Adherence to Empiric Antibiotic Therapy Guideline in a Referral Teaching Hospital, Tehran, Iran

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Abstract- Antibiotic guidelines have proven to be a simple and effective intervention to guide the choice of appropriate empiric antibiotic regimens. The goals of this study were to evaluate adherence to guidelines and streamlining of antibiotics. Hospital records of hospitalized patients in infectious diseases ward Imam Khomeini Hospital, Tehran, Iran, from May 2008 to September 2009 were reviewed. Adherence to guideline was defined as the use of empiric antibiotic in accordance with the clinical diagnosis and local guideline recommendations. In this study, 528 patients with a confirmed infectious disease diagnosis were considered for analysis. The four most frequent diagnoses were skin and soft tissue infections, tuberculosis, respiratory tract infections, and HIV associated opportunistic infections. The most frequent prescribed antibiotic was ceftriaxone. Overall adherence to guideline was 70.8% and the adherence for the most frequent diagnosis was 68%. Frequency of compatibility with the guidelines for were administrated regimes on the basis of drug selection, dosage form and drug dosing were 86.2%, 97% and 84.7%, respectively. The mean lag time between patients' hospital admission and starting empiric therapy was 1.69±4.9 days. In general, physicians' adherence with guidelines for empiric antibiotic therapy was high in infectious disease ward with a justified delay. Larger studies are required to establish these conclusions.

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Keywords: Anti-bacterial agents; Guideline; Adherence, guideline

Introduction

Selecting appropriate antibiotic regimen for patients with bacterial infections has an important role in improvement of the patient outcome, reduction of unnecessary use of antibiotics that may lead to the development of antimicrobial resistance, and accordingly, reduction of antimicrobial cost (1-10). The recent emergence of multidrug-resistant bacteria has complicated patient management and increased risk of mortality (10). Antimicrobial treatment is usually initiated empirically in acute settings following appropriate biological fluid or tissue sampling for gram stain and culture. Timing of empiric therapy commencement is important, especially for critically ill patients, for whom inappropriate or delayed therapy could result in unfavorable outcomes (2,3,8,9,11,12). To guide selection of appropriate empiric antibiotic regimens, use of antibiotic guidelines is practical and effective (2,5,10,13,14). These guidelines facilitate to standardize antibiotic prescription for the most common infectious diseases (IDs) and reduce variability in treatment (5,9). Previous studies have shown that physicians' compliance to guidelines significantly reduced mortality risks but results of some studies are conflicting and most of them have focused on limited IDs (2-10,12-18).

Goals of this study were to assess the extent of physicians' adherence with the local guideline for different IDs and to measure how long patients wait to receive their first dose of antibiotic in the hospital.

Materials and Methods

In this descriptive study, hospital records of 528 patients admitted to infectious diseases ward of Imam Khomeini Hospital, a tertiary referral teaching hospital with 1400-bed, Tehran, Iran, from May 2008 to September 2009 were reviewed in our survey. Diagnosis of infections in our study was based on patients' clinical,

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microbiological, pathological, imaging and laboratory parameters. Patients' demographic and clinical data including age, weight, past medical history, drug history, diagnosis, lag time between hospital admission and first antibiotic dose and adherence to national guideline on basis of choosing appropriate drug, dosage form and dose were recorded. Patients were excluded if antibiotics were started before their admittance in this ward, the first diagnosis which antibiotic therapy was started on its basis was wrong, the patient had multi infections, or if there was inadequate information in the chart to completely assess the course of the patient's illness. Adherence to guideline was defined as the selection of empiric antibiotic in accordance with the clinical diagnosis and guideline recommendations. In this study we used last version (2009) of local antibiotic guideline that was provided by Iranian Infectious Disease Association. Data analysis was performed using the SPSS 11.5 statistical package. Univariate associations were assessed using the Chi-square test. Statistical significance was set at $P<0.05$. Other results were reported as percentages.

Results

The study population consisted of 528 patients, 251 male (47.8%) and 274 female (52.2%). Mean age of population was 45.84±19.01 years. The majority of patients (73.2%) had at least one pre-existing medical disorders (Table 1) and 8.6% of them were injection drug user. In review of past drug history, 12.5% of patients received antibiotic during last three months prior to hospital admission for ongoing infection and 1.5% of them were under treatment with corticosteroids. The four most frequent diagnosis were skin and soft tissue infections including septic arthritis and osteomyelitis (33.5%), tuberculosis (18.4%), respiratory tract infections (11.4%), and HIV associated opportunistic infections (6.1%) (Table 2).

Table 1. Pre-existing medical disorders of the patients.

