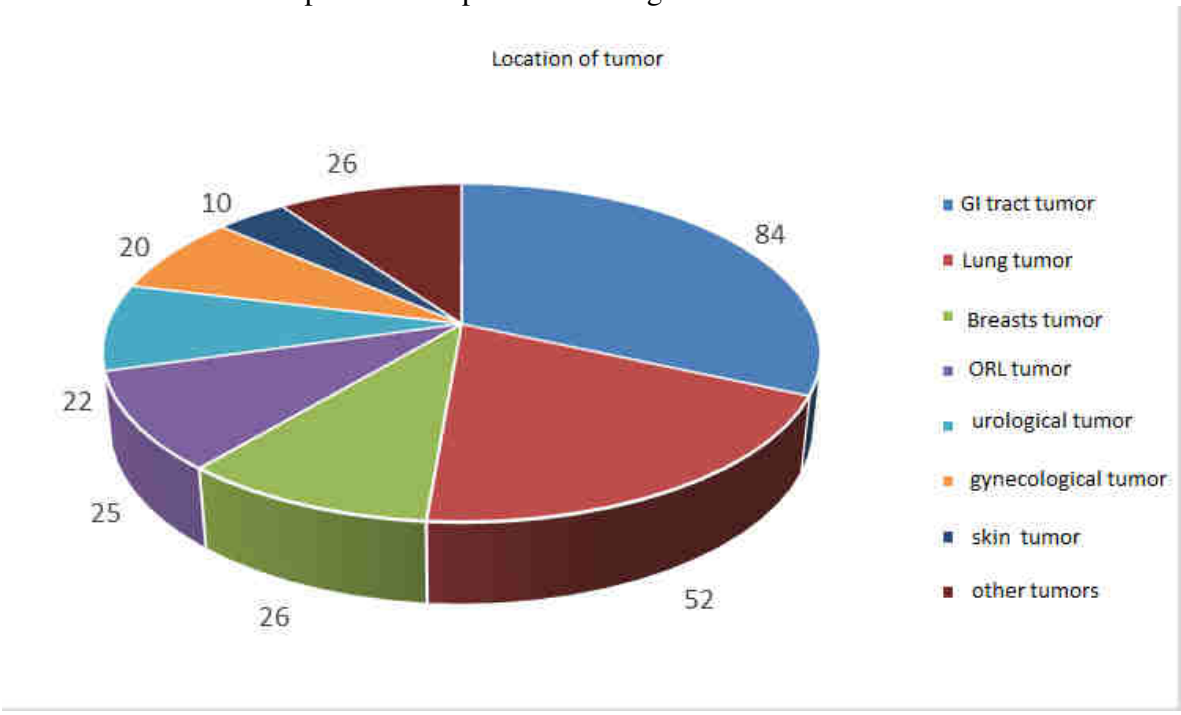

Figure 1. Location of tumor in 265 patients

Out of 78 patients who had clinical signs of infection, at 57 (73.08%) of them had signs of one place of infection, and 21 patients (26.95%) had multiple infections.

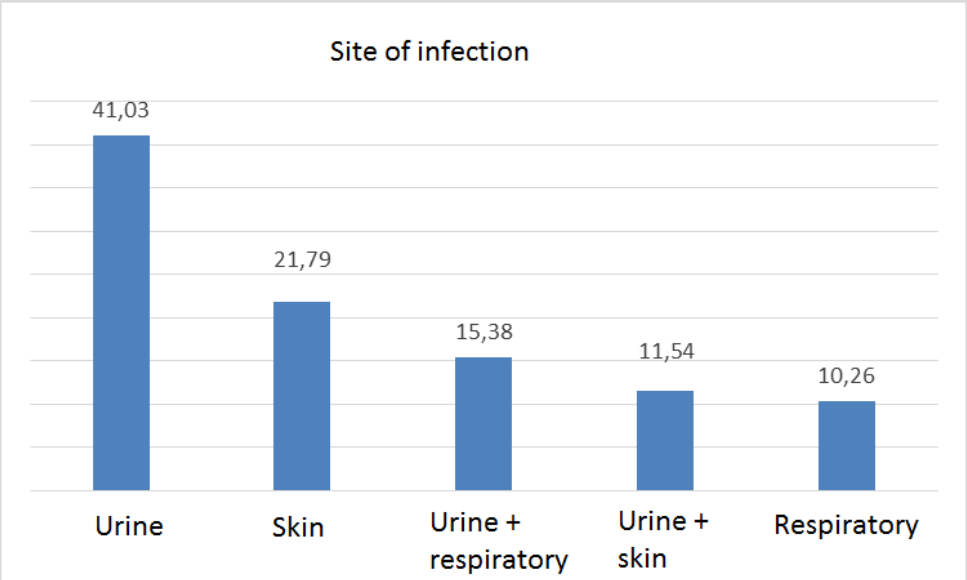

Figure 2. Sites of infections

The most common sites of infections are represented in Figure 2.

