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Vancomycin and Five Broad-spectrum Antibiotic Utilization Evaluation in an Educational Medical Center in One Year

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ABSTRACT

Background: Antibiotics can be life saving if they are used correctly, and can have unwanted side effects specially resistance with incorrect use. Unfortunately in fear of no response, physicians use broad spectrum antibiotics meticulously. In this Drug Utilization Evaluation (DUE), improper use of Vancomycin and five broad-spectrum antibiotics are studied to find faults and solution for this problem.

Methods: This descriptive cross-sectional study performed during the March of 2012 to March of 2013.DUE of Imipenem, Meropenem, Piperacillin-Tazobactam, Cefepime, Ciprofloxacin and Vancomycin was done in 6 wards of Imam Hossein Hospital in Tehran. Demographic, clinical, laboratory, imaging and treatment data were looked for in medical records of 686 patients. Evaluation was done by three infectious disease specialist based on reference text book of Mandell's Principles and Practice of Infectious Diseases 2010 and IDSA Guidelines.

Results: This study showed 38.5% of prescriptions were correct and the remained 61.5% were incorrect with different faults predominantly incorrect overuse in 51.1%.Ciprofloxacin was the most common incorrect used drug in 74.8% cases and Piperacillin-Tazobactam with 48.7% cases had the least common incorrect use. There was no fault in prescription of antibiotics observing age and sex (pregnancy, breast feeding) factors.

Conclusions: Our results reveal a significant high level of the inappropriate use of Antibiotics mostly as overuse and empirically without culture results. It is needed to establish continuing medical education (CME) courses and a locally conformable guideline of antibiotic use based on antibiogram results.

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Introduction

Irrational use of antibiotics can be associated with a number of serious consequences to the patients and community (1).The need to control antibiotic use has grown out of concern for costs and emerging resistance (2).The increasing worldwide emergence of antimicrobial resistance is a major public health problem that significantly impacts patient treatment and outcomes (3).Transmission of resistance between different strains of bacteria is an important and danger event (4).The relationship between antimicrobial use and antimicrobial resistance is complex, with a growing body of data strongly suggesting that higher levels of antimicrobial usage are associated with increased levels of antimicrobial resistance (5).Better understanding of factors influencing prescribing decisions is essential and development of intervention programs

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aimed at optimizing the use of antibiotics in hospitals is warranted (6).Many strategies have been used to improve the prescription of antibiotics and their overall use in the hospital setting (2).

Drug Use Evaluation (DUE) is a system of ongoing, systematic criteria based evaluation of drug use that will help ensure that medicines are used appropriately at the individual patient level (7). DUE performed in in-patient settings to identify trends of use and appropriateness of prescribing pattern have shown that 22-65% antibiotic prescriptions are either inappropriate (8) and in other DUE surveys as 44–97% of prescriptions (9-11).

The spread of antibiotic resistance is associated with complex and interconnected factors, such as excessive and unnecessary prescribing of antibiotics, increased self-prescribing by the people, poor quality of available antibiotics, failure to implement simple infection control practices, and the dearth of routine susceptibility testing and surveillance (12).There are three important factors for choosing appropriate antibiotic including identification of pathogen, antibiotic sensitivity and host factors. The first two are important paraclinical factors which are not available in most instances and we should use the most recently data about the etiology of different infectious syndromes, but host factors should never be overlooked (5). There are surveys about the quality of health care and prescribing behavior around the world (1, 9, 11, 13-17) and limited number of DUEs conducted in our hospital care centers. In most surveys utilization of one or two antibiotics has been evaluated as descriptive studies. These describe patterns of drug utilization in terms of the prevalence of a variety of antibiotic uses including Defined Daily Dose (DDD), frequency, doses, intervals, routes of administration and in analytic studies the appropriateness of antibiotics (13,18-21).This research is an analytical Drug utilization Evaluation aiming to assess whether drug therapy is rational or not. Patient medical records were reviewed for this purpose which is quite exhaustive. Other advantages of this study include large sample (686 Cases) and will describe problems of drug utilization with more details for 6 antibiotics.