Co-morbidity	Number of patients (%)
Diabetes mellitus	97 (16%)
Skin & soft tissue disorders including cellulitis and arthritis	3 (0.5%)
Cardiovascular diseases	38 (6.3%)
HIV infection	16 (2.6%)
HBV or HCV infection	61 (10.1%)
Cancers	21 (3.5%)
Renal impairment	9 (1.5%)
pulmonary disorders including asthma and bronchitis	2 (0.3%)
Transplantation including renal transplant	2 (0.3%)
CNS disorders (Alzheimer, CVA or seizure)	11 (1.8%)
Congenital disorders including heart septal defects	2 (0.3%)
History of recent surgery or trauma	7 (1.2%)

Table 2. Infectious diseases diagnosis of the patients.

ID diagnosis	Percent
Skin and soft tissue infections including septic arthritis and osteomyelitis	33.5%
Tuberculosis	18.4%
Respiratory tract infections	11.4%
HIV associated opportunistic infections	6.1%
Urinary tract infection	5.9%
CNS infection	4.9%
Endocarditis	4.9%
Sepsis	3.4%
GI tract infection including infectious diarrhea	3.3%
Brucellosis	2.3%
Others (leptospirosis, malaria and leishmaniasis)	5.9%

Table 3. Guideline adherence and mean delay of starting antibiotic therapy for different diagnoses.

Diagnosis	Number of cases	Guideline adherence (%)	Mean delay of starting antibiotic therapy (day)
Skin and soft tissue infections	174	68	1.43
Tuberculosis	97	100	3.59
Respiratory tract infections	60	50	0.65
HIV associated opportunistic infections	32	100	1.27
Urinary tract infections	31	80.6	0.27
CNS infections	26	73.1	0.92
Endocarditis	30	53.3	1.07
Sepsis	18	50	0.39
GI tract infections	17	70.6	1.63
Brucellosis	12	50	2.17
Others (leptospirosis, malaria and leishmaniasis)	30	50	0.6

Combination antibiotics therapy for infection control was used in the 76.7% of the patients and only 23.3% of them were in antibiotic mono-therapy group. Considering that many patients received two or more antibiotics concurrently, the most frequently prescribed antibiotics for empiric therapy was ceftriaxone (12.2%), followed by rifampin (8.63%), vancomycin (7.47%), cefazolin and isoniazid (7.39%), clindamycin (7%), ethambutol (6.94%) and pyrazinamide (6.77%).

Most patients with skin and soft tissue infections received cefazolin (23.84%), followed by clindamycin (17.7%) and ceftriaxone (14.23%). In this category most patients with diagnosis of diabetic foot infection received ceftriaxone plus clindamycin. Nearly all patients with diagnosis of tuberculosis received were recommended standard combination of isoniazid, rifampin, pyrazinamide and ethambutol. For respiratory tract infections the most were used antibiotics were ceftriaxone (68.9%), azithromycin (43.5%) and clindamycin (15.6%). The most prevalent opportunistic infections in our patients were tuberculosis, toxoplasmosis and respiratory tract infections. Anti-tuberculosis agents (45.8%), cotrimoxazole (26.5%) and sulfadiazine (15.4%) are the most used antibiotics in this category.

In 70.8% of patients, empirical antibiotic therapy was compatible with guideline. Percentages of compatibility to the guidelines for administrated regimens on the basis of drug selection, dosage form and drug dosing were 86.2%, 97% and 84.7%, respectively. In the less than 20 years old patients, 68.6% of them received appropriate therapy, compared to 70.4% of patients with 20-60 and 65.6% of patients with 61-100 years old. There was no significant difference between these groups regard to appropriateness of antibiotics treatment (P=0.41). The mean lag time between patients' admission and starting empiric therapy was 1.69±4.9 days.

The most incompatible prescribed antibiotic on basis of guidelines, were ceftriaxone (35.6%), cefazolin (13.5%), and vancomycin (9%), respectively (P<0.001). The adherence frequencies for the two most frequent diagnoses (Table 3) were 68% and 100% (P<0.001).

Discussion

Following rapidly expanding of medical sciences, clinicians need access to brief and appropriate guideline. In various therapeutic areas such as community-acquired pneumonia and urinary tract infections, clinical experts have used available evidence and experience to create guidelines that could help clinicians (2-6,12,13,15,19).

Physicians' adherence to local or hospital guideline is important for the successful control of hospital drugs management. A previous Dutch study found that more than 80% of patients admitted to the emergency department with a serious infection received an antibiotic in accordance with the hospital guidelines (20). Galayduyk *et al.* study also showed that about 90% of the patients diagnosed with an infectious course were managed according to the hospital protocol. Result of another research showed that 37% of initial antibiotic combinations administered in the emergency department were considered inadequate based on local hospital guideline (4).

