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ORIGINAL ARTICLE

An analysis of the bacteria produced in pressure ulcers and the costs of antibiotherapy for patients in a long-term intensive care unit

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Abstract
Aim: The aim of this study was to examine the bacteria produced patients with pressure ulcers (PU) in Long-term intensive care unit (LTICU) and to evaluate the costs of antibiotherapy.
Material and Methods: We conducted a retrospective review of patients with PU in LTICU. A record included age, conditions, comorbidities, length of stay (LOS) in LTICU and prognosis. Number and location of PU, the bacteria produced in the tissue taken from the PU were also recorded. The costs of the antibiotics used for each type of bacteria were calculated and the total treatment costs for the stay in ICU were determined. A multi-variable logistic regression model was created for the variables predicted to have an effect on bacteria production in PU.
Results: A total of 142 patients were included in the study. The median LOS in LTICU was calculated as 80.1±64.8 days. The probability of E. coli production in those with a heel PU was 2.335-fold (p=0.023) and MRSA production in those with percutaneous endoscopic gastrostomy(PEG) was found to be 4.511-fold greater than in those without PEG (p=0.035). The total cost per patient was median 71817.5 Turkish liras(TL) and the antibiotic costs were observed to comprise 10.05% of the total treatment costs.
Conclusions: PU reduces quality of life of patients in LTICU, increases infection rates, antibiotherapy costs and mortality rates. The type of bacteria has an effect on antibiotherapy costs. Identification of the factors that effects costs is important and if managed this may reduce the treatment costs of patients with PU.

Keywords: Pressure Ulcers; Long-Term İntensive Care Unit; Costs of Antibiotherapy.

INTRODUCTION

Pressure ulcers (PU) are wounds which generally develop over a bony prominence, associated with pressure to the skin or subcutaneous tissue (1). The development of chronic PU with a high mortality rate is seen to be more widespread in long-term intensive care unit (LTICU) patients and these are one of the most commonly encountered problems for healthcare workers in these centres (2). There is increasing knowledge about the negative clinical and economic effects of PU which continue to be a permanent problem in the healthcare area (3).

With an adjustment of the clinical and functional status of the patient with PU, which is an important indicator in the determination of mortality of LTICU patients, this independent risk associated with PU can be significantly reduced (4). In England, the total cost of PU treatment is £1.4- £2.1 billion per annum and comprises 4% of total healthcare costs (5). In a study of ICU patients, it was reported that infections of the blood circulation related to a central venous catheter increased hospital costs substantially and the cost of antibiotics was a significant expense (6). It has been reported in literature that while a third of the bacteria produced in colonized PU comprise anaerobic bacteria, this rate reaches 50% in infected PU (7). Due to the close proximity of the gastrointestinal and urogenital systems, chronic wounds may become infected by contamination with microbial flora, which can vary depending on the intestinal system of the patient and environmental factors (8). Researchers have found anaerobic, gram negative bacilli and gram

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positive stems in chronic wounds different from normal skin (9). As LTICU is a new concept in Turkey, there has not yet been any study researching the bacteria produced in PU in LTICU patients.

The aim of this study was to examine the bacteria produced in PU in patients hospitalized in the LTICU of Ulus State Hospital and to evaluate the costs of antibiotherapy. To the best of our knowledge, this is the first study on this subject in Turkey.

MATERIALS and METHODS

Approval for the study was granted by the Ethics Committee of Ankara Numune Training and Research Hospital (decision no: 984, dated 29.06.2016). The study was conducted in accordance with the Helsinki Declaration. A retrospective review was made of the records of 503 patients who were followed up in the LTICU of Ulus State Hospital between January 2013 and March 2016, after exclusion of 70 patients with incomplete records and 12 patients who were repeatedly admitted. Of 449 patients with PU, a total of 142 patients with reproduction in PU culture were included for evaluation in the study. For each patient, a record was made of age, gender, Glasgow Coma Scale (GCS), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, conditions and comorbidities, length of stay (LOS) in ICU and prognosis (exitus or survival). Percutaneous Endoscopic Gastrostomy (PEG), tracheostomy and whether or not mechanical ventilator support was applied, number and location of PU (sacrum, trochanter, heel, ischium) and the bacteria produced in the tissue taken from the PU were also recorded. The costs of the antibiotics used for each type of bacteria were calculated and the total treatment costs for the stay in ICU were determined.