Methods

This is a cross-sectional retrospective DUE study conducted in "Imam Hossein" Medical and Educational Center in Tehran, Iran, in 6 different units including: Internal medicine, Infectious Disease, Neurology, General Surgery, Neurosurgery and orthopedic. The required sample size was calculated using simple population proportion formula by considering 40% proportion correct antibiotic use in hospitals giving a maximum sample because there is no similar study conducted in the study area which is published.

$$n = \frac{Z^2_{1-\alpha/2} \times P\,(1-P)}{d^2}$$

n=Required samples = 576 (16 cases for each antibiotic at least in each ward)

Z= Standard score corresponding to 95% C1

P= Assumed proportion of correct antibiotic use to be 0.4

d= the margin of error tolerable 10%.

Patients who received each one of these 6 antibiotics (Vancomycin, Imipenem, Meropenem, Cefepime, Piperacillin-Tazobactam and Ciprofloxacin) were enrolled in this study. This study was decided to be conducted in 6 months but due to low prescription frequency of Cefepime and Piperacillin-Tazobactam, it was increased to one year from April 2012 to April 2013.

The data extracted from patients' medical records including demographic (age, sex, pregnancy, breastfeeding), length of hospital stay, history of drug allergy, renal, hepatic and metabolic disease, CBC, renal and hepatic functional tests, other concomitant administered drugs for potential of interaction, signs and symptoms which contraindicated using mentioned antibiotics, first and final diagnosis, and drugs indicator including treatment regimen, dose and frequency of administration, microbiological culture/ sensitivity testing were recorded in a predesigned data collection form.. Antibiotics were prescribed for kinetic and or prophylactic purpose.

Three infectious disease specialists reviewed each medical record independently. Assessments of the individual reviewers based on text book of Mandel's Principles And Practice Of Infectious Diseases, 2010 and IDSA(Infectious Disease Society of America) guidelines adapted to the local conditions were summarized in a combined evaluation when at least two of the three reviewers evaluated the prescription similar as prepared list including:

A: Appropriate, B: Inappropriate, B1: Unnecessary, B2: Age-related, B3-1: Pregnancy, B3-2: Breastfeeding, B4: Concomitant Disease, B5-1: Insufficient Spectrum, B5-2: High Spectrum, B5-3: Unnecessary Combination of Two Similar Spectrum Antibiotic, B5-4: Ineffective, B6: Improper Dose, B7: Improper Combination, B8: Duration of treatment)

Descriptive analyses of data were performed using SPSS software (version, 20).

Results

A total of 686 patients were included during a 12 month study. They have received at least one of this six studied antibiotic including Vancomycin, Imipenem, Meropenem, Cefepim, Piperacillin-Tazobactam and Ciprofloxacin. They were admitted in 6 different units. Number and percentage of patients in each department is shown in Table 1.

Results showed that the percentage of patients was 65.5% Male (450 Cases) and 34.4% Females (236 Cases) respectively.

Table 1. Number of studied Patients in different wards.

Ward	Number (Percent)
Internal	132 (19.2)
Infectious	126 (18.4)
General Surgery	114 (16.6)
Orthopedics	108 (15.7)
Neurosurgery	104 (15.2)
Neurology	102 (14.9)
Total	686 (100)

Table 2. Antibiotics used in different wards.

Antibiotic	Frequency	Percent
Ciprofloxacin	137	20
Vancomycin	136	19.8
Imipenem	125	18.2
Meropenem	124	18.1
Cefepim	88	12.8
Piperacillin-Tazobactam	76	11.1
Total	686	100

Table 3. Frequency and percent of culture results.

Sample	Frequency	Percent
Positive		
Urine	63	9.2
Ulcer Discharge	50	7.3
Multiple Sample	40	5.8
Sputum	35	5.1
Blood	34	5.0
Ascites	6	.9
Pleural Effusion	1	.1
Deep Abscess	1	.1
Total	230	33.5
Negative	456	66.5
Total	686	100.0

Table 2 shows number and percent of used antibiotics in different wards.