Before they begin to use antibiotic therapy, 45 (57.69%) of them had a fever, 73 (93.59%) had a WBC value over 7.5 x 10^9/L, with increased levels of CRP at 79.49% patients. After completion of antimicrobial therapy, TT was lower for over 20% at 34 patients (75.56%), Le level was lower at 57 patients (78.08%), and CRP level was lowered at 74.19% patients (Table 4).

Table 4. Clinical signs of infection before and after AB therapy

	Before AB therapy – number of patients (average)		After AB therapy (<20%)	P*
Fever (TT) (> 37^{O}C)	45 (**38.22** ± 0.44^{O}C)		34 (**36.65** ± 0.17^{O}C)	< 0.0001
Leukocytes (> 7.5x 10^9/L)	73 (**14.14** ± 3.79)		57 (**8.87**±1.94)	< 0.0001
CRP (mg/L)	62 [median 93.35 (10.7 – 249.2)]		46 [median 31.4 (9.1 – 99.5)]	< 0.0001**
Karnofski	78 (37.56 ± 6.28)		65 (41.69 ± 9.45)	0.0032
Success of therapy	Successful	Partially successful	Not possible to evaluate	Unsuccessful
Σ 78 patients (%)	48 (61.54)	13(16.67)	16 (20.51)	1(1.28)

The success of antibiotic therapy is spotted at 61.54% of patients, partial success at 16.67% (p< 0.0001) of patients, while at 20.51% of patient's success of therapy could not be evaluated (Table 4). In 78 patients, 99 sites of infections were verified, out of which the most common were urinary tract infections (53 or 53.54%), then skin infections (26 or 26.2%) and at the end, respiratory tract infection (20 or 20.2%). There were 9 sterile samples. In 73 samples is only one infection causer found, in 15

samples is two causes of infection found, in 2 samples were 3 bacteria found, so the total number of infection causes was 109 (Figure 3).

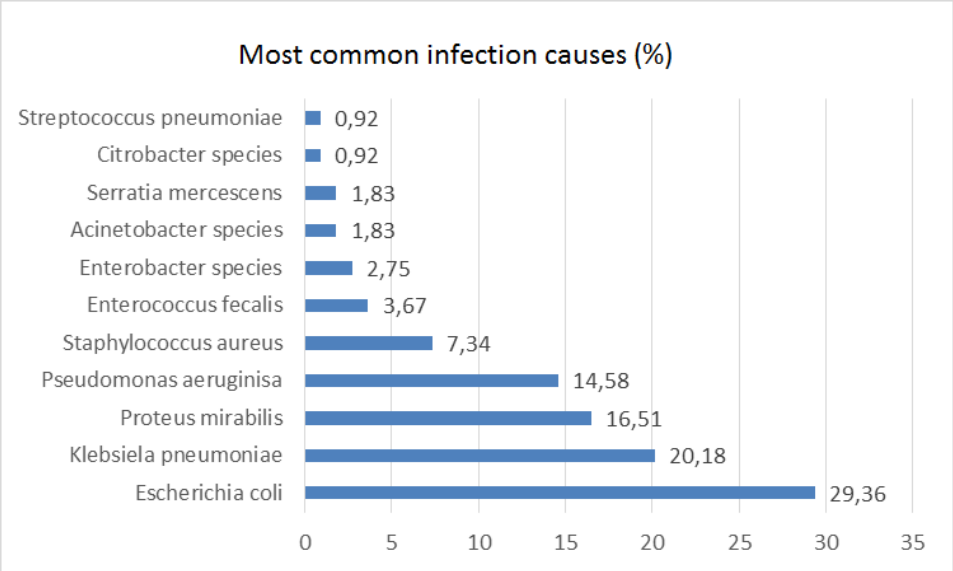

Figure 3. Most common infections cause (% of 109 verified cases)

Infection caused by Escherichia coli was mostly treated with gentamicin, while meropenem was usually used to treat infections caused by Klebsiela pneumonia, Proteus miriablis, and Pseudomonas aeruginis. Antibiotics in infection treatment were used 109 times, from which gentamicin was used 23 times or 21.1%, meropenem 22 times or 20.2%, trimethoprim – sulfamethoxazole 13 times or 11.9%, and amikacin and cefepime 12 times or 11.1% (figure 4).

