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Review

Real-world medical diagnosis: Intuitive process revisited (review)

Taro Shimizu^{1*} and Yasuharu Tokuda²

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One cannot overlook the fact that diagnostic errors which constitute the largest proportion of errors in medical care have a direct bearing on patient's outcomes. Clinical reasoning ability is closely related to the avoidance of diagnostic errors and clinical reasoning during diagnosis has been explained by a "dual processes model" comprising two elements. The first is the intuitive process (System 1), which emphasizes intuition-based rapidity and the other is the analytical process (System 2), which is an analytical and a scientific process. In this review, the underemphasized intuition-based approach of the first system is highlighted and examined from a clinical and practical perspective.

Key words: Diagnosis, analytical, clinical, System 1, System 2.

INTRODUCTION

Diagnostic errors comprise a large proportion of errors in medical care and have been noted to be highly correlated with morbidity (Kohn et al., 2000; Schiff et al., 2009; Kostopoulou et al., 2008; Brennan et al., 1991; Wilson et al., 1995; Thomas et al., 2000; Tokuda et al., 2011). Undiagnosed and erroneously diagnosed conditions exert a major temporal effect on patient outcomes particularly of patients suspected with diseases requiring urgent care and those with life-threatening diseases. Clinical reasoning ability has been noted as a major competency requirement of professional physicians. This ability is closely related to the avoidance of diagnostic errors (Graber et al., 2005).

THE DIAGNOSTIC PROCESS

The diagnostic process, which is generally termed clinical reasoning, has been explained by a "dual processes model" consisting of two elements (Norman, 2009). The first, the intuitive process (System 1), is based on intuitive thinking, while the other, the analytical process (System

2), is based on analytical thinking. This dual-process model has been widely explored in the field of psychology and has also been adopted into the clinical reasoning field of medicine (Evans, 2008; Stanovich, 1999; Croskerry, 2009; Thompson, 2011). The general features of both processes are shown in Table 1.

In System 1, diagnosis is based on intuitive mental simulations performed subconsciously and informed by the extensive clinical experience of the physician (Gary, 2004). Such a process is termed "heuristics" in cognitive psychology. In particular, this involves "pattern recognition" to determine the correct diagnosis from typical clinical symptoms and findings (Ark et al., 2006) or using "clinical pearls" to facilitate rapid diagnosis by methods similar to heuristics (Mangrulkar et al., 2002; Lorin et al., 2008). A skilled physician can often accurately and rapidly make a diagnosis using these processes. The prominent role of intuition in diagnosis has been noted in studies conducted to determine the same, particularly with respect to complex diseases (Shah et al., 2011; Smithline et al., 2003). A drawback of System 1 is its susceptibility to a range of cognitive biases because of its nature as a linear thought process associated with experience-based intuition.

The analytical process (System 2) uses logically and carefully prepared frameworks and algorithms; Bayes'

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Table 1. The general features of Systems 1 and 2.

System 1	↔	System 2
Intuitive	Complementary/switching	Analytical
Heuristics, clinical pearls	Examples	Frameworks, checklists, Bayes' theorem
One-shot diagnosis	Nature of cases	Complex cases
Rapid, artistic	Advantages	Analytical, scientific
May be affected by biases	Drawbacks	Time-consuming, sometimes inefficient, large burden of knowledge
Experts	Used by	Beginners

theorem, a method for determining post-test probability by pre-test probability and likelihood ratios (Moreira et al., 2008) and mnemonics. System 2 is a more logical and systematic approach than System 1. It is a diagnostic method that allows for a mental "safety net" in which few mistakes are made. However, it has the drawback of sometimes being lesser efficient than System 1, as it takes longer for the physician to perform the analysis and follow the pathways in their memory (Norman, 2009). Because of the safer-looking profiles by the use of System 2, there has been greater emphasis on System 2 rather than System 1. However, the time-consuming process as well as the unrealistic application for patients with common and typical presentations of System 2 has brought resurgence of a great interest of the System 1 intuition process.

DISCUSSION

One might well wonder which method is superior, although they differ so much in their features. Which should the clinician employ in the tradeoff between a speedy or comprehensive diagnosis? Let us consider the clinical site. What have we noticed in our experience of busy clinical settings?

In most cases, we seem to unthinkingly use both processes based on the context of the patient's clinical history and the conditions in real clinical settings. For example, it is often possible to make an intuitive diagnosis in cases involving a common differential diagnosis or in cases such as those previously encountered by the physician. Conversely, the analytical process is preferential for complex or unfamiliar cases, but a diagnosis can also be reached by flexibly using a combination of the intuitive and analytical processes. Thus, we flexibly switch between System 1 and 2, as befits the case in question. Cases that would be difficult for any physician can sometimes be diagnosed rapidly. This is often because of an intuitive diagnosis, the speed of which is its selling point. This property of the intuitive thinking process is part of the art of diagnosis and the use of tacit knowledge, and this rapid and skillful diagnostic technique is a source of infatuation among clinicians at present, considering that much remains unknown about the composition of the

thinking process.

When considering its advantages, there is a great clinical advantage to intuitive thinking. There are many cases in which an appropriate level of rapidity takes precedence over comprehensiveness and logic, particularly for clinicians facing the day-to-day reality of the clinical setting. From this perspective, rather than total commitment to a diagnostic style of logically and thoroughly noting differentiation, the development of clinical skills placing a greater emphasis on intuitive thinking, as well as striving toward such an education may be important. Important specific measures for improving intuitive diagnostic techniques include sharing a wealth of excellent, accumulated "clinical pearls." Positive and persistent efforts to apply heuristics with keen powers of observation and ample accumulation of daily clinical experience are additional essential points. Patients should be exposed to no undue risks because of intuitive thinking if the confounding bias that comprises the key point of concern is adequately mitigated by the counterpart method (the analytical process) to avoid cognitive biases.

CONCLUSION

Consciously and complementarily, using dual processing of intuitive and analytical processes lends range and flexibility to every physician's diagnostic technique. Dual processing is important for refining the diagnostic capability of clinicians. There have been intense discussions on the art of diagnosis and clarification of tacit knowledge. Generalizing these metaphysical concepts into an educational, transmittable form should improve the quality of medical care, especially the quality of primary care. Potential benefits include curbing the overreliance on special investigations. In view of health economics, this means striving toward major reduction in personnel and time costs for health professionals, in addition to positively impacting the health of patients as individuals.

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Full Length Research paper

Managing the Buruli ulcer morbidity in the Amansie West District of Ghana: Can indigenous knowledge succeed?

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Buruli ulcer is a disease that eats through the skin, muscle and bone, leaving victims with disfiguring and debilitating craters. This study was conducted in the Amansie West District, which is the most endemic area in Ghana. The purposive sampling technique was used to select the study population. Data was collected using in-depth interviews with the help of questionnaires consisting of both closed and open-ended questions, in addition to focus group discussions. The research revealed that there are knowledge gaps on how the mycobacterium enters the body, although it is clear the bacterium is unable to do so by itself and therefore, curse from the gods and witchcraft were among the perceived causes of the disease. It was also revealed that indigenous form of treatment such as herbs, clay and honey are widely used as a treatment option. Though their effectiveness and efficacy has not been proven scientifically, the positive responses from patients suggests that its reliability cannot be doubted. There is no drug for the treatment of Buruli Ulcer and though certain antibiotics have been tried, their efficacy is still in doubt. The mainstay of treatment is surgical excision of the lesion and this is both costly and dangerous, leading to the loss of considerable amounts of tissues or disability and thus discouraging patients from seeking treatment. This research concludes that the local terminologies, beliefs and all the names associated with this indigenous knowledge should be documented and understood as an effective intervention for treating and managing Buruli ulcer.

Key words: Indigenous, Buruli ulcer, treatment, mycobacterium, herbs.

INTRODUCTION

Buruli ulcer (BU) is the third most common mycobacterium disease after tuberculosis and leprosy. It was first detected in 1948 among farmers in Australia (where it is known as Bairnsdale ulcer). Buruli ulcer incidence is highest among West African nations (WHO, 2001), with cases in some countries exceeding those of tuberculosis (TB) and leprosy (Amofah et al., 2002). Up to 16% of villages are affected in Cote d'Ivoire (WHO, 2001), and Benin has recorded 4000 cases since 1989 (Portaels and Meyers, 1995) (Lagarrigue et al., 2000). A 1999 national survey in Ghana identified over 6,000 cases, making BU the second most prevalent mycobacterial disease (after TB) in that country (Amofah et al., 2002). In West Africa, nearly 25% of people

infected are left permanently disabled (Johnson et al., 2005). There is also evidence of vast under-reporting of the disease. The incidence of infection has increased dramatically over the past decade, even after considering improved reporting rates, largely as a consequence of environmental changes (Connor and Lunn, 1965). Approximately 31 sub-tropical and tropical regions have reported cases of Buruli ulcer (Kotlowski and Portaels, 2004). These countries include: Angola, Australia, Bolivia, Burkina, Faso, Cameroon, China, Congo, Democratic Republic of Congo, Equatorial Guinea, French Guyana, Gabon, Guinea, French Guyana, Gabon, India, Indonesia, Japan, Liberia, Malaysia, Mexico, Papua New Guinea, Peru, Sierra Leone, Sri Lanka,

Sudan, Suriname, Togo and Uganda. A few isolated cases have been reported in non-endemic areas in North America and Europe, but these cases have been linked to international travel (Duker et al., 2004).

Buruli ulcer silently eats through the skin, muscle and bone and in its worst form, leaves victims with disfiguring and debilitating craters. However, the list of questions surrounding Buruli Ulcer is daunting (Oliver and Webster, 1990). No one is sure where the bacterium lives in the environment. It is also a mystery how it enters the body, although it is clear the bacterium is unable to do so by itself.

Buruli Ulcer was first brought to public attention in Ghana in 1993 when severe cases were reported from the Amansie West district of Ashanti Region in August (MOH). Specifically, the most affected town is Tontokrom, although earlier cases have been reported from the Densu and Afram plains, Bayley (1971) and Van der Werf et al. (1989). In Ghana, a national survey conducted in 1999 found 6000 cases and showed that Buruli ulcer is in all 10 regions. Since then, cases have come from many districts and about 2800 new cases have been recorded. In 2003, 739 cases were reported, while for the first half of 2004, 562 new cases were reported. Today, 30 districts regularly report on the disease to the National Control Program (Ministry of Health, 2011). The overall national prevalence rate of active Buruli ulcer is 20.7 per 100,000 of the population, but as high as 150.8 per 100,000 (Ministry of Health, Ashanti Region). The worse affected regions are Ashanti, Central, Brong Aharfo, Greater Accra and Eastern.

Currently, Ghana is the second most endemic country recording about 1,048 cases of Buruli ulcer after Cote d'Ivoire globally (WHO, 2012). Buruli ulcer has lost a profile in public health, hence finding it difficult to even attract donor support. Meanwhile, this is a disease affecting people who live on less than a dollar a day. According to a recent WHO statistics, the total population of Buruli ulcer cases recorded globally including that of Ghana is 5,076, with Africa being the worst affected.

Signs and symptoms

Buruli ulcer infection may begin with a painless, raised skin lesion or papule and infection may extend from the skin into the subcutaneous tissue and often invades the underlying muscle tissue. In other cases, it presents as edema or swelling and covers an extensive area of the skin. The tissue underlying these areas of edema is necrotic and the edematous region usually breaks down to form a large ulcer.

The disease can also present itself as a firm, painless plaque of a well-demarcated lesion of irregular edges with a reddened or discolored appearance. Ulceration can be extensive and disfiguring, often affecting 50% or

more of a limb. Because of the local immune-suppressive properties of mycolactone, the disease progresses with no pain and fever, which may partly explain why those affected do not often seek prompt treatment. However, without treatment, massive ulcers result, with the classical and undermined borders. Sometimes, the bone is affected, causing gross deformities. When lesions heal, scarring may cause restricted movement of limbs and other permanent disabilities in about a quarter of patients. The aim of this research is to investigate the treatment options available for BU patients, especially from the indigenous perspective.

METHODOLOGY

Study setting

Location and size

The Amansie West District is located in the south-western part of Ashanti Region (Figure 1). The District was carved out of the Amansie East District in 1989 as part of the then government's decentralization policy. It shares boundaries with the Amansie East District in the west, Atwima Mponua District in the east, Atwima Nwabiagya District in the north and Amansie Central in the South. The Amansie West District falls within latitudes 6° 35' and 6° 51' North and Longitudes 1° 40' and 2° 05' West (AWDP, 2004). The District covers an area of about 1,364 square km. and forms about 5.4% of the total land area of the Ashanti Region (AWDP, 2004). The entire District comprises 160 communities with Manso Nkwanta as the District capital. It is divided into 12 local councils, 21 area councils and subdivided into 48 electoral areas. The major towns which serve as growth poles include Manso Nkwanta, Mpatuam, Manso Mem, Manso Atwere, Edubia, Watreso, Abore, Keniago, Essuwin, Ahwerewa and Datano.

The District is underlain by Lower Proterozoic volcanic greenstones with intervening sedimentary rocks and granitoid intrusions (Robb et al., 1999). The main soil type of the district is ferric fluvisols. The district lies entirely in the rainforest belt and exhibits most semi-deciduous characteristics. Furthermore, the district is very rich in forest resources, such as timber, herbs of medicinal value and fuel wood. It also abounds in different species of tropical hardwood, notably Odum, Mahogany and Sapele. There are four main forest reserves in the district, these are: Oda River Forest Reserve, Apamprama Forest Reserve, Gyeni River Forest Reserve and Jimira Forest Reserve.

Study population

The study population consisted of Buruli ulcer patients who were medically diagnosed and whose disease had reached the ulcerative stage. An analytical case-control study was used to conduct the investigation. Data for the study was collected from the three most endemic communities of the Amansie West Districts as presented in Table 1. The communities are Tontokrom, Kaniago and Edubea. The purposive sampling technique was used to select the study population.