The culture samples taken from the PU were placed in 5% sheep blood agar and eosin methylene blue agar medium in the hospital microbiology laboratory and incubated at 37°C for 18-24 hours. The bacteria determined to have been produced in the culture were identified with conventional methods according to the colony morphology and gram staining properties. Catalase, coagulase, PYR tests and esculin hydrolysis characteristics were examined for gram positive bacteria. In the identification of gram negative isolates, the oxidase test and biochemical tests were used. Antibiotic sensitivity tests were applied and evaluated according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI) after spreading the bacteria suspension according to McFarland 0.5 concentration on the surface of the Mueller Hinton agar medium with the Kirby-Bauer disc diffusion method. Methicillin resistance in staphylococcus strains was examined with cefoxitin and oxacillin discs and the presence of broad spectrum beta-lactamase (BSBL) in gram negative strains with the double disc synergy method.

As a routine application, the Infectious Diseases Clinic was consulted with the culture and antibiogram results and antibiotics appropriate to the patient were started.

The data related to PU were obtained from the records of the PU care unit of Ulus State Hospital. The detailed total treatment costs for the treatment period of the patients were obtained from the hospital invoices in the patient information management system (Alpdata, Ankara, Turkey) and were updated as costs for March 2016 (10). The March 2016 purchase price as recorded in the patient information system was used as the cost of antibiotics.

Statistical analysis

Statistical analyses and calculations were made using IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 software. Conformity to normal distribution of the variables in the study was evaluated with the Shapiro-Wilk test. Descriptive statistics were stated as median (minimum-maximum) together with mean ± standard deviation values. Categorical variables (eg, age, death) were stated as number (n) and percentage (%). Whether or not a difference was seen in the distribution of bacteria strains produced in PU was examined with the Pearson Chi-square test.

The effects of the LOS in LTICU and APACHE II score which were clinically predicted to possibly affect the production of bacteria in PU culture were examined individually for each bacteria. A multi-variable logistic regression model, the Forward: LR model, was created for the variables predicted to have an effect on bacteria production in PU. At each step, the entry probability was taken as 0.05 and the exit probability as 0.10. Odds ratios (OR) were obtained with logistic regression and 95% confidence intervals (CI) were determined. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

From 449 patients with PU who were monitored in the LTICU of Ulus State Hospital between January 2013 and March 2016, a total of 142 with production in PU culture were included in the study. The patients comprised 52 (36.6%) females and 90 (63.4%) males with a mean age of 72.3±14.6 years (range, 24-94 years). The mean GCS was 7.1±2.8, APACHE-II scores 25.6±5.3 and mean LOS in ICU 80.1±64.8 days. None of the patients were mobile. Only 16 (11.27%) patients were discharged from the unit and mortality in ICU was recorded in 126 (88.73%) cases. The most common comorbidities were hypertension (49.3%) and cerebrovascular disease (43%) (Table 1). PEG was applied to 90 (63.4%) patients, tracheostomy to 112 (78.9%), and mechanical ventilator support to 113 (79.6%) patients with spontaneous respiratory failure (Table 1). PU location was determined in the sacral region (85.9%), the trochanter (41.5%), the heel (33.1%) and the ischium (4.9%) (Table 2).

A single bacteria strain was determined to have been produced in the PU culture in 109 (76.8%) cases, two bacteria strains in 22 (15.5%) and three bacteria strains in 11 (7.7%). The bacteria isolated in the PU were Escherichia coli (E. coli) (33.8%), Pseudomonas spp (35.9%), Acinetobacter spp (33.8%), Proteus spp

(19.0%), methicillin resistant staphylococcus aureus (MRSA) in 10 patients (7.0%), and Enterococcus spp in 2 (1.4%) (Table 3). No significant relationship was determined between the bacteria strain and the exitus status. Of the exitus patients, 43 (89.6%) were determined with E.coli produced in the PU culture, and 83 (88.3%) were not observed to have E.coli production (χ^2= 0.053; p=0.819).