Other recent studies have also found adherence rates to hospital guidelines on antibiotic usage ranging from 70% to 85%, and some studies found pretty low compliance rates (2,5,10,17,21-29). Present study is, to the best of our knowledge, the first one that has

evaluated the adherence rate to national guidelines in our country. We found a relatively high adherence rate, where in 70.8% of patients, empirical antibiotic treatment was compatible with guideline. The guidelines compatibility was 86.2%, 97% and 84.7%, respectively, on the basis of drug selection, dosage form and drug dosing. In a study that was performed by fernandez *et al.* in Spain, to some extent they reached higher percentages. The antibiotic was selected incorrect in 2% of patients, and the treatment length, the interval of administration and dosage were compatible in 88.5%, 90% and 93.5% respectively (27).

The timing of antibiotic administration is well recognized to influence the outcome of different infections (2-4,12,23-25). The timing of antibiotics was considered in only a few studies with conflicting results. For example, Lodise *et al.* and Khatib *et al.* demonstrated that the delay of appropriate therapy for *Staphylococcus aureus* bacteremia more than 44 hours was associated with a higher mortality rate, although Kim *et al*. did not report any differences (3,8,12,26).

It was reported that for ICU patients with severe community-acquired pneumonia, a delay in hospital antibiotic treatment of more than 4 h was associated with a higher mortality and median interval from time of admission to the emergency ward until the administration of antibiotics was 5 hours (20).

Hence because of the probable increased mortality due to treatment delay, in most cases starting empiric therapy at the first suspicion of an infection seems to be logical. However, to avoid the emergence of drug-resistant pathogens, the antimicrobial regimen should be subsequently changed or discontinued based on the patient's clinical course and the culture results.

In our study, the mean delay of starting antibiotic therapy was 1.69±4.9 days and seems to be acceptable based on the results of previous studies.

Forty nine different antibiotics, antiviral and antifungal medications were used. The reason for such a high number of medications may be due to lack of specific hospital treatment guideline, lack of knowledge regarding local bacteria prevalence and personal preferences.

On basis of our study, the most prescribed antibiotics in ID unit were ceftriaxone, followed by rifampin, vancomycin, and cefazolin. Shankar and his colleagues have done a similar study in a teaching hospital in Nepal, and in this hospital gentamycin, coamoxiclave and ciprofloxacin were on top (28). In another research that was accomplished in a medical center, cefuroxime, metronidazole, gentamycin and ampicillin were the most consumed antibiotics (30).

As mentioned previously, the most frequent diagnosis in our study was skin and soft tissue infections. Cefazolin, clindamycin and ceftriaxone were the three most prescribed antibiotic for this category of infections. In Shortt *et al.* study cefazolin, ciprofloxacin, and cefotaxime were on the top of the list (29). Nearly all patients with diagnosis of tuberculosis received were recommended standard combination of isoniazid, rifampin, pyrazinamide and ethambutol.

Respiratory tract infection, the third frequent infection in this study, were most treated by third-generation cephalosporins and macrolides respectively, similar to the result of Higashi and Fukuhara's study (31).

The four most frequent treated infection groups were skin and soft tissue infection (24.8%), tuberculosis (18.4%), respiratory tract infection (11.4%), and septic arthritis (7%). In Raveh *et al.* study, respiratory tract infection (27%), urinary tract infection (15%), sepsis (11%), and intra-abdominal infections (10%) were the most frequent ones. In this study the most incompatible antibiotics were ciprofloxacin, ceftazidime and cefuroxime (30) that is different from our results in which cefazolin was on the top of the list. In another study that was conducted by Fraga *et al.* betalactam antibiotics , fluoroquinolons and macrolides were the most inappropriate prescribed ones (32).

We found the most adherences to guidelines in HIV related opportunistic infections, tuberculosis, and urinary tract infection treatment. This can be explained, in part, by the fact that we have relatively consistent regimen for treatment of HIV related infections and tuberculosis.

There are several limitations to our study that should be noted. First we did not examine the relationship between the specific antibiotic administered and patient outcomes. Also numbers of patients, who had participated in this study, were not enough for some IDs. Finally, based on design of our study, the results may be subject to particular physician or hospital characteristics. However, the fact that our data on the appropriateness of antibiotic treatment and adherence to guidelines are consistent with prior data, suggests that the results reported here could be applicable to the general.

In conclusion, in infectious diseases ward of the hospital, the adherence of physicians to guidelines in terms of a correct empiric treatment of infections was relatively high. These data support the recommendations of local guideline. This study also showed an acceptable

delay in starting empiric therapy after admitting the patients into the hospital. But the potential adverse outcomes resulting from delayed treatment must be balanced with the potential benefit of limiting excessive antibiotic use.

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