This technique was preferred because the study subjects were already defined in hospital record forms. Data was collected using in-depth interviews with the help of questionnaires consisting of both closed and open-ended questions. In addition, focus group discussions were held with interest groups such as mothers who

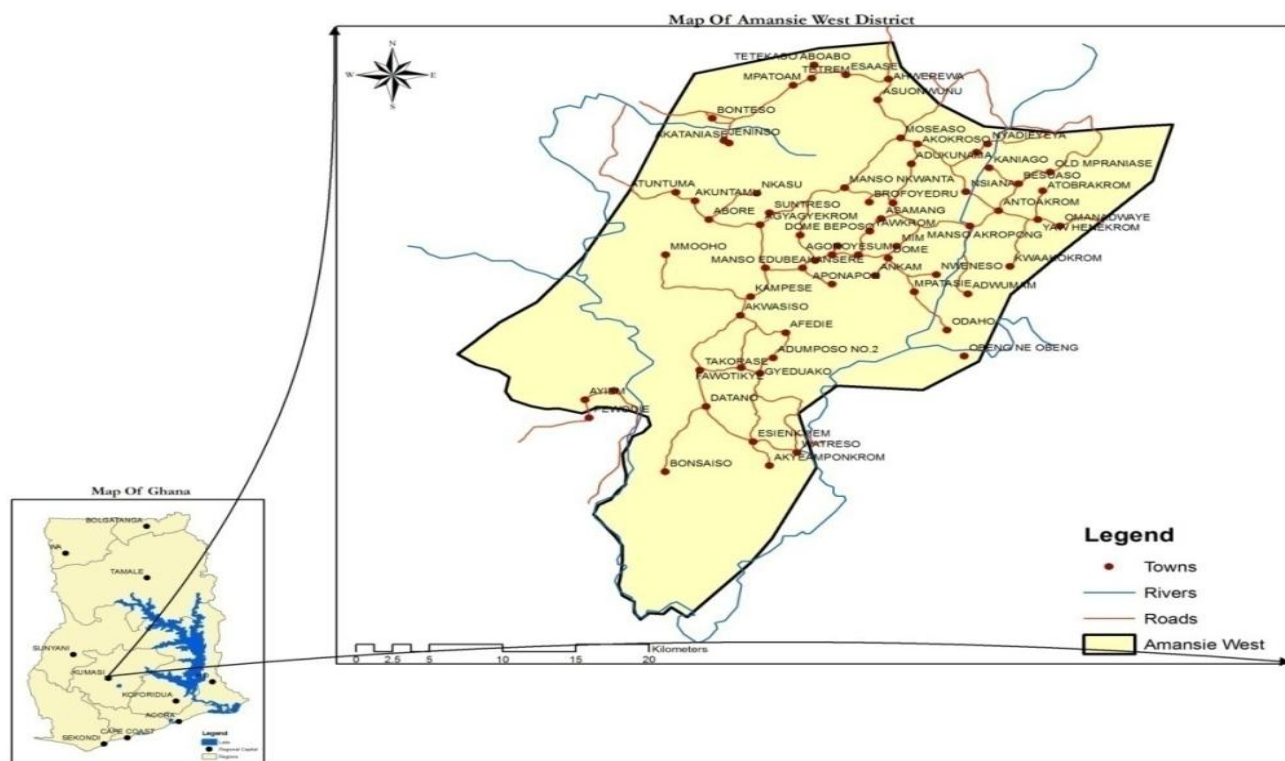


Figure 1. Map of the Amansie West District. Source: Field work.

Table 1. Sample distribution.

Community	No. of male	Percentage (%)	No of female	Percentage (%)	Total no. of participants
Tontokrom	22	44	28	56	50
Kaniago	23	46	27	54	50
Edubea	21	42	29	58	50
Total	66	100.0	84	100.0	150

Source: Field work.

were entirely measured with the respondent’s responses and observation for reasons of logistics.

RESULTS

The exact causes of Buruli ulcer in the Amansei District is still a mystery. However, the causes may not be different from the other endemic areas of the world, although the local conditions may vary from one endemic area to other. From the research, 27.3% were not able to identify the causes of the disease in the community, 30% attributed the cause of the disease to curse from the gods of the land. They believe that the infected patients might have incurred the displeasure of the gods or they are paying for the wrongs committed by their fore fathers.

Moreover, 17.7% attributed the causes to witchcraft, whereas 25% attributed the cause to environmental factors.

The perception of cause influenced the type of treatment option sought by patients. In a focus group discussion (FGD), one infected woman had this to say

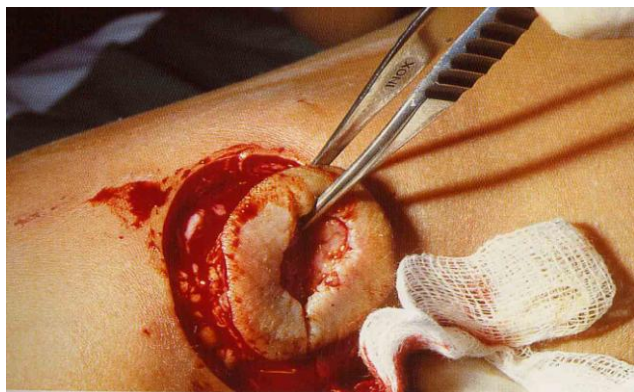
“I do not understand how I got the disease because none of my family members have it even though we live in the same house, drink water from the same source and virtually share everything in common. Because am the only person infected, the family believes it is the work of the evil spirits”.

This assertion was generally agreed by all. A young male infected person also had this to say in another FGD.

Table 2. Preferred choice of treatment.

Source of treatment	Percentage (%)
Orthodox	35
Traditional	65
Total	100

Source: Field work.

**Figure 2.** Surgical excision of ulcerative lesion.
Source: WHO (2000).**Table 3.** Species of herbs for treatment of Buruli ulcer.

Scientific name	Common name	Local name
<i>Barassus aethiopum</i>	Fan palm	
<i>Azadirachta indica</i>	Neem Tree	
<i>Leea guineensis</i>		Agyaben
<i>Cleistopholis patens</i>	Salt and oil tree	
<i>Ficus asperifolia</i>	Sand paper tree	Onyannkyeren
<i>Gardenia ternifolia</i>		Akpetekplebii
<i>Mitracarpus villosus</i>		susubiribi

Source: Field work.

"I certainly believed that it is the work of the supernatural forces, my late grandfather told me that there was once a popular fetish priest in this village who wanted to marry my mother but our family members objected. The fetish priest cursed our family members; it is believed that my sickness is the result".

The responses from the focus group discussions (FGD) indicate that the people in the community do not know the exact cause and mode of treatment. This is however, contrary to a study by Asiedu and Etuful (1998). They contended that the disease is caused by a multiplicity of factors which can be grouped under socio-economic and

physical factors. They listed some of the socio-economic factors as poverty, poor access to quality healthcare, poor education and so on. The physical factors included excessive flooding, deforestation, mining activities and many more. In their survey, these factors were responsible for the high presence of Buruli ulcer in the Amansie West District.

Treatment

Different methods of treatment are used depending on the level of income of the infected, beliefs, religious background, as well as the level of information available to the infected. There are two options of treatment namely scientific or orthodox method and traditional method. As shown in Table 2, 65% of the patients indicated they use traditional medicine as source healing than any other available method. These patients gave various reasons for their choice of treatment, such as no health facility in the community, long distance between place of residence and the nearest health facility, inadequate funds and many others. On the other hand, 35% relied on orthodox medicine for treatment. Again, the perceived cause of the disease influenced the type of treatment sought. The research also showed that cases of the ulcerative stage of the disease were high. The high cases of ulcer were because most of the patients did not seek early treatment due to the high cost of surgical treatment, fear of surgery and concerns about the resulting scars and possible amputations, disfiguration, and stigmatization.

The management of Buruli ulcer is recognized to be frustrating and often unrewarding. The chronic and often recurrent nature of the ulcer makes it expensive to manage both for the patient and the health service providers. In the absence of an effective drug treatment of the disease, the mainstay of treatment is surgical excision of the lesion (Figure 2). This is both costly and dangerous, leading to the loss of considerable amounts of tissues or disability. Again, the research revealed that heat treatment and hyperbaric oxygen therapy has also had clinical success, but is not practical for use in rural areas. Early detection of nodules and surgical excision of small lesions could prevent complications (WHO, 2000). Several anti-mycobacterial agents have *in vitro* activity, but no single compound has proven regularly useful for treatment (WHO, 2001). Current research indicates that a combination of amikacin or streptomycin and rifampicin can kill *Mycobacterium ulcerans* cultured from human lesions (Johnson et al., 2005). Majority of the patients have therefore sought treatment from indigenous sources. Two types of indigenous treatment options were identified by the researcher, and these were treatment with herbs and treatment from spiritualist. These two options, however, played complementary roles as none



Figure 3. A patient receiving traditional treatment from a native doctor.

was mutually exclusive.

Herbal treatment

The results indicate that various species of herbs are combined to offer effective treatment for Buruli ulcer. Some of the common herbs are listed in Table 3. In an interview with one herbalist to find out the right combination of herbs and the mode of administration, he had this to say:

“as for the combination of trees, I will not tell because that is my secret but with the administration, I spread the herbal paste in the area of the ulcer and one must go through this procedure for three to eight months, depending on the state of the disease before there is complete healing”.

Though the effectiveness and efficacy of this method could not be proven by the researcher, the high level of patronage by patients could be an indicative of its ability to treat the disease. One patient who had gone through the treatment from the herbalist explained why she chose the option.

“ I first went to the hospital only to be told that I must go and look for money and then come for surgical operation but how do I get the money? Here nothing is paid until one sees improvement in ones condition”.

Again the permanent skin scare and sometimes the

contractures resulting from skin grafting was enough reason for a twenty-eight year old woman to seek treatment from indigenous source:

“my brother went to do the surgical operation and has been deformed permanently because part of the skin was cut to replace the destroyed one”. “With this man if he heals you, there are no traces of the disease”.

Patients using this option were further interviewed as regards the efficacy of the treatment. A twenty year old man had this to say:

“before I came here, my leg was swollen and very painful, at a point my friends said if I go to the hospital, my leg will be amputated, but since I came here, the pain has reduced drastically, the swelling is gone and as you can see I am getting healed. This man is really good”.

Another native doctor revealed another dimension of their activities. He, unlike his colleagues, adds another dimension to the herbal treatment. He adds clay to the herb to aid treatment (Figure 3). Special clays which have high content of calcium and sodium are used for the treatment of the disease. The clay first absorbs the toxins (heavy metals, free radicals, etc) attracting them to its extensive surface area where they adhere and are absorbed. Healing clays do not only draws toxic materials from the body, but also reduces pain and infection on wounds.

The activities of faith based spiritual leaders were considered for the study as the second form of indigenous

treatment. The research concentrated on a popular spiritual leader because of the claimed potency of his concoctions. He uses honey to treat patients. According to him, the disease has spiritual connotations and therefore he communicates and receives direction from the spirits before the honey is used. One patient at his center had this to say:

“anytime he picks the honey, he makes some recitation before he spreads it on my affected hand. I can see my situation has improved and I trust that he can do it because he has done for many others”.

Honey had been found to treat wounds rapidly, replacing sloughs with granulation tissues. It also promotes rapid epithelialization and absorption of edema from around the ulcer margins.

DISCUSSION

This study investigated the role of indigenous knowledge in the treatment of Buruli ulcer morbidity in the Amansie West District, in the Ashanti Region of Ghana. Using herbs for its therapeutic properties has been part of the Ghanaian livelihood since time immemorial. It is an accepted and unquestioned way of life perceived to be practiced in almost every Ghanaian home. The use of herbs links the living and the dead, the spiritual and physical, the seen and the unseen and the natural and the supernatural. In view of this, many rituals surrounded the use of herbal medicine. These rituals were meant to seek the favor of the ancestors, who are believed to have the ability to diagnose and heal. It is the belief among most indigenous Ghanaians that illnesses were the results of disobedience to the ancestral spirits. So for one to be fully healed, there must be forgiveness from the ancestors. It is for this reason that majority of traditional healers performs spiritual incantations before administering their concoctions.

Honey, which is one of the treatment options, is known to have bactericidal, bacteriostatic and anti-fungal activity. According to Molan (1998), the various antimicrobial activities in honey are achieved through its osmotic effect; it is characterized by a pH value of between 3.2 and 4.5, which is low enough to inhibit many pathogenic growths. The major anti-microbial activity in honey was found to be due to the presence hydrogen peroxide. The use of traditional method in the management of Buruli ulcer has gained grounds in the endemic areas of the Amansie West District of Ghana. Typical among the traditional methods are the use of clay and herbs. Although the effectiveness and efficacy of the traditional method has not been proven scientifically, response from majority of the patients covered in this research suggest that the traditional treatment is very

effective. It is believed that a combination of these herbs provide liquid substances that when properly applied could heal the wounds.

Conclusion

From this research, it is about time indigenous knowledge was given its proper place in the management of Buruli ulcer. Comparatively, the traditional method could be cheaper and readily available than the scientific method which is very expensive. It is believed that when this is done, a lot of resources could be saved, which could then be channeled to the other areas of economic development.