Table 1. Demographic and clinical characteristics of the patients

Variables		
Age *		72.3±14.6
Gender **	Male	90 (63.4)
	Female	52 (36.6)
APACHE – II*		25.6±5.3
GCS*		7.1±2.8
LOS (days) *		80.1±64.8
Death and survival**	Death	126 (88.7)
	Survival	16 (11.3)
Conditions/comorbidities**		
	Alzheimer's–Dementia	27 (19.0)
	Parkinson	7 (4.9)
	Diabetes Mellitus	33 (23.2)
	Hypertension	70 (49.3)
	Cardiovascular Disease	8 (5.6)
	Cerebrovascular Disease	61 (43.0)
	Pulmonary Disease	26 (18.3)
	Hypoxic Ischemic Brain Damage	22 (15.5)
	Traumatic Brain and Spinal Cord Injury	12 (8.5)
	Cancer	14 (9.9)
Concomitant problems**		
	Tracheostomy	112 (78.9)
	PEG	90 (63.4)
	Mechanical ventilation	113 (79.6)

* values are stated as mean±standard deviation evaluated with. Student's t test
** values given as number(n) and percentage (%)
LOS: length of stay; PEG: percutaneous endoscopic gastrostomy

Table 2. Pressure ulcers locations in the patients

	Present n (%)	Absent n (%)
Sacrum	122 (85.9)	20 (14.1)
Trochanter	59 (41.5)	83 (58.5)
Heel	47 (33.1)	95 (66.9)
Ischium	7 (4.9)	135 (95.1)

Table 3. The amount of production of the bacteria strains isolated in pressure ulcer

	Not produced n (%)	Once n (%)	Twice n (%)	3 times n (%)	Total production n (%)
E. coli	94 (66.2)	42 (29.6)	5 (3.5)	1 (0.7)	48 (33.8)
Pseudomonas spp	91 (64.1)	42 (29.6)	8 (5.6)	1 (0.7)	51 (35.9)
Acinetobacter spp	94 (66.2)	43 (30.3)	5 (3.5)	-	48 (33.8)
Proteus spp	115 (81.0)	23 (16.2)	3 (2.1)	1 (0.7)	27 (19.0)
MRSA	132 (93.0)	10 (7.0)	-	-	10 (7.0)
Enterococcus spp	140 (98.6)	2 (1.4)			2 (1.4)

E. coli: Escherichia coli; MRSA: methicillin resistant staphylocooccus aureus

The effects of the variables of GCS and APACHE II scores, the application of PEG, tracheostomy or mechanical ventilation and the entry PU status in the sacrum, trochanter, heel and ischium, which were clinically predicted to affect bacteria production in the PU cultures, were examined separately for each bacteria strain (Table 4). When all the defined variables were examined together, as a result of the staged method, a heel PU was determined to have had an effect on the production of E. coli, and PEG on the production of MRSA. The probability of E. coli production in those with a heel PU was 2.335-fold greater compared to those with no heel PU (95% CI: 1.126;4.842) (p=0.023). The probability of MRSA production in those with PEG was found to be 4.511-fold greater than in those without PEG (95% CI: 1.113-18.286) (p=0.035).

When the median expenses of the antibiotherapy were compared for each bacteria strain produced in PU, the highest antibiotherapy cost was determined for MRSA at 915.8 TL, followed by Acinetobacter spp at 619.0 TL, E. coli at 610.7 TL, Proteus spp at 585.5 Turkish Liras

(TL) and Pseudomonas spp at 516.6 TL. The total antibiotic cost was determined as median 721.8 TL (11.5; 39985.0). The total cost per patient was median 71817.5 TL (3122.0; 386775.0) and the antibiotic costs were observed to comprise 10.05% of the total treatment costs (Table 5).