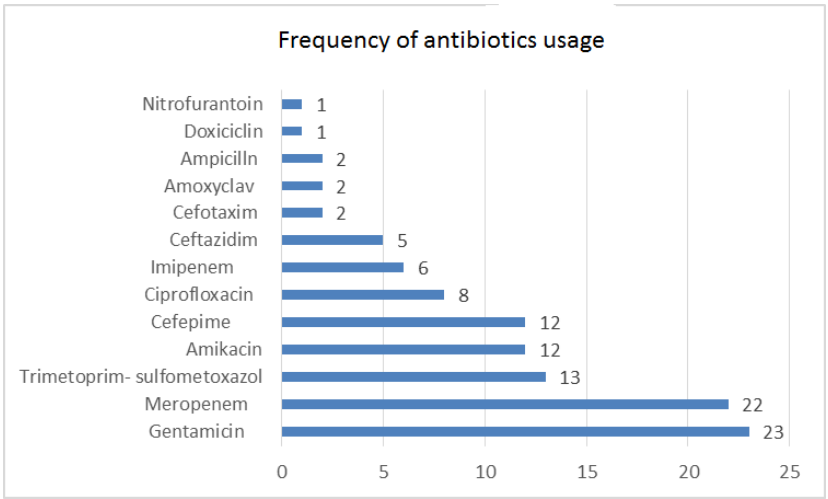

Figure 4. Most commonly used antibiotics in antimicrobial therapy

For treatment that includes antibiotics, 5 329.69 € is spent. Parenteral application of antibiotics was used 82 times (spent 5 232.36 €), and peroral 27 times (spent 97.33 €) ($p < 0.0001$). Death outcome was recorded in 13 patients (16.7%) during antimicrobial treatment, with costs 698.51 €, compared to 4 631.18 €, which was spent for

patients who finished their antibiotic treatment ($p < 0.0001$). Side effects of anti-infective therapy (nausea and diarrhea) were recorded in 3 (3.85%) of 78 patients treated with antibiotics.

Discussion

A study done in Taiwan on 1670 patients, shows that 307 (28.37%) patients died within 3 days, 271 (16.23%) in the period from 4-7 days and 391 (23.41%) patients died in the period from 8-14 days from the reception day (13). In our study, which had 486 patients hospitalized in the year 2015, 263 (54.12%) of them died, of which 78 (29.7%) died within 48 hours of reception, 90 (33.5%) in a period of 3-5 days, 53 (20.4%) in a period of 6 – 9 days. 56 patients (71.79%) were hospitalized for the first time, while 22 (28.21%) were hospitalized more than once. Nakagawe et al (14) determined the relation of anti-infective therapy to decrease of C-reactive protein level (CRP), Le numbers, fever as well as symptom intensity. According to that, the decreased level of CRP was 42.4%, number of Le 56.7%, fever 28.4% to symptom improvement of 33.1%. In our study, fever decrease after antibiotic treatment was recorded at 43.6%, CRP in 58.97%, Le in 73.1% with the decrease of symptom intensity in 61.5% of patients. Study from Seoul (15) states big infection frequency in patients at the terminal stage of cancer disease (80.1%), frequent application of antibiotic therapy (84.4%), frequent fever (75.2%) which decreases with antimicrobial therapy (48%), a decrease of CRP in 29 % of cases and the decrease of Le in 17% of cases. Symptom improvement was noticed in totally 15.1% of patients, while the improvement did not happen in 55.4% patients. Mirhosseini et al study (10), identified 31-episode infections 1.2/pat). After antibiotic therapy in 48.4% patients, small improvement related to infection (statistically significant for dysuria and coughing) is noticed. However, 25% of patients died in the first week during antibiotic intake, yet 50% within seven days after the end of antibiotic therapy. In 78 patients from our study, 99 sites of infection (1.3/pat) were identified, and 13 (16.7%) of them died during the antibiotic treatment. Rosenberg et al. (6) article, state that there is high mortality (27%) of patients in palliative care centers during antibiotic treatment. Symptom improvement related to infection after antimicrobial treatment varied from 21.4% - 56.7% cases, and decrease of fever from 47.9% to 54.4% cases. In a retrospective study from Sweden (16), the „positive effect „of antibiotic therapy (fatigue decrease, better energy, loss of fever) is spotted at 37% patients, while the side effect (diarrhea and nausea) was spotted in 4% of patients (in our study at 3.85%). Unlike this study where 50% of samples had a positive culture, in our study 90.9% of samples was microbiologic positive. In both studies, E. Coli and Klesiella pneumonia were the most common infectious causes. Vitetta study (4) states the positive effect of antimicrobial therapy in 40% of cases and E. Coli was most common infectious causes. Similar to our study, the most common site of infections was: urinary tract (42.5%), respiratory tract (22.9%), blood (12.5%), skin and subcutaneous tissue (12.5%). The Lam et al. (17) made research in 87 patients with advanced cancer, and found 70 (80.5%) patients who had 120 infection episodes, where, unlike in our study, the most common lung infection (52.5%), urinary tract (29.2%) and skin (6.5%). At 67.5% are clinical signs of infection microbiologically confirmed. 45.7% of patients received antibiotics in their last 7 days of life, and 55.7% even during their death. Medicines are, similar to our study, usually prescribed parenteral (in 61.5% cases) and orally in 38.5% of cases. Reinbolt et al. (11) study say that in 623 patients 685 infections were