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Full Length Research Paper

The relationship between job characteristics of emergency medical technicians and scene time in traumatic injuries

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Scene time (time at the scene) is one of the performance indices for pre-hospital emergency system, and is defined as the time interval in which an emergency technician reaches a scene, provide the emergency medical services, and leaves the scene. The present study was performed to examine the relationship between job characteristics of emergency medical technicians and scene time in traumatic injuries. Data were collected from 45 emergency medical technicians in Mashhad, North-east of Iran. To evaluate job characteristics of the technicians, "John Wagner's job cognition questionnaire" was used. The scene time was specified using "time scene information form" and for each technician, a mean score of three scene time was calculated to get a more precise estimate of the scene time. Data were analyzed using Pearson's correlation coefficient and Mann Whitney U test. The findings reveal that there is a significant correlation between technicians' job characteristics and scene time ($r = -0.28$). Three variables, that is, skill diversity ($r = -0.44$), job importance ($r = -0.37$), and taking feedback ($r = -0.34$), showed a significant relationship with scene time. No significant relationship between demographic variables and scene time was observed. Decreasing scene time is one of the key indices of pre-hospital emergency system's performance which is achievable through increasing motivation of employees by considering their job's characteristics. The results of the present study show that the investigated technicians do not have an ideal feeling about their job's identity. This can have a negative effect on their performance, especially scene time.

Key words: Job characteristics, scene time, emergency medical technicians, traumatic injuries.

INTRODUCTION

"Time" is an important factor for severely injured traumatic patients' survival (Altintas and Bilir, 2001; Mohd et al., 2008). The available statistics reveal that "trauma-related injuries are the fourth leading cause of death in the United States and they are the primary cause of death among individuals under the age of 45" (Hamilton and Hodge, 2011). Similar condition could also hold true for many other countries around the globe, even worse than this can be seen. Some researchers believe that the shorter the time between the accident and operation start, the more increase in patients' surviving is seen (Altintas and Bilir, 2001).

'Scene time' is one of the operation indices of pre-hospital emergency system. According to global protocols, scene time is defined as the time between arrival of

emergency technician at the scene and leaving the scene. Based on international standards, this time is 10 min (Bledsoe et al., 2003). Therefore, improvement of time indices is amongst the priorities of hygiene and cure systems. Previous investigations show that fast help with standard quality can reduce accident deaths by about 30% (Hamilton and Hodge, 2011). Thus, pre-hospital emergency systems can play a significant role in reducing death, disabilities, and injuries in accidents. Time indices and human resources are of significant importance.

In organizational behavior management literature, human being is considered as the main factor of movement and evolution in organization and the society, and management of the organization should utilize this worthy

and unique resource to achieve the goals of the organization. This is possible through generating motivation in employees by knowing and attending to their real needs.

In the same literature, job design is known as one of the effective approaches to enhance employee motivation, and mechanical, biological, and perceptual approaches as well as motivational approaches which are amongst strengthening methods of job design.

In motivational approach, job design improves effectiveness and attitude interaction of employees, such as job satisfactory, internal motivation, and a set of behavioral consequences such as being absent, displacement, and operation of employees. This approach consists of four methods: job enlargement, job rotation, job enrichment, and an ad-hoc theory called job characteristics model (JCM). JCM studies the factors that make a particular job satisfying. This theory was developed by Hackman and Oldham (1980). "The job characteristics model is based on the idea that the task itself is a key to employee's motivation" (Anonymous, 2012). In other words, "work motivation arises from the characteristics of jobs" (Edgar, 1999).

According to this theory, any job can be described in terms of the following five core job dimensions: skill variety, task identity, task significance, autonomy, and feedback. This theory is seen as being more motivating and satisfying to workers who perform jobs with these characteristics, the five core job dimensions influence psychological states of workers that are more likely to lead to favorable work outcomes: high work productivity and low absenteeism and turnover. The theory further asserts that people with high growth needs are more likely to experience the psychological states with motivating jobs than people with weaker growth needs (Torraco, 2005).

Hackman and Oldham (1980) developed an index called "motivating potential score (MPS)" to determine the motivating power of the job to each employee as well (the corresponding formula is provided in the materials and method). This researcher also adapted the same model and formula to estimate the MPS of the job for the emergency medical technicians.

The main purpose of the present study was to determine the relationship between job characteristics and scene time of emergency medical technicians in traumatic injuries.

MATERIALS AND METHODS

In order to achieve the goal of this study, 45 technicians of emergency medical services in Mashhad, North-east of Iran participated in the study. Minimum sample size was estimated by a pre-test:

$$n \geq \frac{N \times Z_{\alpha/2}^2 \times \sigma^2}{(N - 1) \times \varepsilon^2 - Z_{\alpha/2}^2 \times \sigma^2}$$

$$N = 140, \varepsilon = 0.06, \sigma^2 = 0.05, n \geq 43$$

In the aforementioned formula, N is the number of population, ε is the accuracy of the estimation, σ^2 is the sample variance, and n is the number of the sample. According to the formula, sample size was estimated to be 43. Practically, 55 people were chosen for this study.

Sample description and trainings

Most of the investigated subjects (84.44%) were trained as emergency medical technicians and the rest (15.55%) as operation room or anesthesia technicians. The stated technicians underwent different training before they were fully involved with their job responsibilities. First, they got a formal training for 24 months in the college and received a technician degree. Then, they were hired by the traumatic medical emergency office which supervises various emergency units of this nature in each province in Iran (the so called Emergency Medical Services, 115). As the technician started the job, they were tested on their knowledge and more materials were provided for them to read while simultaneously they will be trained in the field for 100 h. During this period, they will rotate between the traumatic emergency units to get experience and skill. Finally, they were placed in the dispatch unit to get experience and skills of working in this unit. This part of training lasted for 20 h.

A simple random sampling procedure was used to select the samples. The selection was from the list of the technicians who provided the traumatic injuries emergency services during the second half of 2009.

In this study, John Wagner's (1980) job recognition questionnaire was used to measure the job characteristics of emergency medical system technicians. This questionnaire consist of two sections: the first section included questions on personal characteristics of respondents and the second section included questions on Wagner's job characteristics. This section had five dimensions and each dimension had three questions (total of 15 questions), which were scored according to the five point Likert scale where incorrect = 1 and completely correct = 5.

As stated earlier, the main elements of the job can be combined and indicated by a predictable index called MPS. MPS can be calculated by:

$$MPS = \frac{\text{Skill diversity} - \text{Work identity} - \text{Work importance}}{3} \times \text{Independence} \times \text{Feedback}$$

The first three dimensions (job diversity, job identity, and job importance) combine together to make a valuable and significant work. If a person has a job which has high freedom and liberty, it will give him the sense of responsibility about his/her operational results, and if in a job, a feedback about the result and the employee's work is offered to him/her, the person can understand how to do his/her job in an effective way. Considering motivation, this model argues that when the person learns (knowledge of result) to do his work on his/her own (accept the responsibility of the work and experiences that his/her work is valuable), internal reward is the outcome. The more these triple occasions are available, the more motivation and satisfaction appear, and being absent from work and leaving the work will decrease. The relation between main dimensions of work and the result are adjusted through the amount of person's need for development. Personal development can be seen in somebody's respect for himself/herself and self-efflorescence. It means that when a job has these five dimensions, people in whom trend to personal development is in high level, experience more psychological conditions in comparison with the people whose trend to personal development is in low level.

Table 1. Demographic characteristics of emergency medical technicians.

Variable		Frequency	Percentage
Marital status	Married	34	75.6
	Single	11	24.4
Education level	Emergency Medical Technician (EMT)	38	84.44
	Operation Room Technician (ORT)	5	11.11
	Anesthesia Technician (AT)	2	4.44
Work sector	Government	17	37.8
	Private	27	60
	Unknown	1	2.2
Type of employment	Tenure	2	4.4
	Contractual	12	26.7
	Convention employment*	5	11.1
	Company	26	57.8

*Is a kind of contractual employment with less job benefits

Therefore, they will respond to their experiences.

Jobs which have high motivational power should be at least amongst one of the three factors which lead to job worth. Furthermore, considering independence and liberty in doing a work and feedback of the work, these jobs should be in high levels. If MPS is high, the model predicts that motivation, performance, and satisfaction will be positively affected and the possibility of being absent from work and leaving the work will be reduced (Robbins, 2010).

The score of MPS on the stated questionnaire ranged from 1 to 125, and the categorization of MPS score is as follows: < 50 = low; 50 to 87.5 = medium; and > 87.5 = high. To measure the scene time, for each technician, a mean score of scene time was calculated. That is, the scene time of the incidences for each technician was randomly selected and then their mean was estimated.

The validity of this questionnaire has been approved in a study by Faraji et al. (2008). To measure the reliability of John Wagner's job recognition questionnaire in this study, 20 questionnaires were distributed amongst emergency medical technicians. Cronbach, α , was calculated to be 0.76.

RESULTS

In this research, 55 questionnaires were distributed among the selected emergency technicians from which 45 were completed and returned to the researcher. The findings revealed that the age mean score of the participant was 28 years, with standard deviation (SD) = 3.95 year. The youngest emergency technician was 22 and the oldest one was 42 years old. The mean score of working experience was also 4.0 years with SD = 2.05 years. The minimum and maximum of technicians' working experience was 1 and 8 years, respectively. With regards to the marital status, 75.6% were married and 24.4% single (Table 1). Information on technician's educational level, working sector, and the type of employment are presented in Table 1.

To investigate the job characteristics of emergency technicians, the second part of the questionnaire was used, which contained 15 questions. These questions used 5-point Likert scale. Table 2 represents the mean score, and standard deviation of each dimension of job characteristics model, potential motivational power, and scene time.

The findings in Table 2 reveal that the mean score of each dimension of job characteristics is above the amount of average, and there is no much dispersion among the stated scores. The mean score of scene time was estimated to be 11.93 min, with SD of 4.17 min; where, minimum and maximum values were 5.64 and 28.43 min, respectively.

A negative correlation between technicians' mean scene time, and the skill diversity, job importance, feedback, and motivational power score was observed in this study (Table 1). This means that an increase in skill diversity of technicians, importance of their job, their feedback, and potential motivational power will lead to decrease in average scene time. No significant relationship was observed between job identity and average scene time (Table 3). This result shows that increase or decrease in job identity do not have any effect on average scene time. The results on job independence are the same.

The relation between personal characteristics (age and work history) and mean scene time was evaluated using a Pearson correlation test. The findings did not show any significant correlation between age variable and mean scene time ($r = -0.05$, $P = 0.7$), and work history and scene time ($r = -0.1$, $P = 0.55$).

The mean scene time for married and single technicians was 23.07 and 22.77 min, respectively (Table 4). To investigate the effect of marital status on scene time,

Table 2. Statistical indices for five dimensions of Wagner's job characteristics questionnaire and potential motivational power (MPS).

Variable	Statistical index				
	Frequency	Average	Minimum	Maximum	SD
Skill diversity	45	2.8	1.33	5	0.8
Job identity	45	2.7	1	4.68	1.33
Importance	45	2.65	1	5	0.91
Independence	45	3.05	1	5	0.902
Feedback	45	3.03	1.33	4.67	0.81
Potential motivational power	45	29.18	4.89	93.33	21.82

Table 3. Coefficient of correlation between scene time, on one hand and job characteristics' dimensions and potential motivational power, on the other hand.

Parameter	Skill diversity	Job identity	Job importance	Independence	feedback	Potential motivational power
Average scene time	-	-	-	-	-	-
P-value						

Table 4. The average rating, considering marital status of emergency medical technicians.

Variable	Marital status	Frequency	Average rank	Total rank
Average scene time	Married			
	Single			

Table 5. Results of comparison between Hackman and Oldham's job characteristics dimensions' average scores and potential motivational power (MPS) with global standards.

Job characteristic	Average score	Standard score	T- value	P-value	Average difference
Skill diversity	.	.	- .	0.075	- .
Job identity	.	.	- .	<0.001	- .
Job importance	.	.	- .	<0.001	- .
Job independence	.	3.5	-3.	.	- .
Job feedback	.	.	- .	<0.001	- .
Potential motivational power (MPS)	.	45.5	- .	<0.001	- .

Mann Whitney U test was used (the number of single people was less than 30 people). The findings reveal that marital status have no significant effects on the scene time (Mann Whitney U: 184.5, test statistic: -0.066, P = 0.94).

In order to compare the average scores obtained on Hackman and Oldham's job characteristics model's dimensions and MPS, with the global standards, a T-test was used in this research. The findings are shown in Table 5. The results show that the average amount of all variables, except the skill diversity, is below the standard score, and these differences are significant.

DISCUSSION

The findings of this study reveal that there is a significant relationship between motivational power of the job and average scene time. These findings support Oldham and Hackman (1980) job characteristics model. If the time is considered as a performance criteria, jobs which show better characteristics regarding Oldham and Hackman (1980) model, can improve somebody's performance and enhance his/her job satisfaction.

In this research, the average score of "job identity" was lower than that of global standard. Khalili (2000)

mentioned that all the investigated jobs, except computer services and communication job groups, do not have job identity. As Khalili (2000) performed his study in a hospital, it can be said that the results of this study support his results. In this study, no significant relationship was observed between "job identity" and "scene time" of Mashhad emergency medical technicians. If "time" is considered as an efficiency index, the results of this study agree with those of Faraji et al. (2008).

The findings indicate that the average score of "skill diversity" dimension for the investigated emergency medical technicians (2.8) is almost equal to the global average score (3.1). Therefore, it can be said that job design has been made possible for employees to use all their skills and capabilities. In this field, Majidi (1998) obtained similar results for job holders and management jobs in "construction ministry".

According to the results of this study, there is a significant relationship between "skill diversity" and "scene time" for Mashhad emergency medical technicians. With regards to the "job importance" of emergency medical technicians, the results of this study show that the average score of this dimension (2.65) is lower than that of global standard. This indicates that technicians believe that their job has a moderate effect on life of other people. These results do not agree with those obtained by Miresmaili (2005), who carried out his researches on nurses. Furthermore, according to the results of this study, there is a significant relation between "job importance" and "scene time" of Mashhad emergency medical technicians. In other words, if the person thinks that his/her job can have a considerable effect on others' life, he/she will show a better performance regarding scene time.