Table 4. The results of the multiple logistic regression models of the variables thought to be related to bacteria production in pressure ulcer cultures *

	Variable	$\hat{\beta}$	$\hat{SE}(\hat{\beta})$	Wald	p	OR	95% CI for OR lower limit; upper limit
[1]E. coli	Heel	0.848	0.372	5.198	**0.023**	2.335	1.126;4.842
	Constant	-0.976	0.230	17.989	**<0.001**	0.377	-
[2]MRSA	PEG	1.507	0.714	4.451	**0.035**	4.511	1.113;18.286
	Constant	-3.367	0.587	32.882	**<0.001**	0.034	

*Forward:Likelihood ratio method was used
[1]sensitivity: 0.0% / -2loglikelihood: 176.473
[2]sensitivity: 0.0% / -2loglikelihood: 67.393
E. coli: escherichia coli; MRSA: methicillin resistant staphylocooccus aureus

Table 5. Antibiotherapy costs for each bacteria strain

	n	Median	(min; max)
E. coli	48	610.7	(11.5; 2963.5)
Pseudomonas spp	51	516.6	(41.0; 13681.0)
Acinetobacter spp	48	619.0	(0.0; 26810.0)
MRSA	10	915.8	(466.0; 12997.0)
Proteus spp	27	585.5	(59.0; 1692.0)
Enterococcus spp	2	-	(653.0; 746.0)
Total antibiotic cost (TL)	142	721.8	(11.5; 39985.0)
Total cost (TL)	142	71817.5	(3122.0; 386775.0)

E. coli: escherichia coli; MRSA: methicillin resistant staphylocooccus aureus; TL: Turkish liras

DISCUSSION

By transferring patients with a prolonged treatment period and critical patients who are not recovering to better equipped ICUs of the University and Training and Research Hospitals, the 34-bed ICU of Ankara Ulus State Hospital provides a service of LTICU without restricting the LOS. Due to the service profile of our hospital, as PU were determined in 449 of the 503 patients followed up in ICU between January 2013 and March 2016, the rate of PU determined at 89.26% was extremely high. In 2 different LTICUs in Canada, the prevalence of PU was determined as 36.8% and 53.2% and the incidence of PU as 11.7% and 11.6% (11). While 26.1% (n=142) of patients were accepted with PU in the palliative care centre, the rate of newly developing PU during stay in the unit was reported as 12.0% (n=65) (12).

Our study, the high rate of PU observed was thought to be due to the admittance to our unit of those with a poor prognosis (GCS 7.1±2.8, APACHE-II scores 25.6±5.3), that patients with a prolonged treatment process or non-recovering critical patients were not transferred, and that the LOS was not restricted as there were no care institutions to which patients could be discharged. The mean age of the patients in the current study was observed to be extremely high and the LOS was long (72.3±14.6 years, 80.1±64.8 days, respectively). Consistent with the current study results, in previous studies conducted in LTICU, reduced mobility and activity, advanced age, malnutrition, comorbidities, chronic diseases, and conditions such as pressure, friction and humidity have been reported to be high risk factors in the development of PU[1, 11]. Of the patients in the study, 63.4% had PEG applied, 78.9% tracheostomy and mechanical ventilator support was required by 113 patients because of spontaneous respiratory failure. The areas of the body with a predisposition for the development of PU are the sacrum and heel regions in particular (13). In a study in an LTC hospital, Neiva et al. (14) reported that PU were observed primarily in the sacral region and in the calcaneus and trochanter regions. In a multicenter (1 university and 11 general hospitals), cross-sectional study in China, PU was determined to be seen most often in the sacrum, heel and iliac crests (15). In concordance with these results in literature, PU location in the current study was seen at the highest rate in the sacral region (85.9%) followed by the trochanter (41.5%), heel (33.1%) and ischium (4.9%).