detected (15 patients with 3 infections, 32 to 2 and 576 with one infection). There is no significant difference between the survival of patients with and without infections, as well as those who did or didn't receive antimicrobial therapy. E Coli (27%), Staphylococcus aureus (14.9%), Enterococcus species (14.7%), Klebsiella pneumonia (8.3%), Candida albicans (7.5%), Proteus mirabilis (7.2%) and Pseudomonas aeruginosa (6.3%) are the most common infection causes, and urinary tract, lungs, and skin and subcutaneous tissue are the most common sites of infection. A study conducted in the USA (8 studies with 957 patients in palliative care) (18) states that the frequency of infections is from 29% to 83% (average 41.6%). The most common is the urinary tract infection (30.5%), following by respiratory tract (17.9%), skin (15.7%) and blood (14.4%). The most common infectious causes are E. coli (19-37%), S.Aureus (9–11%), P. Aeruginosa as well as K. Pneumonia (11%), and Enterobacter sp (20%). The frequency of empirical antibiotic application was very high (75%) before the infection was microbiologically confirmed. The oral antibiotic application was in two studies used in 72-82% of cases, contrary to the Homsi et al. (19) study, in an acute palliative care unit where the parenteral application was used in most cases. The average of antibiotic treatment was 11 days. In White et al. (20) study performed in 255 patients of palliative care whose Karnofski score was ≤ 60, the most common infections were infections of the urinary tract (54 patients), respiratory tract (45), mouth and pharynx (13) and skin (12). The most common causes of urinary infections were E. Coli, Enterococcus, Klebsiella pneumonia, sensitive to trimethoprim/sulfamethoxazole (TMP/SMX), ciprofloxacin and amoxicillin; respiratory - Staphylococcus aureus, Klebsiella pneumonia and Pseudomonas aeruginosa sensitive to a levofloxacin and TMP/SMX, and skin infections - Staphylococcus aureus sensitive to cephalexin and TMP/ SMX. With the antimicrobial drugs, the infection symptoms of urinary tract were well controlled, but the efficiency was worse controlled in symptoms caused by respiratory tract infections, pharynx and skin. The research done in palliative care units in Germany (21) states that 63.8% of patients received the antibiotic therapy, where 20% of patients had bad or very bad effect, and the therapy had to be discontinued because of the worsening the general health (41.4%) or ineffectiveness of therapy (25.7%). Doctors usually decided about the therapy beginning, while other team members decided when to stop with the therapy. In Furuna et al. (22) study, with many controversy „for and against „of starting with antimicrobial therapy in palliative care, can be concluded that the decision of beginning with this therapy needs to be made from case to case and according to individualized care aims for every patient.

Conclusion

Antibiotic therapy reduces the symptom intensity in patients with proven infection by microbiological analysis, with very rare side effects. According to that, the main principle of palliative treatment is satisfied – to reduce the suffering and not harming the patients. The positive effect of antimicrobial treatment does not have any influence on the final result of oncological treatment, improvement of Karnofski score or prolongation of life. The doctor who works in palliative care and meets every day with the dilemma to begin or not with antimicrobial therapy, in cooperation with the patient and family, needs to have the freedom to evaluate and make a decision. It needs to be taken into consideration that the guidelines about the use of antibiotics don't exist on the palliative stage of the disease.

The patient satisfaction may be the best "guideline" which tells about the correct decision.

Acknowledgements

Concept and design of the article: Husić S; Acquisition of data: Halilović Dž.; Analysis and interpretation of data: Husić S; Drafting the article: Smajić J.; Improvement the intellectual Content of the article: Husić S; Final approval for publishing: Husić S.

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