The results of this study indicate that the average score for "operation freedom" and "feedback" dimensions were 3.05 and 3.03, respectively, which are below the global standards. It means that the investigated emergency medical technician did not feel independence and feedback in their job. This result agrees with that of Khalili (2000) and Miresmaili (2005). Khalili (2000) concluded that employees of all of job groups, receives no feedback from their activities. Miresmaili (2005) in his research on nurses found that there is no feedback in different jobs.

Based on the findings of this study, there is no significant relationship between action freedom (independence) and scene time of Mashhad emergency medical technicians. Considering the degree of sensitivity of these technicians' job, such results are acceptable. Certainly, these technicians are not allowed to do whatever they want and apply their own opinions to their work. Furthermore, it was found that there is a significant negative correlation between the feedback and scene time of technicians. This means that an increase in feedback received by technicians leads to a decrease in scene time.

The average amount of "scene time" in this research was

11.93 min, which is an acceptable score in comparison with global standards. The estimated scene time by global standard is 10 min, which is not much far from 11.93. As there are many interfering variables in Iran, this result is an acceptable-arbitrary treatment for injured people, people who gather around the location of the accident, emotional behaviors while facing an accident, and lack of correct disaster management by parties being involved are amongst interfering factors which increase the average scene time. Therefore, taking all of these interfering factors under consideration, an average of about 12 min for scene time obtained in this research is an acceptable figure.

An important point on demographic characteristics of the investigated subject is the type of cooperation between Mashhad emergency medical services (EMS) system and its personnel. According to the findings of this study, only 4.4% of the employees have tenure track position and 57.8% do not have. This indicates that rate of job insecurity among these technicians is high. The results of this study showed that marital status and work section (public or private) do not have any effects on average scene time.

Decreasing scene time is one of key indices of pre-hospital emergency system's performance. One of the effective factors for this index is increasing motivation of employees by considering their job's characteristics and their job security. The results of the present study reveal that the investigated technicians do not have an ideal feeling about their job's identity which can have a negative effect on their performance, especially scene time. A question which might arise here is "how to enhance emergency medical technician motivation at job and improve their feeling about their job identity", Since about 60% of the investigated technicians have little job security in this organization, awarding a tenure track position to these employee is highly recommended. Furthermore, since the MPS and the score on its components (job identity, job importance or significance, job independence or autonomy and feedback) are lower than the standard, therefore, job redesign and job enrichment using the JCM approach is also recommended. As Chareonvan (2011) reported, "motivation in the work place can be achieved through both external (compensation) and internal factors" and JCM focuses on internal aspects. Useful details for applying the JCM and its core components at work by human resource officers can be seen in the work of Chareonvan (2011), and this researcher, to a large degree, recommended the same solutions for improving the emergency medical technicians motivation and job identity as well.

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Full Length Research Paper

Clinical and electrophysiological correlation of patients with chronic renal failure: The contributions of quantitative neurological scores

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Neuropathy is the most common neurological consequence of uremia and has the scarce symptoms and definition. Therefore the sensitivity/specificity of clinical scores the neuropathy symptom score (NSS) and the neuropathy disability score (NDS) were evaluated for uremic neuropathy in the present study. 38 hemodialysis patients (23 males, 15 females) and 15 age-sex matched healthy subjects were enrolled. Neurological interrogation and examination of the subjects has been performed before neurophysiological examinations. After the usual 2 days interval in dialysis, electrophysiological studies (EPS) have been performed. Before the EPS, blood samples has been taken before a midweek dialysis; hemoglobin, Hct, and albumin concentrations were measured. The Kt/V value was taken as the average of previous 12 sessions Kt/V values. The mean NSS was 1.66 ± 2.2 , mean NDS was 5.02 ± 6.9 in the patient group. According to EPS, 25 patients (65.8%) were diagnosed as having neuropathy [Np (+)] and 13 (34.2%) were normal [Np (-)]. The mean values of median, sural nerve sensory, common peroneal and posterior tibial nerve motor conduction velocities were lower in the patient group compared to controls. Np (+) patients was older than that of Np (-) subjects (50.1 ± 13.8 versus 36 ± 13.6 ; $p = 0.006$). Age was the only significant predictor of neuropathy (OR = 1.08, 95% CI, 1.017 to 1.150; $p = 0.013$). Logistic regression analysis revealed that both NSS (OR = 2.651, 95% CI, 1.1 to 6.4; $p = 0.03$) and NDS (OR = 1.26, 95% CI, 1.001 to 1.6; $p = 0.049$) were significantly associated with increased risk of neuropathy. The current study showed that both NSS and NDS are sensitive and specific in the diagnosis of uremic neuropathy and could be used at least as a first step before turn towards the electrophysiologic studies.

Key words: Uremic neuropathy, neuropathy symptom score, neuropathy disability score, electrophysiological studies, risk prediction.

INTRODUCTION

Neuropathy is the most common neurological consequence of uremia, occurring in at least 60% of patients who begin dialysis for chronic renal failure (Raskin, 2001).

The prevalence of clinical signs of polyneuropathy in patients undergoing hemodialysis has ranged between 10 and 83%, with larger series in the range of 50 to 60% (Bolton and Young, 1990). Using electrophysiologic studies as a more sensitive index, the prevalence of polyneuropathy has been somewhat higher, ranging from 57 to 100% (Dyck et al., 1995). Symptoms of uremic polyneuropathy are restless legs, cramps, weakness, paresthesias, dysesthesia, pain, and burning feet (Nielsen,

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1971). The earliest signs of neuropathy are impaired vibratory sensation in the lower limb and loss of tendon reflexes, first the Achilles and then the patellar responses. Other signs are muscle atrophy, weakness and hypoesthesia. Sensory loss develops two-point discrimination, position sensation and light touch, pain and temperature sensation (Tyler, 1968; Bolton, 1976).

In routine clinical practice, the scarce symptoms definition and recording cause some problems in the defining and following process of the subjects. The quantitative scoring system for neuropathy symptoms and also examinations can be more beneficial in this aspect.

The electrophysiologic features of uremic neuropathy include prolonged distal motor latencies, conduction velocity slowing, and declines in the amplitudes of compound muscle action potentials (CMAPs) and sensory nerve action potential amplitude (SNAPs) (Bolton and Young, 1990; Nielsen, 1974). Although there is lot of electrophysiological study of uremic neuropathy, optimum methodological process and the real contributions of long latency reflexes (that is, F response, H reflexes) are also unclear (Ackil et al., 1981; Panayitopoulos et al., 1977). Slowed nerve conduction velocity (especially sural nerve in the early phase) is frequent in uremic patients without other symptoms or signs of neuropathy. Although there are some suggestive data about the contributions of late responses in the process, the correlation between motor nerve conduction studies and late responses are not clearly reported (Ackil et al., 1981).

In spite of some studies suggested, a negative correlation existed between serum creatinine elevation and decreased velocity of motor nerve conduction (Jebsen et al., 1967; Nielsen, 1973; Ackil et al., 1981). There is also conflicting evidence in the relationship between the severity of neuropathy and age, gender, biochemical variables and type of renal disease (Dyck et al., 1995). The neuropathy generally evolves over several months but on occasion follows a fulminate course (Ropper, 1973). The factors that determine these differences in the clinical course of the neuropathy and the optimum method for the follow-up process are unclear.

Peripheral neuropathy has a high prevalence in diabetic patients also (Dyck et al., 1993). Objective and quantified measures of diabetic neuropathy are recommended in the follow up of disease and for epidemiological studies or therapeutic trials (Diabetes Care, 1992). Clinical scores have been developed and validated to quantify the severity of neuropathy such as the neuropathy symptom score (NSS) and the neuropathy disability score (NDS) in patients with diabetic neuropathy (Dyck, 1988, 1985). Significant associations between both NSS and NDS and some individual variables in nerve conduction studies were reported in diabetic neuropathy (Dyck, 1985). A combined index of polyneuropathy derived from nerve conduction studies was found to be well correlated with both NSS and NDS in diabetic subjects also (Feki and Lefaucheur, 2001). However clinical applicability and reliability of those clinical scoring sys-

tems in uraemic patients is not extensively studied.

In the present work, our aim was to investigate peripheral nervous system abnormalities in the light of clinical scoring systems and broad electrodiagnostic surveys, to correlate demographic, laboratory and clinical data with the objective and subjective determinants of neuropathy in hemodialysis patients. Furthermore, we investigated the contributions of quantitative neurological scoring systems (NSS and NDS) when neuro-physiological diagnosis is accepted as the gold standard.

PATIENTS AND METHODS

Patients and clinical evaluation

We studied 38 patients undergoing chronic maintenance hemodialysis treatment two or three times weekly, for 3 to 5 h per session. The mean length of hemodialysis treatment before the study protocol was 4.5 ± 2.3 years (range: 1 to 11 years). The etiology of uremia was as follows; atherosclerosis in 12 patients (31.6%), polycystic renal disease, interstitial nephritis or glomerulonephritis in 9 patients (23.7%), obstructive nephropathies in 4 patients (10.5%) and other etiologies in 5 patients (13.2%). The real etiology of renal failure in 8 patients (21%) was not known. All the patients were taking medications including calcium containing phosphate binders, a standard B+C vitamin complex pill after dialysis session, oral or intravenous iron supplementation and erythropoietin alpha/beta 4000 to 5000 IU subcutaneous 1 to 3 times in a week, to stabilize hemoglobin levels > 10.5 gr/dl. Patients with other possible causes of neuropathy such as diabetes mellitus, alcoholism, amyloidosis, or other systemic causes were excluded from the study. All patients gave written informed consent for the study protocol and detailed explanation has been made according to Helsinki declaration.

Neurological interrogation and examination of the subjects has been performed before neurophysiological examinations. After the usual 2 days interval in dialysis, electrophysiological measurements have been performed. Before the electrophysiological investigations, blood samples have been taken before (fasting) a midweek dialysis session; hemoglobin, hematocrit, and albumin concentrations were measured using appropriate biochemical methods. The Kt/V is defined as dialyzer urea clearance (K), multiplied by the dialysis session length (t), divided by the urea distribution volume (V) (Basile et al., 1990). Kt/V value was taken as the average of previous 4 weeks (12 sessions) Kt/V values per session.

The major symptoms encountered in peripheral neuropathy are listed in the neurological symptom score (NSS) developed by Dyck et al. (1999) specifically for diabetic neuropathy; where a total of 18 points. (1) Symptoms of muscle weakness (bulbar/limbs), (2) sensory disturbance [(negative/positive symptoms), autonomic symptoms] are questioned and the presence of each symptom is considered as 1 point to reach a maximum total 18 points. Neurological impairments of the subjects has been calculated using neuropathy impairment score (NIS) developed by Dyck et al. (1995) after the neurological disability score for the specific follow-up of neuropathy patients. Where neuropathic deficits for cranial nerves (3rd nerve, 6th nerve, facial weakness, palate weakness, and tongue weakness) were examined and scored as 1 point for each of them. Muscle weakness is scored: normal = 0; 25% weak = 1; 50% weak = 2; 75% weak = 3; and paralyzed = 4 for 18 separate joints handled by the different muscle groups. Respiratory muscle weakness is scored as present = 1, absent = 0. Reflexes were graded as normal = 0, decreased = 1, or absent = 2 (Nielsen et al, 1972).

Touch-pressure, pinprick and vibration are assessed on the dorsal surface of the terminal phalanx of index finger and great toe

Table 1. Demographic characteristics of patient and control groups.

Parameter	Patient (n = 38)	Control (n = 15)	p
Age	45.7±15.1	41±12	NS
Sex	23M/15F	11M/4F	0.04
Time on dialysis	4.5±2.3	-	-
BUN	96.4±29.1	-	-
Creatinine	4.1±1.7	-	-
Albumine	3.8±0.96	-	-
NSS	1.7±2.2	-	-
NDS- total	20±5.2	-	-
Neuropathy (+/-)	26(68.4%)/12(31.6%)	- /15	0.000

and were graded as normal = 0, decreased = 1, or absent = 2. Right and left extremities are scored separately and total score were calculated as the sum of the right and left sides, the highest possible score being 208. This score has been recommended to use extensively in medical practice simply to worsening or improvement of neuropathies. Total score has been calculated for each subject and used in the statistical analysis.

Nerve conduction studies

The whole neurophysiologic measurements were done using Medelec Synergy EMG Equipment (Medelec-Oxford, England) and appropriate analysis programs. The temperature of the extremities kept at least 29°C. If they were cooler, the limbs were warmed. The motor and sensory nerve conduction studies have been performed from each extremity of the subjects except if the extremity has arteriovenous (AV) fistula for hemodialysis. The motor nerve conduction velocity, distal motor latency, and CMAP amplitude of the median, ulnar (one side), peroneal and posterior tibial nerves (two side) were measured. The F-wave minimal, mean and maximal latencies and chronodispersion of F-waves were studied after 10 supramaximal stimuli. The sensory nerve conduction velocity and SNAP of median, ulnar (one side) and sural (two side) nerves were measured. The exact details of the methods for each nerve have been described elsewhere (Flack B-1991, EMG yöntem kitabı). Electrophysiological values of patients were compared with those of control group. Values exceeding the mean ± 3 standard deviation (SD) of the control group were considered as abnormal.

Statistical analysis

The results of descriptive analyses were tested and found to show normal distribution, thus data were given as the means and standard deviations. Parametric data were compared using unpaired t test and nonparametric data were compared using the χ^2 or Fisher exact tests. The correlations between the neuropathy, quantitative neurological scoring and the biochemical or demographic variables were determined using appropriate statistics. Binary logistic regression analysis was used to determine the predictive factors including NSS and NDS for neuropathy development.