Ciprofloxacin utilization was the most common with 137 (20%) prescription followed by Vancomycin, Imipenem, Meropenem, and Cefepim in order; and Piperacillin-Tazobactam (the least one 76 (11.6%)).

There were 231 patients with positive cultures from different samples as shown in Table 3. From 686 studied samples, 33.7% of them were positive.

In 5.8% of patients multiple samples were positive. The isolated germ in 18% of patients with positive culture were sensitive to the used antibiotic, but 24% of cases the germ were resistant to prescribed antibiotic and in 58% the disk of the ordered antibiotic wasn't used and the sensitivity of the microorganism is unknown as showed with details in Table 4.

Antibiotic Use was rational in 264 (38.5%) cases and irrational in 422 (61.5%).As the results shows the most common reason for inappropriateness was suing very broad-spectrum antibiotics in 20% of cases. The second most common reasons were the use of two similar broad-spectrum antibiotics in 16.2% and the unjustified (not indicated) use of antibiotics, which was found in 14.4% of cases. No inappropriate use was related to age, pregnancy and breastfeeding (Table 5).

There was no drug discontinuation due to adverse reactions and no contraindication for any studied drug in this study.

The most frequent inappropriate use was in Neurologic Ward (71%) followed by General Surgery, Internal Ward, Orthopedics, and Neurosurgery in order; the least frequent inappropriate use was in Infectious Disease Ward (46.3%). There was no significant difference between internal wards(Internal Medicine, Neurology) and surgical wards(General Surgery, Orthopedics, Neurosurgery) as shown in Table 6 (P<0.17).

The most frequent inappropriate antibiotic use was for Ciprofloxacin (74.8%) and the least one for Piperacillin-Tazobactam (48.7%) (Table 7).

Table 8 shows the number and percent of appropriate and inappropriate use of each antibiotic with the causes of inappropriate utilization.

With regard to the diagnosis, antibiotic prescription was not the same in different wards. In infectious ward Piperacillin–Tazobactam with 24 prescription had the least incorrect use (19 cases=79.2% rational, 5 cases=20.8%irrational) mostly due to unnecessary combination with similar spectrum antibiotic. Cefepime with 20 prescription had the most common incorrect use (7 cases=35% rational, 13 cases=65%irrational) mostly due to insufficient spectrum.

In Internal ward Meropenem with 23 prescription had the least incorrect use (10 cases=43.5% rational, 13 cases=56.5%irrational) mostly due to unnecessary use in 30.4% cases. Piperacillin-Tazobactam with 20 prescription was used correctly in 6case=30% and incorrectly in 14 cases=70% mostly due to high spectrum in 25% cases. Ciprofloxacin was used in 26 cases, correctly in 8 cases=30.8% and incorrectly in 18 cases=69.2% mostly due to unnecessary use in 34.6%. The two later drugs had the most common irrational use in this ward.

In General Surgery department Vancomycin with

Table 4. Frequency and percent of antibiogram results of used antibiotics.

Antibiotic Sensitivity	Frequency	Percent
Imipenem Sensitive	6	0.9
Imipenem Resistant	15	2.2
Imipenem No Disk	17	2.5
Meropenem Sensitive	2	0.3
Meropenem Resistant	2	0.3
Meropenem No Disk	39	5.7
Tazocine Sensitive	2	0.3
Tazocine Resistant	5	0.7
Tazocine No Disk	18	2.6
Cefepim Sensitive	1	0.1
Cefepim Resistant	4	0.6
Cefepim No Disk	28	4.1
Ciprofloxacin Sensitive	20	2.9
Ciprofloxacin Resistant	20	2.9
Ciprofloxacin No Disk	11	1.6
Vancomycin Sensitive	10	1.5
Vancomycin Resistant	9	1.3
Vancomycin No Disk	21	3.1
Total	230	33.5
Without Culture	456	66.5
Total	686	100

Table 5. Overall appropriate antimicrobial therapy causes.