In a study by Heym et al. (8) which evaluated the efficacy of antibiotherapy applied to PU in patients with spinal cord damage and infected PU, it was reported that of 289 patients, E. Coli was produced in 33, Pseudomonas spp in 20, Proteus spp in 30, Acinetobacter spp in 8, MRSA in 38, and Enterococcus spp in 45. In a review which evaluated studies published between 1966 and 2014, the bacteria most produced in infected PU were determined to be Staphylococcus aureus, Proteus mirabilis, Pseudomonas aeruginosa, and Enterococcus faecalis (13). In the current study, the bacteria most produced in PU were determined to be Pseudomonas spp (35.9%) E. Coli (33.8%), Acinetobacter spp (33.8%), Proteus spp (19.0%), MRSA (7.0%) and Enterococcus spp (1.4%). In another study of patients with similar demographic and clinical characteristics to those of the current study, mean age was reported to be 61.2 years,

duration of hospital stay 69.6 days, tracheostomy catheter was applied in 50.5% of cases, mechanical ventilation support was required by 32.4%, PEG was applied to 145 patients and colonised or infected PU were determined in 111 patients (16). Lunawat et al. (17) reported the isolation of predominantly staphylococcus aureus (42%), pseudomonas (28%), streptococcus (18%) and E. coli (14%) in PU. In addition, production rates of S. aureus, gram negative bacilli and the two together have been reported as 20.7%, 32.5% and 46.8% respectively (16).

In the current study, a single bacteria strain in PU was isolated in 109 (76.8%) cases, two strains of bacteria in 15.5% and three strains in 11 (7.7%) cases. When the total numbers of bacteria isolated in PU were examined, the most frequently produced bacteria were observed to be E. Coli in 48 (33.8%) patients, Pseudomonas spp in 51 (35.9%) and Acinetobacter spp in 48 (33.8%), and at lower rates, Proteus spp in 27 (19.0%), MRSA in 10 (7.0%) and Enterococcus spp in 2 (1.4%). Although larger PU are not associated with a greater risk, it has been suggested that other unmeasured clinical conditions could contribute to increased mortality related to PU (4). In a study which determined PU recovery and mortality rates in a patient group in the final stages of life, the 180-day mortality rate was reported as 68.9%, the 1-year rate as 78.4% and the 2-year mortality rate as 83.8% (18). In our study, 126 of 142 patients were exitus in ICU and the mortality rate was determined as 88.73%. The patient group in the current study comprised patients at the end of life and the majority of patients had more than one diagnosis with DM at 23.2%, HT at 49.3%, CVE at 43.0% and Alzheimer's -dementia at 19.0%.

When the median expenses of the antibiotherapy were compared for each bacteria strain produced in PU, the highest antibiotherapy cost was determined for MRSA at 915.8 TL, followed by Acinetobacter spp at 619.0 TL, E. coli at 610.7 TL, Proteus spp at 585.5 TL and Pseudomonas spp at 516.6 TL. The total antibiotic cost was determined to comprise 10.05% of the total treatment costs. It has been reported that as the grade of PU increases, so the treatment costs increase varying from £1.064 (grade 1) to £10.551 (grade 4) (5). Other studies which have evaluated the antibiotherapy costs of hospital infections have shown that antibiotherapy costs as a proportion of the total hospitalization costs vary in a very wide range from 1.8%-39% (6, 19-21). There are a few studies evaluated the effect of PU infection on the LOS and hospital costs (22, 23). However, to the best of our knowledge, there has been no study which has evaluated the contribution of the type of micro-organism isolated in PU cultures to the LOS. From the profile of the current study patients, a lengthy hospitalization period was predicted.

There are a great many factors which affect treatment costs and a difference may be seen in these factors affecting each specific patient. Therefore, there is a need for further studies of a more extensive population and including more factors to evaluate the effect of bacteria on the costs of patients with PU. In our study can be considered of importance in respect of the effect on costs of the infection agent in PU. The current study can be considered a guide for future studies on this subject.

CONCLUSION

PU not only reduces quality of life of patients being followed up in LTICU but also increases infection rates, antibiotherapy costs and mortality rates. The type of bacteria causing the infection has an effect on antibiotherapy costs. There is a need for more extensive studies to be able to clarify the factors that have an effect on the treatment costs of patients with infected PU. It can be considered that the identification of these factors could reduce the treatment costs of patients with PU.

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