The sensitivity, specificity, and positive predictive value (PPV) were calculated for NSS and NDS using ROC-curve analysis and the electrophysiological neuropathy diagnosis as the gold standard. Sensitivity here refers to the proportion of patients with these NSS or NDS abnormality who meet the neuropathy diagnosis. Specificity refers to the proportion of patients who do not have these NSS or NDS abnormality and who did not meet the neuropathy diagnosis. PPV refers to the proportion of patients with the NSS or NDS

abnormalities who actually have the disease. Significant differences (two-tailed p) less than 0.05 were regarded as significant. Neural network analysis was performed to determine the sensitivity, specificity and the cut off values of NDS and NSS for differentiation of polyneuropathy types including motor or sensory or mixed polyneuropathy. Radial basis function was used for the classification of neuropathy types according to NDS score due to having better performance for this data set than the other models.

RESULTS

The mean age of our patients was 44.4 ± 14.3 years (from 21 to 75 years) and males were predominating (61%, 23 patients). Fifteen volunteers have been interviewed as control subjects. Similar to the patient group, males were predominating (73%, 11 subjects) in the control group. The mean age of the control subjects was 41.1 ± 12.02 years (from 26 to 67 years). According to selection criteria, groups were comparable for age and gender. Demographic features of the study and control groups have been shown in Table 1.

The mean NSS score was 1.66 ± 2.2 (0 to 8) and the mean NDS score was 5.02 ± 6.9 (0 to 20). There was a strong positive correlation between NSS and NDS results ($r = 0.844$; $p = 0.001$). NSS and NDS examinations revealed superficial sensory loss in 4 patients (10.5%), deep sensory loss in 7 patients (18.4%), abnormality in deep tendon reflexes in 9 patients (23.7%), trophic defect in 3 patients (7.8%) and autonomic defect in 1 patient (2.6%). Electrophysiological study (EPS) results showed that the mean values of median and sural nerve sensory, common peroneal and posterior tibial nerve motor conduction velocities were lower in the patient group compared to controls. However, ulnar sensory and motor conduction velocities were similar between patient and control groups.

Median motor distal latency was longer in patients compared to control subjects. Except for posterior tibial nerve, all motor nerve amplitudes studied were shown to be decreased in patient group compared to controls. Minimum F wave latencies and F wave chronodispersion values were not different between patient and control groups (Table 2) while the EPS results of each of the

Table 2. Comparison of the values in nerve conduction studies between patient and control groups.

Parameter	Patient (n = 38)	Control (n = 15)	p
Median sensory conduction velocity	52.1±5.5	56.2±3.8	0.011
Ulnar sensory conduction velocity	52.6±4.8	54.3±2.7	0.113
Sensory distal latency difference of median and ulnar nerves recorded IVth digit	0.3±0.02	0.2±1.12	0.02
Median motor distal latency	3.9±0.6	3.4±0.3	0.000
Median motor conduction velocity	54.2±4.5	54.2±4.5	0.985
Median motor amplitude	7.0±3.2	9.6±3.5	0.014
Ulnar motor conduction velocity	57.0±4.9	57.8±6.1	0.619
Ulnar motor amplitude	8.3±2.2	10.2±1.7	0.005
Common peroneal motor conduction velocity	40.8±7.2	46.7±3.4	0.004
Common peroneal motor amplitude	3.2±2.0	4.6±1.7	0.02
Posterior tibial motor conduction velocity	37.3±4.2	43.6±2.8	0.000
Posterior tibial motor amplitude	5.7±2.5	7.3±2.6	0.051
Sural sensory conduction velocity	32.5±18.7	44.4±4.3	0.001
Median F min	27.5±2.5	26.3±1.6	0.08
Median F chronodispersion	2.3±1.0	2.7±1.4	0.323
Ulnar F min	28.7±3.3	27.9±2.2	0.411
Ulnar F chronodispersion	1.7±0.9	1.9±0.8	0.47
Tibial F min	52.2±9.0	48.2±4.7	0.11
Tibial F chronodispersion	3.4±1.9	3.1±1.3	0.663

patients compared with the mean values of normal controls separately; 3 patients (7.8%) showed a decrease in median nerve conduction velocity, 7 patients (18.4%) showed a decrease in sural nerve conduction velocity, 3 patients (7.8%) had decreased peroneal BKAP amplitudes, 3 patients (7.8%) had decreased common peroneal conduction velocity, 9 patients (23.7%) had decreased tibial nerve conduction velocity, 11 patients (28.9%) showed an extended median nerve F wave latency. Ulnar F wave latency was extended in 11 (28.9%) and tibial F wave latency was extended in 12 (31.6%) patients.

According to those results, 25 patients (65.8%)

were diagnosed as having neuropathy [Np (+)] and 13 (34.2%) were normal [Np (-)]. Among the Np (+) patients, 5 patients (20%) had sensory neuropathy, 1 patient (4%) had motor neuropathy and 19 patients (76%) had mixed neuropathy. Entrapment of the median nerve in carpal tunnel (Carpal Tunnel Syndrome) was observed in 11 patients (28.9%). Np (+) patients was older than that of Np (-) subjects (50.1 ± 13.8 versus 36 ± 13.6 ; $p = 0.006$). Haemoglobin, hematocrit (%), serum albumin, kt/V and time on dialysis values were similar between Np (+) and Np (-) patients. Np (+) patients had significantly higher NSS and NDS scores than that of Np (-) subjects (Table 3).

Logistic regression analysis revealed that both NSS (OR = 2.651, 95% CI, 1.1 to 6.4; $p = 0.03$) and NDS (OR = 1.26, 95% CI, 1.001 to 1.6; $p = 0.049$) were significantly associated with risk of neuropathy. The determinative values for the occurrence neuropathy in NSS and NDS were as follows: for NSS = 0.5 [Se = 0.654, Sp = 0.667; $p = 0.014$, positive predictive value (ppv): 81%, negative predictive value (npv): 47.1%], for NDS = 1.5 (Se = 0.538, Sp = 0.833; $p = 0.033$, ppv = 87.5%, npv = 45.5%), (Figure 1). A logistic regression analysis performed on the possible predictive factors (age, time on dialysis, Kt/V, hemoglobin, albumin for neuropathy showed that

Table 3. Comparison of demographic features, laboratory analyses, NSS and NDS scores between Np (+) and Np (-) patients.

Parameter	Np (+)	Np (-)	p
Age	50.1±13.8	36 ±13.6	0.006
Sex (male/female)	16/9	8/5	NS
Time on dialysis	4.6±2.4	4.3±2.1	NS
Hb	8.3±1.4	7.8±1.3	NS
Hct	28.2±1.8	27.3±3.7	NS
Albumin	3.6±0.9	4.1±0.9	NS
Kt/v	1.27±0.04	1.28± 0.05	NS
NSS	2.3±2.2	0.3±0.5	0.008
NDS	6.9±7.6	0.8±1.9	0.009

NSS: neural symptom score, NDS: neural disability score, Np: neuropathy.

Table 4. Classification of patients with different neuropathy types using NDS (neural network analysis).

Parameter	Classification			
	Mixed PNP	Absence of PNP	Motor PNP	Sensory PNP
Total	19.0	13.0	1.0	5.0
Correct	11.0	13.0	0.0	0.0
Wrong	8.0	0.0	1.0	5.0
Unknown	0.0	0.0	0.0	0.0
Correct (%)	57.9	100.0	0.0	0.0
Wrong (%)	42.1	0.0	100.0	100.0
Unknown (%)	0.0	0.0	0.0	0.0

the age was only a significant predictor of neuropathy (OR: 1.08, 95% CI, 1.017 to 1.150; $p = 0.013$).

Neural network analysis revealed that the NDS was the most sensitive test for discrimination of neuropathy types sensory, motor or mixed. However, NSS was neither sensitive nor specific for the classification of neuropathy types. Radial basis function was used for the score due to having better performance for this data set classification of neuropathy types according to NDS than the other models. 58% of the patients with mixed type polyneuropathy and 100% of Np (-) patients have been accurately diagnosed using NDS. However, patients with motor or sensory polyneuropathy were not correctly diagnosed due to low patient numbers in those groups (Table 4). Increase in NDS score led to increase in the probability of having mixed type polyneuropathy. Patients with a NDS > 12 had 0.75 probability of having mixed type polyneuropathy. Patients with NDS < 7 had a probability between 0.5 to 0.7 to be np (-). The probability of being np (-) progressively decreased in patients with NDS > 7 (Figure 2).

DISCUSSION

The present study showed a high prevalence of uremic

neuropathy (65.8%) according to EPS results that was in line with the reports in literature (Zochodne, 2005). Male predominance of our patient group may contribute to this high prevalence also (Galassi et al., 1998). Neuropathic patients were older than non-neuropathic subjects. Likewise, Bazzi et al. (1991) reported a more severe electrophysiologic impairment of ulnar and sural nerves in older hemodialysis patients compared to younger ones. They reported a more severe neurologic impairment in patients with longest duration of dialysis (more than 10 years).

In present study, duration of dialysis, weekly Kt/v, hemoglobin, hematocrit and albumin values were not different between neuropathic and non-neuropathic subjects. However, in our patient group, mean duration of dialysis was shorter (4.5 ± 2.3 years) compared to their results. Laaksonen et al. (2002) could not find an association between occurrence of neuropathy and duration or efficiency of dialysis also. Uremic neuropathy can affect motor, sensory, autonomic and cranial nerves (Galassi et al., 1998); however it clinically presents a symmetrical distal sensory loss for all modalities which is more pronounced in lower extremities (Raskin, 2001).

In the current study, the most prevalent neuropathy type was mixed (sensory + motor) polyneuropathy (76%), followed by isolated sensory (20%) and isolated motor

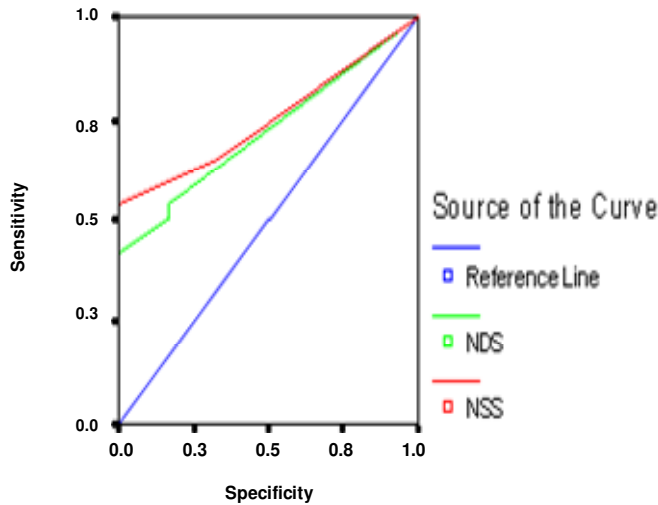


Figure 1. ROC-Curve analysis showing sensitivity and specificity of NSS and NDS in electrophysiologic diagnosis of neuropathy in uremic patients.

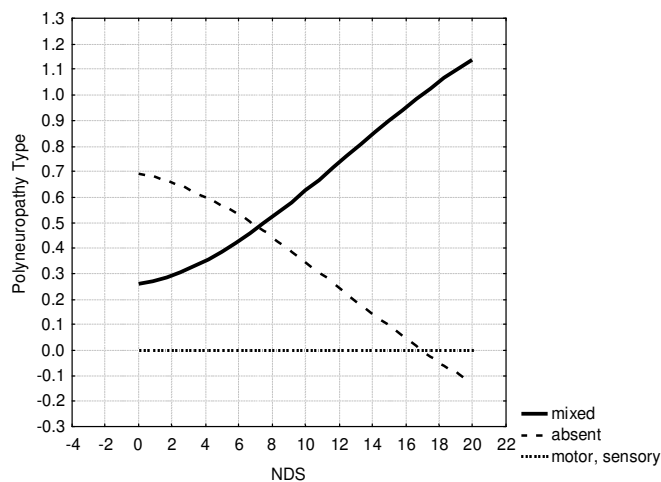


Figure 2. Confidence response graph showing the determinative effect of NDS on mixed type polyneuropathy and the absence of neuropathy.

neuropathies (4%). Although we did not perform an objective test for autonomic neuropathy, NSS results determined autonomic defect in 1 patient (2.6%). There is no strict definition for a predominant type of neuropathy in uremic patients. However, the pathological state uremic neuropathy is a multiple neuropathy due to axonal degeneration of the sensory and motor nerves, starting from the lower extremities with secondary development of demyelination (Thomas et al., 1971). Furthermore, as a support to our findings, previous studies based on either EPS results or quantitative neurologic scoring systems revealed the synchronous presentation of sensory and

motor neuropathies in uremic subjects (Laaksonen et al., 2002; Ogura et al., 2001).

Original description of uremic neuropathy were made by Marin and Tyler (1961) as subacute weakness, distal sensory loss to pinprick, cold, light touch, vibration and position and loss of deep tendon reflexes. The electrophysiologic features of uremic neuropathy include prolonged distal motor latencies, conduction velocity slowing and declines in the amplitudes of CMAPs and SNAPs (Bolton and Young, 1990; Nielsen, 1974). Sural nerve conduction slowing is suggested to be most sensitive electrophysiologic parameter of early polyneuropathy (Ackil et al., 1981). In agreement with those previous findings, our results revealed significant slowing of sural sensorial conduction velocities in patient group compared to healthy controls.

Slowing in common peroneal and tibial motor conduction velocities, prolongation of median motor distal latencies and decrease in motor amplitudes except posterior tibial nerve were noticed in patient group compared to controls. Although slowing in median sensorial conduction velocity is observed, median motor, ulnar motor and sensorial conduction velocities were not seemed to be affected. That may be due to entrapment of the median nerve in carpal tunnel (Carpal Tunnel Syndrome/CTS) which was observed in 11 patients (28.9%). Significant difference in sensory distal latencies of median and ulnar nerves recorded IVth digit was a further evidence for important entrapment of median nerve in carpal tunnel. It is well known that hemodialysis patients are prone to compression of median nerve in carpal tunnel secondary to dialysis associated amyloidosis or uremic tumoral calcinosis (Gejyo et al., 1997; Cofan et al., 2002). So, the abnormalities seen in the median nerve recordings were probably not caused by the polyneuropathy alone. The latencies of "long loop" F waves and H reflexes are prolonged in uremic neuropathy (Panayitopoulos, 1980, 1977).