Appropriateness	Number	Percent
A	264	38.5
B	422	61.5
B1	99	14.5
B2	0	0
B3-1	0	0
B3-2	0	0
B4	2	0.3
B5-1	43	6.3
B5-2	148	21.6
B5-3	111	16
B5-4	5	0.7
B6	10	1.5
B7	1	0.15
B8	3	0.45
Total	686	100

A: Appropriate, B:Inappropriate, (B1:Unnecessary, B2:Age, B3-1:Pregnancy, B3-2:Breastfeeding, B4:Concomitant Disease, B5-1:Insuficient Spectrum, B5-2:High Broad Spectrum, B5-3:Unnecessary Combination of Two Similar Spectrum Antibiotic, B5-4:Ineffective, B6:Improper Dose, B7:ImproperCombination, B8:Duration of treatment)

20 prescription had the most common incorrect use (16 cases=80% irrational, 4 cases=20%rational) mostly due to insufficient spectrum. Piperacillin-Tazobactam with 19 prescription had the least common incorrect use (9 cases=47% rational, 10cases=53%irrational) mostly due to use of unnecessary combination of two similar spectrum antibiotic in 21.5% cases.

In Orthopedics ward Ciprofloxacin with 22 prescription had the most common incorrect use (19 cases=86.4% irrational, 3 cases=13.6%rational) mostly due to unnecessary combination of two similar spectrum antibiotic in 27.3% cases. Vancomycin with 26 prescription had the least common incorrect use (16 cases=61.5% rational, 10 cases=38.5%irrational) mostly due to use of high spectrum antibiotic in 23.1% cases.

In Neurology ward Imipenem with 20 prescription had the least common incorrect use (9cases=45% irrational, 11cases=55%rational) mostly due to unnecessary use in 15% cases. Cefepime with 10 prescription had the most common incorrect use (9cases=90% irrational, 1cases=10%rational) mostly due to use unnecessary combination of two similar spectrum antibiotic in 50% cases.

In Neurosurgery ward Piperacillin-Tazobactam with 24 prescription had the least common incorrect use (5 cases=20% irrational, 19 cases=80%rational) mostly due to unnecessary combination of two similar spectrum antibiotic in 16.7% cases. Cefepime with 20 prescription had the most common incorrect use (13 cases=65% irrational, 7 cases=35%rational) mostly due to use insufficient spectrum antibiotic in 35% cases.

Discussion

This study was conducted in order to evaluate and improve the rate of appropriate use of Vancomycin and five of the broadest-spectrum antibiotics. The control of infectious disease is seriously threatened by the steady increase in the number of resistant microorganisms (19). Emergence of antimicrobial resistance is a result of the use, over use and misuse of antibiotics (20). The best way of antibiotic therapy is based on culture and antibiogram results.

Our study showed that 94% of antibiotic courses in our hospital were empirically selected based on clinical judgment and only 6% on relevant culture results. Some of previous studies about antibiotics had also shown that

Table 6. Appropriateness of antibiotic use in different wards.

Appropriateness Wards	A:Appropriate		B:Inappropriate	
	Number	Percent	Number	Percent
Infectious Ward	66	52%	60	48%
Neurosurgery	43	41%	61	59%
Internal Ward	47	36%	85	64%
General Surgery	40	35%	74	65%
Orthopedics	39	35%	69	65%
Neurology	29	29%	73	71%

Table 7. Appropriateness of different antibiotic use.

Appropriateness Antibiotic	A:Appropriate	B:Inappropriate
Piperacillin- Tazobactam	51.3%	48.7%
Imipenem	44.6%	53.4%
Vancomycin	43.9%	56.1%
Meropenem	40.7%	59.3%
Cefepime	33%	67%
Ciprofloxacin	25.2%	74.8%

the vast majority of courses as 77% (22), 98% (23), 94% (24) were empirically prescribed. In one study Ultra broad spectrum combination therapy (U-bSCT) was employed for 11 patients but was necessary in only 2 (24). In a septic work-up result showed positive cultures in 57% of cases and 78% antibiotics were changed according to the sensitivity data to narrow-spectrum antimicrobials. In 22% cases, pathogens were susceptible to narrow-spectrum antibiotics even though broad-spectrum was continued (25). In an educational intervention among professionals, the use of bacterial culture and sensitivity tests improved by 88.29% from 65.22% and the correct indication rate improved to 94.59% from 84.38% after one month education course (26).The vast majority broadest-spectrum antibiotic treatments were initiated empirically and rate of appropriateness decreases significantly and if they do not respond, leading to change to even Ultra broad spectrum combination therapy. These situations facilitate emergence of multi-drug-resistant organisms, as well as significant expenses.

In our center antibiotic use was rational in 264 (38.5%) cases and irrational in 422 (61.5%). This incorrect overuse of antibiotics is due to unavailability of culture and antibiogram and in fair of time wasting in critically ill patients. Other studies have shown that 22-65% antibiotic prescriptions are inappropriate (8, 21) and in other DUE surveys as 44–97% of prescriptions (9-11). Our results showed nearly 90% antibiotics are prescribed empirically in critical conditions. There were 33.5% positive cultures in next days with only 0.059% sensitive bacteria to used antibiotic overall. Fahmi et al., showed that initial use of Piperacillin-tazobactam as empirical therapy was inappropriate in 43% of cases but decreased to 22% after switching to an alternative antibiotic with narrow spectrum after receipt of culture and susceptibility data (25). Study of Kambaralieva et al., also showed similar finding as unjustified use of antibiotics in 48.6% the most common reason given for inappropriateness (13). In other studies evaluation of drug use was based on response to therapy, antibiogram (1) dose, duration and interval (8,18, 21-23), average number of antibiotics, mean duration, route of administration and diagnosis with different results (13, 24,27).There is not any study similar to ours evaluating antibiotic use with a significant impact on variables including: identification of pathogen, antibiotic sensitivity of the organism and host factors

including allergy, age, sex (pregnancy, breastfeeding), metabolic disease, renal and hepatic function and site of infection in different internal and surgical wards. Fonseca et al., showed that in 78.9% of surgeries, the antibiotic was correctly chosen; but in only 15.9% of surgeries was the initial antibiotic administration correctly timed; and the use of antibiotics in the post-operative period was appropriate in only 29.8% of cases (27), in another study the overall compliance rate of surgeons with guidelines for antibiotic prophylaxis was 36.3%.as 81%(28). But there is no comparison between medical and surgical ward in that center. In Tarcea et al., study 42.92% prescriptions were considered inappropriate. In 49.82 % the dose was incorrect, 20 % were inadequate in terms of treatment duration and 15.44 % were wrongly indicated. Inappropriate use was significantly higher among empirical prescriptions than the documented ones (29). The wide range of appropriate use in different evaluations is based on studied factors.

In this study Ciprofloxacin has the most common use usually as polypharmacy in empirical therapy which is similar to 3 other studies (6, 21, 22) and the most frequent inappropriate antibiotic use (74.8%) nearly similar to other investigation as 60% (13) and 74% (22), mostly due to no indication and unnecessary combination of two similar spectrum antibiotic. It is usually combined with Anti-pseudomonal drugs in sever ill patient mostly without positive culture.

Piperacillin-tazobactam has the least inappropriate use (48.7%). In Raveh et al., study it was used appropriately in 90% of cases (22). In drug utilization evaluation of Piperacillin-tazobactam by Fahmi et al., appropriate use was 57% mostly in surgical wards (86%) and the surgical intensive care unit (66.7%) (25), and in another study rate of appropriateness was 86% (30). It has the lowest rate of use because it is not well known and not available every time in our center.

There is no study comparing results of appropriateness of Cefepim, Imipenem, and Meropenem use with variables similar to this study.