Laaksonen et al. (2002) showed that the F wave latencies of the lower extremity nerves were by far the single most sensitive neurophysiologic parameter in detection of uremic neuropathy. Although comparison of mean F wave recordings were not different between our patient and control groups, comparison of the patients individually with the mean values of control group revealed prolongation of F wave latencies in median (11 patients; 28.9%), ulnar (11 patients; 28.9%), and tibial (12 patients; 31.6%) nerve recordings. Similar F wave latency values between patient and control groups may be caused by the low patient number in our study.

The current study is mainly conducted to evaluate the predictive roles of subjective neurologic symptom (NSS) and neurologic disability scores (NDS) which are mainly validated for diabetic neuropathy (Dyck, 1988) on EPS results as a gold standard in the diagnosis of uremic neuropathy. Both NSS and NDS in our patient group were higher than that of controls. Furthermore, both NSS and NDS were found to be sensitive and specific tests in de-

termination of uremic neuropathy. Previously, vibration perception threshold (vibrometer testing) was shown to be a valid and valuable, simple, quick and non-invasive method for evaluation of severity in peripheral uremic neuropathy by different authors (Klima et al., 1991). Krishnan et al. (2006) reported a significant correlation between total NSS and both pre-dialysis subexcitability and depolarizing threshold electrotonus.

Significant correlations between different neurophysiologic records (sural conduction velocity and amplitude, tibial conduction velocity and amplitude, tibial F wave latency) and related local symptoms were reported also (Laaksonen et al., 2002). However to our knowledge till date, no study evaluated the sensitivity and specificity of NSS and NDS in diagnosis of occurrence or typing of uremic neuropathy. The present study showed that both NSS and NDS were sensitive and specific tests in diagnosis of uremic neuropathy. Our results demonstrated that NDS may also predict the occurrence of mixed type polyneuropathy in hemodialysis patients. Because of the low patient numbers in motor and sensory neuropathy groups, we could not make a comment about the predictive role of NDS on these neuropathy types.

Conclusion

Uremic polyneuropathy is probably the most common complication of chronic renal failure and affect the significant proportion of the hemodialysis patients. To date, there is no universally accepted approach to the diagnosis and the management of neuropathy in hemodialysis patients. Although EPS is the gold standard for the diagnosis of neuropathy, it is time consuming and not feasible for all the patients. Both NSS and NDS are simple, quick and practicable tests and could be applicable to hemodialysis patients with regular intervals. The current study demonstrated that both NSS and NDS are sensitive and specific in the diagnosis of uremic neuropathy and could be used at least as a first step before turning towards the electrophysiologic studies.

ABBREVIATIONS

OR, Odds ratio; **EPS**, electrophysiologic study; **Se**, sensitivity; **Sp**, specificity; **ROC**, receiver operating characteristic; **BUN**, blood urea nitrogen; **NSS**, neuropathy symptom scale; **NDS**, neurological disability scale.

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Full Length Research paper

Clinical status and pulmonary function in patients with long standing (more than 30 years) asthma

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Asthma is the most common chronic lung disease. The fate of patients with long standing (LS) asthma is of interest. The large number of LS asthmatics at two inner-city hospitals was an impetus to this study, LS asthma: > 30 years. All patients were non-smokers or minimal smokers and had no other lung disease. Data obtained: gender, race, age, body mass index (BMI), forced expiratory volume in 1 second (FEV1), FEV1% predicted, forced vital capacity (FVC), FVC% predicted, FEV1/FVC, diffusion capacity for carbon monoxide percent (DLCO%) predicted, functional residual capacity (FRC), inhaled bronchodilator (BD) usage and response, and inhaled corticosteroid (ICS) usage. For the 65 patients, 37 (57%) were black, 48 (74%) were females, mean age was 53.0 ± 14.7, and 58 (89%) were overweight/obese. FEV1 and FVC% predicted were slightly/moderately reduced in 26 and 24 patients; severely reduced in 27 and 17%, respectively. FEV1/FVC was slightly reduced in 17%, moderately/severely reduced in 11% and was normal in 37%. DLCO% predicted was normal in 28%, slightly/moderately reduced in 31% and was severely reduced in 6%. FRC was increased in only 37%. A typical LS asthmatic is an overweight/obese woman who has a decreased DLCO, FEV1 and FVC, a normal or slightly decreased FEV1/FVC and FRC, and regularly uses BD/ICS without an acute BD response. Using FEV1/FVC ratio to diagnose or follow patients with asthma can be misleading.

Key words: Long standing asthma, obesity, bronchodilator response, restrictive impairment, diffusing capacity, pulmonary vasculopathy.

INTRODUCTION

Asthma is characterized by bronchospasm and inflammation. It is the most common chronic lung disease and there is considerable interest in longstanding (LS) asthma, particularly concerning airway remodeling and overlap with chronic obstructive pulmonary disease (COPD). There has been speculation about the sequelae of LS asthma and whether it transits into COPD in certain patients (Savage-Brown et al., 2005; Ulrik, 1999; Pascual and Peters, 2005). We used readily available non-invasive pulmonary function (PF) indices to provide information on the following: forced expiratory volume in 1 second percent (FEV1%) predicted, forced vital capacity

percent (FVC%) predicted, FEV1/FVC ratio, total lung capacity (TLC), functional residual capacity (FRC), and diffusing capacity for carbon monoxide percent (DLCO%) predicted. Diffusing capacity is generally considered normal in asthma. Several investigators have reported increased DLCO on the basis of increased pulmonary capillary volume secondary to greater negative intrathoracic pressure and inspiration against obstructed airways (Keens et al., 1979) and capillary recruitment due to redistribution of pulmonary blood flow (Weitzman and Wilson, 1974).

METHODOLOGY

This study was undertaken at the Catholic Medical Centers of Brooklyn and Queens, consisting of two inner city teaching hospitals in the borough of Queens, New York City. It was approved

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Table 1. Age, BMI and mean predicted pulmonary function values in 65 long standing asthmatics.

Parameter	Mean \pm SD
Age	53.72 \pm 14.66
BMI	33.29 \pm 8.64
Mean predicted values \pm SD	
FEV1%-preBD	62.49 \pm 17.57
FEV1%-postBD	64.69 \pm 19.24
FVC%-preBD	71.14 \pm 15.83
FVC%-postBD	74.06 \pm 16.88
FEV1/FVC-preBD	70.55 \pm 11.96
FEV1/FVC-postBD	70.03 \pm 12.09
TLC%(n = 61)	102.31 \pm 20.73
FRC(n=60)	121.65 \pm 40.71
DLCO%	77.00 \pm 16.40

SD, Standard deviation.

Table 2. Gender, race, weight and BD use and response in 65 long standing asthmatics.

Parameter	%
Female	74
Minority	95
Black	57
Overweight or obese	89
BD usage	100
ICS usage	100
BD response	37

Table 3. Pulmonary function in 65 long standing asthmatics.

FEV1% predicted	Number (%)
≥ 80	12 (18.46)
$\geq 60 < 80$	26 (40.00)
< 60	27 (41.54)
FVC% predicted	
≥ 80	24 (36.92)
$\geq 60 < 80$	24 (36.92)
< 60	17 (26.15)
FEV1/FVC	
≥ 70	37 (56.92)
$\geq 60 < 70$	17 (26.15)
$\geq 50 < 60$	9 (13.85)
< 50	2 (3.0)
DLCO% predicted	
≥ 80	28 (43.08)
< 60	6 (9.23)

by the Institutional Research Board as a retrospective record review over the years 2001 to 2007.

Asthma was defined as a diagnosis made by a pulmonologist which remained the treating diagnosis over the years of observation based on variable symptoms and PF and an acute response to bronchodilator (BD) or a positive response to methacholine (8%). The group consisted of moderate to severe persistent asthmatics for > 30 years.

All patients were non-smokers (cigarettes, cigars or marijuana) or had smoked less than 5 years and quit > 30 years ago. Most patients had lived in New York City all of their lives without exposure to biomass fuels or agricultural processes; the remaining patients had lived in New York more than half of their lives. All patients had no other lung disease by history or imaging, no continuing exposure to passive smoking, no cancers, no physical abnormalities affecting the chest wall and no surgeries to the chest wall or lungs.

Spirometry adhered to the current American Thoracic Society/European Respiratory Society Standards (American Thoracic Society, 1987). Lung volumes were measured by body plethysmography and diffusing capacity by single-breath technique using rapid gas analyzers and assuring clearance of deadspace. The reported FEV1/FVC was defined by the pre BD value. Miller's predicted values were used (Miller et al., 1986).

In order to assure that the values for DLCO expressed as percent predicted would not be unrealistically low, the predicted values were selected because they are in the midrange of published predicted values and preferred for many studies of DLCO (Aduen et al, 2007; Wise et al, 2007), best fitted a recently published survey of almost 1000 healthy adults (Thompson et al., 2008) and were shown to give normal values in normal subjects when higher predicted values gave abnormal results (Najm and Farber, 2008).

A list of all asthmatics was obtained from the PF database from 2001 to 2007. Clinical charts were reviewed on 169 patients; all patients were investigated for asthma. Because of the earlier listed criteria, 104 patients were excluded from the study. We obtained data about gender, age, body mass index (BMI), FEV1, FEV1% predicted, FVC, FVC% predicted, FEV1/FVC, DLCO%, FRC, TLC, inhaled BD usage, BD response and inhaled corticosteroid (ICS) usage.

There were 26 patients who had more than one study. The studies were compared to each other for these patients. For statistical analysis, the student t-test was used.

RESULTS

Results of age, BMI, mean pre and post BD pulmonary function are given in Tables 1 and results of sex, obesity, BD, ICS usage and BD response are given in Table 2. All patients used ICS and inhaled bronchodilators (BD) on a regular basis; they did not pass > 3 to 6 months without having to use BD and ICS.

Of the 65 patients, 48 (74%) were females. The mean age of all the patients was 53.7 ± 14.7 years; 14 (22%) patients were ≥ 65 years (10 females), 16 (25%) patients were ≤ 40 years (11 females). Mean BMI was 33.29 ± 8.64 ; 36 (55%) patients were obese (BMI >30) [31 females, 65% of the females] of whom 22 patients were morbidly obese (BMI >35) and 22 patients were overweight (BMI 25 to 30) [14 females]. Only 7 patients had a BMI <25 . Almost all patients (62) were minority; 37 (57%) were black.

Data on pulmonary function test (PFT) are shown in Table 3. Only 18% of the patients had a normal FEV1,

Table 4. Demographic and Pulmonary Function values in 65 long standing asthmatics with normal and reduced DLCO.

Parameter	DLCO%>80 predicted n = 28 (Mean ± SD)	DLCO%<80 Predicted n = 37 (Mean ± SD)	P value
Age	50.86 ± 12.51	55.89 ± 15.92	0.1732
Black	54	59	
BMI	34.93 ± 8.41	32.05 ± 8.72	0.1863
FEV1%-preBD	66.11 ± 17.32	59.76 ± 17.49	0.1504
FVC%-preBD	74.75 ± 17.28	68.41 ± 14.28	0.1102
FEV1/FVC-preBD	71.43 ± 9.26	69.89 ± 13.75	0.6119
TLC% (n = 27, DLCO>80; n = 34, DLCO<80)	98.63 ± 18.68	105.24 ± 22.06	0.2193
FRC (n = 27, DLCO>80; n = 33, DLCO<80)	118.04 ± 38.11	124.61 ± 43.19	0.5393
BD Response	46%	30%	

SD, Standard deviation.

Table 5. Frequency of normal and abnormal PF in 65 long standing asthmatics with normal and reduced DLCO.

Parameter	n = 65 (%)	DLCO%>80 predicted n = 28	DLCO%<80 predicted n = 37 (%)
FEV1% predicted			
normal	12 (18)	7 (25)	5 (13)
decreased	53 (92)	21(75)	32 (87)
FVC% predicted			
normal	24 (37)	14 (50)	10 (27)
decreased	41 (63)	14 (50)	27 (73)
FEV1/FVC			
normal	37 (57)	16 (57)	21 (57)
decreased	28 (43)	12 (43)	14 (43)
FRC	n = 60	n = 27	n = 33
increased	22 (37)	8 (30)	14 (42)

while 42% had a severe decrease in FEV1. Only 37% of the patients had a normal FVC, while 26% had a severe decrease in FVC. On the other hand, the FEV1/FVC was normal in 57% when compared with 18% for FEV1 and 37% for FVC. Abnormal airways were better demonstrated by FEV1% predicted than by FEV1/FVC ratio. For the 37 patients with normal FEV1/FVC, 25 (65%) had an abnormal FEV1.

More than half of the patients (37 of 65, 57%) had an abnormal DLCO and 6 patients had a severe decrease. Of these 6 patients, all were females, age range 62 to 79 years, mean age 71.3 ± 8.0 years. All the patients had reduced FEV1, while FEV1/FVC was reduced in 5.

There were 26 (41%) patients that had more than one study. Of these, 11 (42%) had a change in DLCO ≥10%. Of the 6 patients in whom the DLCO increased, 5 had an increase in FEV1 and 1 had a decrease. Of the 5 with a decrease in DLCO, 3 had increase in FEV1, 1 did not

change and 1 had a decrease. The FVC changed in the same direction as FEV1 for 10/11 patients. Statistical analysis did not show any differences. Change in DLCO was therefore unrelated to change in FEV1 or FVC in these 11 patients.

When the group was subdivided into those with normal DLCO versus reduced DLCO, all other PF variables were more abnormal in the reduced DLCO group, there was no significant difference (Table 4). Differences between those with normal versus reduced DLCO are better seen in frequencies of abnormal values than in differences in mean values (Table 5).