Result of this study showed appropriate use of Cefepime was 33%, of course this low rate actually would have been due to low antibiotic sensitivity test for Cefepime as 0.7% in patients. In Raveh et al., study, rational use of Cefepime was 91% (22). In another survey correct indication rate was 84.38% which improved 94.59% after one month education course along with bacterial culture and sensitivity tests improvement by 88.29% from 65.22% (26).

In Mahini et al., study Carbapenem Utilization was justified in 72% of Critically Ill Patients but according to the culture results, continuation of treatment in 47% cases was unjustified (32), which is mildly more than ours (40.7- 44.6%).In one center Meropenem appropriate use was 79% which raised to 89% with one month education. Most antibiotic courses were empirical and only minorities (22%) were based on a relevant culture result; the rate of appropriateness of empiric treatment was significantly lower than that of treatment based on a relevant culture result (22). In Khan et al., study 97.52% of Meropenem prescriptions were indicated in diseases encouraged by guidelines but empirical therapy was the major problem reported in this study as in 43% of the cases (33). Utilization Evaluation of Meropenem at a Hospital in Thailand showed 95.7% agreed with indication criteria (34). In evaluating the use of restricted antibiotics in an academic hospital in Romania in ICU Meropenem and Imipenem were prescribed inappropriate in 46.55% and 44.06 % of cases in order (29). The large differences between studies as ours are based on intervention, education and culture results.

Vancomycin was used incorrectly in 56.1% cases due to High Broad- Spectrum in 31% MSSA (Methicillin Sensitive Staphylococus aureus) and unnecessary use in 23% cases. Another studies demonstrated appropriate use of Vancomycin in 16% (1), 74.2% (18), 49.7% (29), 30% (35), 36.3% (28), 35% (36), 70% (37) and 91% (38) cases. The finding of high rate of appropriate use of antibiotics in one center (74.2%) may indicate the effectiveness of the AOF(Antibiotic Order Form) as well as the cooperation of all health personnel, the better follow-up system and of course the support of the policy makers (18). Serum samples should be drawn to assess trough concentrations before the fourth dose, when steady state levels are likely achieved which is usually ignored, in one study serum levels were below target in 72% of the time (39). In our center there was no assessment of trough level of Vancomycin and drug might have been delivered in sub therapeutic level.

Antibiotic prescriptions were seriously inappropriate in this survey with prescribing patterns failing to strictly adhere to the international guidelines. There was no study conducted on this topic in the hospital and in the study area. The selection of appropriate antimicrobial therapy requires the knowledge of infectious diseases, and a thorough understanding of the likely microbial cause of the infection, the properties of the antimicrobials available for treating these infections, pharmacokinetic profile, tolerability, and safety (6).The majority of patients have been admitted from emergency room; it seems probable that critical condition of patients admitted to these wards may have caused such a broad-spectrum antibiotic use. Drug utilization studies are helpful in understanding the current practice in clinical settings. The results of this study may be helpful for clinicians to improve the patient care. It is also very helpful for health systems decision makers to reduce the costs of treatment by utilizing culture and sensitivity testing in hospitals. The importance of providing basic information about drugs to physicians can't be overlook for the rational use

of drugs, and this insight should not be restricted to drug visitors' activities. The meta-analysis supports the use of restrictive interventions when the need is urgent, but suggests that persuasive and restrictive interventions are equally effective after six to more than 24 months (31).

Conclusion

Our results reveal a significant high level of the inappropriate use of Antibiotics mostly as overuse and empirically without culture results. It is advised to establish continuing medical education (CME) courses for physicians to familiarize them with standards, and adoption of a locally conformable guideline of antibiotic use can resolve this problem. Regarding empiric treatments which were common can increase risk of antimicrobial resistance by using ineffective antibiotics.

Limitations

There was one limitation in this study as it was designed in prospective plan but awareness of the physicians would bias to interpret the results so was conducted as a cross sectional retrospective Drug Use Evaluation study.

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