DISCUSSION

In these inner city community hospitals, a typical LS asthmatic patient that regularly uses BD/ICS, has about a 74% chance of being female, 57% of being black, 89% of

being overweight or obese, 37% chance of having an increase in FRC and a 57% chance of having a reduction in DLCO%. This study confirms the great frequency of obesity in asthma, especially LS asthma (89%), which has been noted by many authors (Gwynn, 2004).

The FEV₁ was far more likely to be abnormal than the FEV₁/FVC, especially when the patients were divided with respect to normal and abnormal DLCO: 87% of the latter had a reduced FEV₁, 74% had a reduced FVC, while 43% had a reduced FEV₁/FVC.

Although, DLCO is generally considered to be normal or slightly elevated in asthma, 57% of these LS asthmatics had low values (Weitzman and Wilson, 1974). A recent study from our institution reported that 32 of 413 (8%) patients with asthma of any severity or duration had a low DLCO after all other explanations for a low value were ruled out (Miller and Palecki, 2007).

This study demonstrates an even greater frequency of a restrictive or "nonspecific" pattern of spirometric impairment (decreased FEV₁ and FVC with normal FEV₁/FVC) in this group with long standing asthma. We have previously reported this pattern in 10% of patients with asthma (Miller and Palecki, 2007). It has also been reported in many patients with asthma or similar airways disorders and described as "volume loss" or "volume de-recruitment" due to airways closure. Obesity was frequent (Hyatt et al., 2009). In this study, in which patients were selected solely by the chronicity and persistence of their asthma, this pattern was even more frequent than in the previous reports in which patients had asthma of varying persistence and duration. This pattern is not attributable to air trapping in most of our patients in whom FRC was normal. This pattern has been the striking and consistent finding in many large carefully studied cohorts exposed to World Trade Center gases, fumes and dusts and diagnosed as "asthma" or "reactive airways" (CDC, 2004; Feldman et al., 2004; Skloot et al, 2009).

We were interested in whether change in DLCO correlated with worsening or improvement in airflow as reflected in FEV₁; there was no correlation.

In this group of patients with LS asthma, 57% showed a decreased DLCO and 9% showed a severe decrease. We can hypothesize that reduced DLCO is due to alveolar, capillary or other vascular damage perhaps associated with airway remodeling, despite daily ICS. What pathologic basis do these findings of reduced DLCO, spirometric restriction, absent air trapping (in most cases) and absent response to inhaled corticosteroids point to? Similar findings in WTC "asthma" have raised the question of bronchiolitis, where inflammation may involve surrounding alveoli (Guidotti et al., 2011). Bronchiolitis may occur with normal pulmonary function. When pulmonary function is impaired, evidence of airways obstruction and/or reduced DLCO is seen. Elucidating the underlying pathophysiology will require a larger population and other techniques (oscillometry, lung compliance, inspiratory/expiratory high resolution CT, open lung biopsy).

Conclusions

We observed that long standing asthma is associated with a reduced DLCO in more than half of the subjects, obesity was common and a reduced FEV₁ and FVC with a normal FEV₁/FVC ratio often in the absence of air trapping reflecting a restrictive pattern was also common.

The majority of these subjects did not show reversibility during bronchodilator study.

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Full Length Research paper

Multidrug-resistant pathogens causing ventilator-associated pneumonia: Risk factors, empirical antimicrobial therapy and outcome of patients in an intensive care unit (ICU) of a Brazilian university hospital

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Ventilator-associated pneumonia (VAP), multidrug-resistant (MDR) microorganisms and inappropriate empirical therapy poses a major therapeutic challenge in developing countries. The aim of this study was to investigate the risk factors of VAP due to MDR pathogens, to assess the rate of inappropriateness of empirical antimicrobial therapy and its subsequent impact on the outcome of VAPs. From May 2009 to August 2010, in a clinical-surgical intensive care unit (ICU) of a Brazilian hospital, patients with VAP were empirically treated with antibiotics. A case-control study was carried out using patients with VAP by MDR pathogens (case) and non-MDR pathogens (control). Appropriateness of empirical antimicrobial therapy and 30-day hospital mortality were evaluated. We found that among 320 patients requiring tracheal intubation for more than 48 h, 81(25.3%) developed VAP and 43(47.3%) due to MDR pathogens. The risk factors for this latter group were: Length of hospital stay, use of corticoids and prior use of antibiotics. Empirical antimicrobial therapy was inappropriate in 30.9% of patients, with 84.0 and 70.0% these with VAP by MDR pathogens and mixed etiology, respectively. VAP caused by MDR pathogens and the inappropriate empirical antimicrobial therapy were significantly associated with 30-day ICU mortality.

Key words: Ventilator-associated pneumonia, antimicrobial resistance, intensive care unit, empirical antimicrobial therapy, 30-day hospital mortality.

INTRODUCTION

Ventilator-associated pneumonia (VAP) is the main infectious complication in the intensive care unit (ICU) because of its frequency, high mortality and considerable hospital cost (Depuydt et al., 2008; Garcin et al., 2009; Nicasio et al., 2010).

Brazil and Latin American countries, in general, have higher levels of bacterial resistance among most of its key pathogens, compared with Europe and United States, particularly among non-fermentative Gram-negative bacilli and extended-spectrum beta-lactamase

(ESBL)-producing Enterobacteriaceae, but also among some Gram-positive organisms (mainly *Staphylococcus aureus*) (Rossi, 2011).

Gram-negative organisms predominate in hospital-acquired pneumonia, particularly *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and the Enterobacteriaceae. Unfortunately, the resistance of these organisms to antibiotics, mainly to carbapenems, challenges the appropriateness of empirical antibiotic prescription (Peleg and Hooper, 2010; Magnotti et al., 2011). To ensure appropriate empirical antimicrobial therapy, current guidelines for the treatment of VAP advocate for empiric combination therapy with broad-spectrum antibiotics in those patients with risk factors for resistant microorganisms (Joffe et al., 2008; Nicasio et

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al., 2010), which are more frequently associated with late-onset VAP, prior hospitalization or previous antibiotic therapy within the past 90 days (Joseph et al., 2010).

Inappropriate empirical antimicrobial therapy is known to adversely affect outcome in pneumonia associated with mechanical ventilator (Waele et al., 2010) and needs to be tailored to the institutions microbial ecology and the length of time the patient was in hospital before pneumonia developed (Peleg and Hooper, 2010). Appropriate antibiotic use in hospitals entails finding a middle road between their potent ability to reduce the mortality and morbidity of patients with infectious diseases and their potentially hazardous effects, that is, serious adverse events, drug interactions, and induction of resistant strains (Hulscher et al., 2010).

The aim of this study was to investigate the risk factors for developing VAP due to multidrug-resistant (MDR) pathogens, to assess the rate of inappropriateness of empirical antimicrobial therapy and its subsequent impact on the evolution of VAPs in patients interned in a clinical-surgical ICU in a Brazilian University Hospital.

MATERIALS AND METHODS

Setting

The Uberlândia Federal University Hospital Clinic (UFU-HC) is a teaching hospital with 500 beds and a clinical-surgical ICU of adults with 15 beds.

Study design

From May 2009 to August 2010, all patients admitted to the ICU requiring tracheal intubation and mechanical ventilation for more than 48 h and developed VAP were eligible for inclusion in the study. A retrospective case-control study was carried out using patients with VAP by MDR pathogens (case) and non-multidrug-resistant (non-MDR) pathogens (control).

Only the first episode of VAP was considered for each patient. Endotracheal aspirate was collected by probe no. 12 early in the morning by health professionals (physiotherapists or nurses) in charge of the procedure, and transported in a sterile tube to the Microbiology Laboratory. Isolates were identified by conventional biochemical tests as previously described (Koneman, 2008).

The following patient data were retrieved: age, gender, invasive procedures, admission diagnosis, previous use of antibiotics and corticoids, length of hospital stay and duration of mechanical ventilation. Empirical antimicrobial therapy was evaluated according to American Thoracic Society guidelines (ATS, 2005) and microbiological findings were used to determine whether the empirical treatment targeted the identified bacteria. The hospital mortality was assessed within 30 days after VAP onset. The Ethics Committee for Human Research of the Uberlândia Federal University (UFU) approved the project.

Definitions

1. Ventilator-associated pneumonia: The patients were under mechanical ventilator for a period \geq 48 h after being admitted to the ICU, with new and/or progressive radiological infiltrate and at least

under two of the following criteria: purulent sputum, temperature higher than 38.5°C or lower than 35°C, and leukocyte count higher than 10000/ μ l with deviation to the left or lower than 3000/ μ L; and positive quantitative culture of the endotracheal aspirate (count \geq 10⁶ CFU/ml). Early-onset VAP was defined as VAP that occurred during the first four days of mechanical ventilation, and late-onset VAP after four or more days (Trouillet et al., 1998; Leroy et al., 2003; Alp and Voss, 2006, Joseph et al., 2010).

2. Multidrug-resistance: MDR pathogens were defined as those resistant to three or more antimicrobial classes. *A. baumannii* was classified as multidrug-resistant if resistant to four or more antimicrobial classes. Data on the disk diffusion susceptibilities of these organisms were interpreted according to Clinical and Laboratory Standards Institute (CLSI, 2009) criteria, by the diameter of inhibition halo formed, using the following antimicrobial discs (Oxoid LTD., England): oxacillin (1 ug), penicillin (10 mg), erythromycin (15 mg), cefoxitin (30 mg), clindamycin (2 mg), rifampicin (5 mg), chloramphenicol (30 mg), vancomycin (30 mg), ciprofloxacin (5 mg), gentamicin (10 mg), cefepime (30 mg), tetracycline (30 mg) and sulphazotrim (25 mg) for Gram-positive; imipenem (10 mg), ciprofloxacin (5 mg), ceftriaxone (30 mg), gentamicin (10 mg), piperacillin-tazobactam (100/10 mg), polymyxin B (300 u), cefepime (30 mg), aztreonam (30 mg), sulphazotrim (25 mg) and tetracycline (30 mg) for Gram-negative.

3. Inappropriate empirical antimicrobial therapy: This was defined when at least one isolated bacteria were not covered by any antibiotic administered, or when the microorganism was resistant to all antibiotics included in the empiric regimen (Kollef, 2000; Magnotti et al., 2011).

Statistical analysis

Univariate comparisons were carried out by the Qui-Square (χ^2) and Fisher's exact tests. Multivariate analysis was carried out by simple or multiple logistic regression when appropriate. The survive curve was drawn using Kaplan-Meier method. The results were considered statistically significant at level of 5%. The epidemiological data were analyzed through the programs Epi-Info version 5.0 (Stone Mountain, GA, USA), and BioEstat 5.0 (Belém, PA, Brazil).

RESULTS

A total of 617 adult patients were admitted to adult ICU of the UFU-HC from May 2009 to August 2010. Among the 320 (51.9%) patients who were submitted to mechanical ventilation for longer than 48 h, VAP was diagnosed in 81(25.3%) patients, comprising 71(87.7%) with mono-microbial and 10(12.3%) polymicrobial etiology. The pathogens responsible for VAP are listed in Table 1. MDR pathogens were isolated in 43 of 81(47.3%) episodes. Twenty (24.7%) patients developed early-onset VAP including six (30.0%) patients with VAP due to MDR organisms. Sixty-one (75.3%) patients developed late-onset VAP, and 34 (55.7%) among them caused by MDR pathogens.

Risk factors for VAPs due to MDR pathogens

The characteristics identified by univariate analysis of patients with VAP caused by MDR versus non-MDR

Table 1. Multidrug-resistant (MDR) and non-multidrug-resistant (non-MDR) pathogens associated with ventilator-associated pneumonia (VAP).

Microorganism	Total N=91 (%)	MDR pathogens N=43 (47.3%)	Non-MDR pathogens N=48 (52.7%)	P
Gram-positive	13 (14.3)	4 (9.3)	9 (18.7)	0.97
<i>S. aureus</i>	11 (12.1)	4 (9.3)	7 (14.6)	0.65
coagulase negative	1 (1.1)	-	1 (2.1)	1.00
<i>S. pneumonia</i>	1 (1.1)	-	1 (2.1)	1.00
Gram-negative	78 (85.7)	39 (90.7)	39 (81.3)	0.32
NF-GNB^a	59 (72.8)	33 (76.7)	26 (54.2)	0.04
<i>P. aeruginosa</i>	32 (39.5)	18 (41.9)	14 (29.2)	0.29
<i>A. baumannii</i>	24 (29.2)	13 (30.2)	11 (22.9)	0.58
Other NF-GNB ^b	3 (3.3)	2 (4.6)	1 (2.1)	0.60
Enterobacteriaceae	19 (23.5)	6 (13.9)	13 (27.1)	0.20
<i>K. pneumonia</i>	9 (11.1)	6 (13.9)	3 (6.3)	0.30
<i>Enterobacter</i> sp.	4 (4.9)	-	4 (8.3)	0.12
<i>M. morgannii</i>	2 (2.5)	-	2 (4.2)	0.50
<i>S. marcescens</i>	2 (2.5)	-	2 (4.2)	0.50
<i>E. coli</i>	2 (2.5)	-	2 (4.2)	0.50

^aNon-fermentative-Gram-negative bacilli, ^b*Stenotrophomonas maltophilia*, *Burkholderia cepacia*.

pathogens are provided in Table 2. Multiple logistic regression revealed that the risk of VAP by MDR pathogens was more than twice as large among patients with length of hospital stay greater than seven days before VAP onset and those who used corticoids, and more than three times as large among patients who had prior use of antibiotics (Table 3).

Empirical antimicrobial therapy

Twenty-five (30.9%) of the 81 patients with a clinical diagnosis of VAP received inappropriate antimicrobial treatment, with 56(69.1%) patients receiving appropriate antimicrobial agents. The risk of inappropriate antimicrobial therapy was significant, with more than 10 times as large among patients with VAP by MDR pathogens (21 of the 25 patients who were inappropriately treated), by both univariate (OR, 10.22; 95% CI, 2.75 to 41.43; $P < 0.0001$) and multivariate analysis (OR, 10.22; 95% CI, 3.07 to 34.08; $P = 0.0002$). Six (30.0%) of the 20 patients with early-onset VAP received inappropriate treatment due to MDR pathogens. Moreover, inappropriate antimicrobial treatment among patients with polymicrobial VAP was significantly higher than among patients with VAP caused by a single pathogen (70.0 versus 25.3%) by univariate (OR, 6.87; 95% CI, 1.38 to 38.19; $P = 0.008$) and multivariate analysis (OR, 6.87; 95% CI, 1.60 to 29.42; $P = 0.009$).

Outcome

The overall 30-day mortality rate was significantly higher

in patients with VAP caused by MDR than in patients with non-MDR VAP [21 (52.5%) vs. 8 (19.5%), $P = 0.01$] (Figure 1), and in the inappropriate antimicrobial treatment group than in the appropriately treated group [13 (23.2%) vs. 16 (64.0%), $P = 0.0004$] (Figure 2).

DISCUSSION

In the present study, the independent risk factors of VAP due to MDR pathogens were previous antibiotic exposure (less than 2 weeks), length of hospital stay greater than seven days before VAP onset and use of corticoids. These factors correspond to those reported in the literature besides the following ones: prolonged time of mechanical ventilation and prior hospitalization in the ICU (Trouillet et al., 1998; Zavascki et al., 2006; Depuydt et al., 2008; Sheng et al., 2010; Park et al., 2011; Ulldemolins et al., 2011).

The administration of previous antibiotic therapy has an important effect on the ecology of patient's microflora, which can ultimately lead to infection with resistant strains of high-risk pathogens, and extended length of stay in the hospital also increase the likelihood of being colonized by resistant bacteria which are likely to lead to subsequent severe infections (Rello et al., 1993; Trouillet et al., 1998; Tacconelli et al., 2008; Ulldemolins et al., 2011).

The emergence of ESBLs has necessitated the increased use of carbapenems, but this increased use of "drugs of last resort" may be contributing to the emergence of MDR non-fermenters (Isturiz, 2008). In health-

Table 2. Characteristics of patients with ventilator-associated pneumonia (VAP) by multidrug-resistant (MDR) and non-multidrug-resistant (non-MDR) pathogens.

Variable	MDR pathogens N=40 (49.4%)	non-MDR pathogens N=41 (50.6%)	P
Gender			
Male	30 (75.0)	28 (68.3)	0.67
Female	10 (25.0)	13 (31.7)	0.67
Age > 60	13 (32.5)	10 (24.4)	0.57
Length of hospital stay before VAP > 7 days	29 (72.5)	19 (46.3)	0.03
Duration of MV ^a before VAP > 7 days	26 (65.0)	18 (43.9)	0.09
Invasive procedure			
Tracheostomy	9 (22.5)	4 (9.8)	0.06
CVC ^b	36 (90.0)	38 (92.7)	0.71
VP ^c	38 (95.0)	40 (97.6)	0.62
NP ^d	35 (87.5)	37 (90.2)	0.74
Drain	4 (10.0)	6 (14.6)	0.75
Early-onset VAP	6 (15.0)	14 (34.1)	0.08
Late-onset VAP	34 (85.0)	27 (65.8)	0.08
Use o corticoids	23 (57.5)	13 (31.7)	0.03
Previous antibiotic therapy	29 (72.5)	20 (48.8)	0.05
Use of three or more antibiotics	14 (35.0)	12 (29.3)	0.75
Admission diagnosis			
Clinical	13 (32.5)	12 (29.3)	0.94
Surgical	11 (27.5)	7 (17.1)	0.39
Trauma	16 (40.0)	22 (53.7)	0.31
Inappropriate antimicrobial therapy	21 (52.5)	4 (9.8)	<0.0001
Mortality	21 (52.5)	8 (19.5)	0.004

^aMecanical ventilation, ^bcentral vascular catheter, ^cvesical probe, ^dnasogatric probe.

Table 3. Independent risk factors for ventilator-associated pneumonia (VAP) caused by multidrug-resistant pathogens.

Variable	P	OR ^a	CI ^b
Length of hospital stay before VAP > 7 days	0.03	2.95	1.09-8.00
Use o corticoids	0.04	2.73	1.03-7.25
Previous antibiotic therapy	0.02	3.22	1.17-8.84

^aOdds ratio; ^bConfidence Interval.

care setting, multi-drug resistance in Gram-negative bacillary infections has severely restricted therapeutic options, and sometimes no effective drugs are available to treat life-threatening infections (Carlet et al., 2011).

In our study, the empirical antimicrobial therapy was inappropriate in 25 (30.9%) of 81 patients with clinical diagnosis of VAP. In a study of Willemsen et al. (2007), antimicrobial therapy was deemed inappropriate in 351 (37.4%) of the total of 938 patients who were on antimicrobial therapy, and in a study of Teixeira et al.

(2007), 69(45.7%) of 151 patients with a clinical diagnosis of VAP received inappropriate antimicrobial treatment.

The presence of MDR or unexpected pathogen may reduce the appropriateness of antimicrobial treatment (Teixeira et al., 2007, Welte and Pletz, 2010; Ullidemolins et al., 2011). We identified multidrug-resistant bacteria and polymicrobial VAP as independent risk factor for inappropriate empirical treatment, which itself was significantly related to increased in-hospital mortality. Empirical

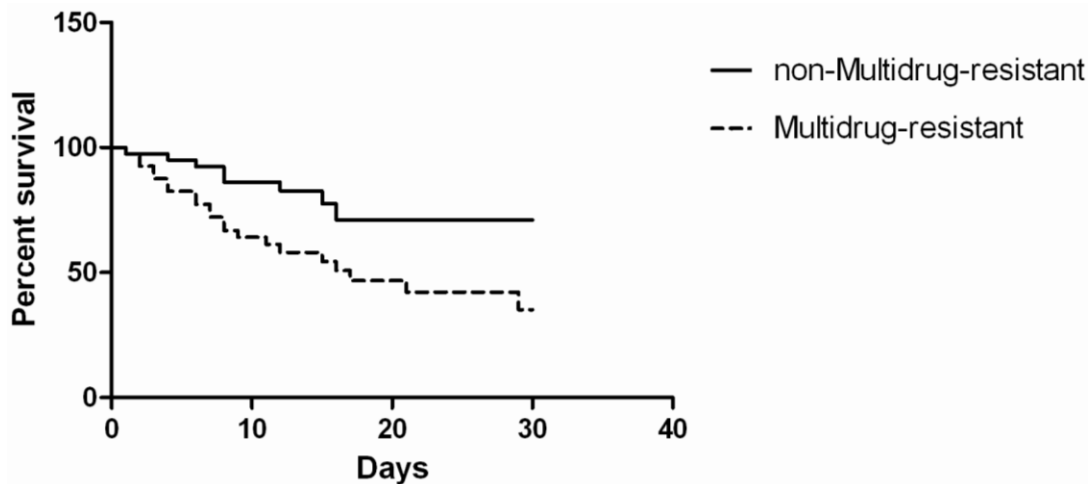


Figure 1. Kaplan-Meier analysis of multidrug-resistant (MDR) or non-multidrug-resistant (Non-MDR) pathogens causing ventilator-associated pneumonia (VAP) episodes according to 30-day mortality ($P = 0.01$) log rank test.

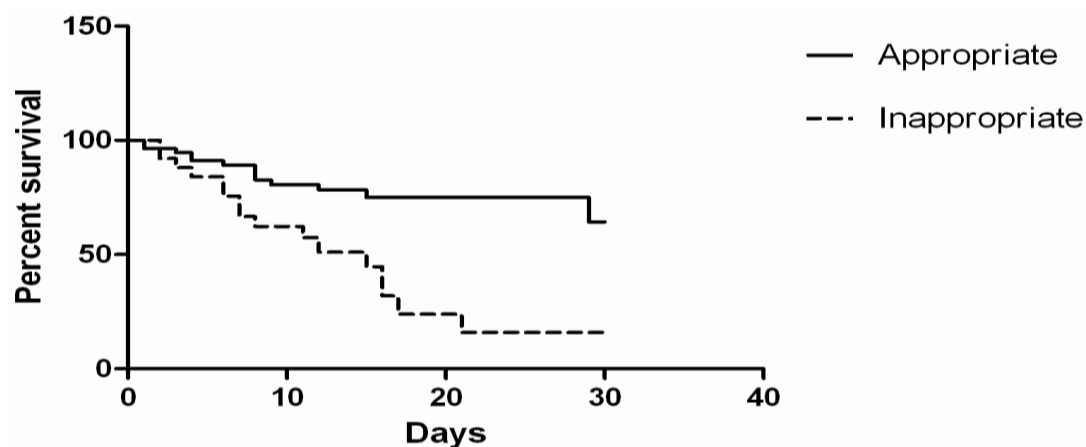


Figure 2. Kaplan-Meier analysis of empirical antimicrobial treatment of all ventilator-associated pneumonia (VAP) episodes according to 30-day mortality ($P = 0.0004$) log rank test.

antimicrobial therapy was inappropriate; it was higher (52.5%) in patients with VAP due to MDR pathogens versus 9.8% in that cause by non-MDR pathogens and in 70.0% of the patients with polymicrobial VAP versus 25.3% in case of patients with monomicrobial VAP. Most cases of MDR, VAP are expected to occur later, but 30.0% of our patients with early-onset VAP received inappropriate antimicrobial therapy due to MDR pathogens. These findings may be explained by the fact that many patients previously exposed to antibiotics, were previously admitted in other hospital wards, or with history of recent hospitalization or transferred from other healthcare facility (Friedman et al., 2002; Teixeira et al., 2007; Uildemolins et al., 2011).

Broad-spectrum antibiotics used empirically to assure appropriate initial therapy paradoxically increase the

selection pressure for antibiotic resistant microorganisms and are associated with development of resistant microbial flora (Joffe et al., 2008). To limit selection pressure, de-escalation of initial broad-spectrum antibiotics has been suggested: narrowing the spectrum of antibiotics, shortening the duration of the antibiotics, or both (Höffken and Niederman, 2002; ATS, 2005; Joffe et al., 2008).

In our investigation, 32.1% patients were given three or more antibiotics empirically, any without adopting the de-escalating antibiotic strategy after microbiological results. These conditions contribute to the emergence of antibiotics-resistant and multidrug-resistant microorganisms reported by many authors (Trouillet et al., 1998; Kollef, 2005; Waele et al., 2010).

The initial choice of the empirical antimicrobial scheme for the treatment of VAPs is of critical importance in

determining the patient's clinical evolution, particularly against hospital mortality, especially for those with antibiotic-resistant pathogens (Kollef et al., 2006; Chang et al., 2011). Early aggressive and appropriate therapeutics directed against more probable microorganisms, based on local vigilance data, is associated to reduced mortality rates and is important to optimize the management of VAP (Rello et al., 1997; Luna et al., 1997; Hoffk en and Niederman, 2002; Masterton, 2007; Chang et al., 2011).

In our study, the overall 30-day mortality rate was significantly higher in patients with VAP caused by MDR than in patients with non-MDR VAP and in the inappropriate antimicrobial treatment group than in the appropriately treated group. Depuydt et al. (2008) showed similar results with 30-day ICU- and in-hospital mortality rate significantly higher in patients with VAP caused by MDR pathogens than in patients with non-MDR VAP (37.0 vs. 20.0%; $P = 0.02$). Use of appropriate empirical antimicrobials greatly affects morbidity and mortality in hospitalized patients (Uldemolins et al., 2011).

A large multicenter international study evaluated the effect of appropriateness on mortality and hospital length of stay in a large cohort of hospitalized patients with severe infections. All-cause 30-day mortalities were significantly higher in patients with inappropriate initial antibiotic treatment (20.1 vs 11.8%; $P = 0.001$), and hospital length of stay was increased by more than 2 days in the inappropriate treatment group ($P = 0.02$) (Fraser et al., 2006).

In Brazil, Teixeira et al. (2007) showed that inappropriate antimicrobial therapy was significantly associated with 28-days mortality and MDR bacteria was the main cause of inappropriate empirical antimicrobial therapy. Other studies showed that the inappropriateness of empirical antimicrobial therapy for VAP is associated with a poor prognosis (Kuti et al., 2008; Garcin et al., 2009; Uldemolins et al., 2011).

Our study has limitations. First, this was a single-center study and our findings may be attributed to institution-specific variables. Thereby, it raises the possibility of institutional bias either in patient selection or in other institutional practices. Second, determinants of MDR were identified using a case-control design, with patients with VAP caused by non-MDR pathogens as controls rather than patients at risk of developing VAP (source patients). As antibiotic exposure is likely to suppress the growth of susceptible bacteria, these control patients may have received fewer antibiotics than the overall source patients, leading to overestimation of the association between antibiotic exposure and MDR (Depuydt et al., 2008). Third, information about patient's condition and severity of underlying illness (for example, the APACHE II score) was unavailable and the analysis of co-morbidity conditions was compromised by the lack of data on the patient's underlying disease status. Another limitation was the small sample size.

In conclusion, length of hospital stay greater than seven days before VAP onset, use of corticoids and previous use of antibiotics were independent risk factors for VAP by MDR microorganisms. The empirical antibiotic treatment was inappropriate in 30.9% of the patients with VAP and 84.0 and 70.0% due to MDR bacterial and mixed etiology, respectively. Moreover, VAP caused by MDR pathogens and the inappropriate empirical antimicrobial therapy were significantly associated with 30-day ICU mortality.

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