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Research Article

Rational Drug Use Evaluation of Metronidazole at an Egyptian Tertiary Care Hospital

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ABSTRACT

Objective Antimicrobial resistance has become a global crisis and misuse of these agents may raise the economic burden of both the health care system and the individual. This study aimed at evaluating the rational use of metronidazole at a tertiary care hospital, Egypt, in which this drug was observed to be extensively used.

Methods Eighty-seven prescriptions were collected from different nine departments at the hospital in this observational cross-sectional study. Data regarding the rational use of metronidazole comprises its indication, dosage, frequency, storage, and drug interactions were assessed and presented as percentages then compared with the predicted threshold values of these criteria. A Chi-square test was used to compare observed with the predicted threshold of assessed criteria. P-value <0.05 was inferred statistically significant.

Results Data revealed that 58.6% of total cases received metronidazole with its optimum indication. All cases who fulfilled the indication criteria received the drug with the right dose, while 82.4% of cases received it with the right frequency. Only 70.1% of total cases stored the drug in right storage conditions and 19.5% prescriptions included metronidazole drug interactions. When comparing these assessed criteria with their relevant predicted threshold, there were significant differences in favor of the indication, frequency, and storage criteria.

Conclusion Metronidazole was shown to be misused and there is a need for optimizing its rational use. Recommendations with proper use, frequency, storage, and drug interactions of metronidazole should be informed to all health care professionals at this hospital.

Keywords: Metronidazole, Rational use, Egyptian tertiary care hospital.

1. INTRODUCTION

The rational drug use evaluation (DUE) program is a systematic quality improvement activity for evaluating the appropriateness of drug use. It aims at improving the quality and cost-effectiveness of drug use and thereby improving patient care in various practice settings including hospitals according to current medical literature.[1]

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The misuse of antibiotics is a serious global problem leading to the emergence of resistance, which is one of the most serious health threats.[2] Infections from resistant bacteria are now much common, and some pathogens have even become resistant to multiple types or classes of antibiotics, so the appropriate use of antibiotics is necessary.[3] As a result, antibiotics gained priority for the DUE program.

Metronidazole is a nitro-imidazole antimicrobial agent used for the treatment of anaerobic infections and parasites. It has been considered the drug of choice for the treatment of anaerobic infections since its development in 1959.[4]

According to the updated American Hospital Formulary Service (AHFS) drug monograph, metronidazole

is used for the treatment of anaerobic bacterial infections caused by Bacteroides species.[5] These infections include intra-abdominal infections (peritonitis, intra-abdominal abscess, and liver abscess), skin and skin structure infections, gynecologic infections (endometritis, endomyometritis, tubo-ovarian abscess, and postsurgical vaginal cuff infection), bacterial septicemia, bone and joint infections (as adjunctive therapy), central nervous system infections (meningitis and brain abscess), lower respiratory tract infections (pneumonia, empyema, and lung abscess), and endocarditis. Additionally, it is used for the treatment of symptomatic and asymptomatic trichomoniasis and amebiasis.[5]

According to recent British National Formulary (BNF 73), metronidazole can be used for eradication of Helicobacter pylori, fistulating Crohn's disease, leg ulcers, and pressure sores, bacterial vaginosis, pelvic inflammatory disease, acute ulcerative gingivitis, acute oral infections, surgical infection, intestinal and extra-intestinal amebiasis including liver abscess, urogenital trichomoniasis, giardiasis, and established case of tetanus.[6]

Metronidazole has been shown to be carcinogenic in mice, therefore the unnecessary use of the drug should be avoided.[7] This fact in addition to the antibiotic resistance crisis, relatively high cost, and extensive usage at a tertiary care hospital in Egypt, prompted us to evaluate the relevant use of metronidazole in this hospital.

2. MATERIALS AND METHODS

2.1. Study Design

This observational cross-sectional study was conducted from October 2016 to April 2017. Data were collected from the following nine departments: Internal Medicine, Emergency, Nephrology, Surgery, Gynecology, Cardiology, Recovery, Neurosurgery, and Intensive Care Unit (ICU). Collected data were gathered after a verbal consent from the patient or family relatives and documented using planned DUE form (Supplementary material Table 1).

2.2. Assessment Criteria

The assessment criteria for metronidazole are illustrated in Table 1. Criteria for evaluation of drug indications were selected using labeled and off-labeled uses mentioned in the AHFS and BNF drug monograph, guidelines, systematic reviews, and meta-analyses. Doses, frequencies, and storage data were evaluated regarding AHFS and BNF metronidazole monograph. Drug interactions were double-checked using online drug interaction checkers on Lexicomp online database[8] and other reliable websites.[9,10] Data about concomitant antibiotics used with metronidazole were also collected.

2.3. Statistical Analysis

Data were analyzed using Microsoft Excel Version (2010) and the Statistical Package of Social Science (SPSS) version 22, 2013, IBM corporation software group, Armonk, NY. Descriptive statistics such as frequencies and percentages were calculated. Data were expressed as mean ± standard deviation (SD) and percentage for continuous and categorical data, respectively. Graphic representations were used for visual interpretation of the analyzed data. A Chi-square test was used to compare categorical data of observed and predicted threshold of assessed criteria. A p-value of less than 0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

Eighty-seven prescriptions were collected and analyzed during the study period which includes 36 female and 51 male patients received intravenous metronidazole treatment. The mean age of the patients was 45.3 ± 20.8 years. The percentage of these 87 prescriptions according to the nine selected departments at the studied hospital is illustrated in Table 2.

3.1. Antibiotics Prescribed in Combination with Metronidazole

The combined therapy of antibiotics was recorded from all 87 prescriptions, and 83 (95.4%) prescriptions were shown to have combined antibiotic therapy with metronidazole. From these 95.4% prescriptions, the percentage of antibacterial therapy prescribed with metronidazole was 55.4%, 34.9%, and 9.6% for one antibiotic, two antibiotics, and ≥ three antibiotics, respectively. It was observed that metronidazole + ceftriaxone combination was found to be more prescribed at the studied hospital (45.8%), followed by metronidazole + ampicillin/sulbactam (20.5%), then metronidazole + amoxicillin/clavulanic acid (16.9%). The percent of combined antibiotics used with metronidazole is illustrated in Figure 1.

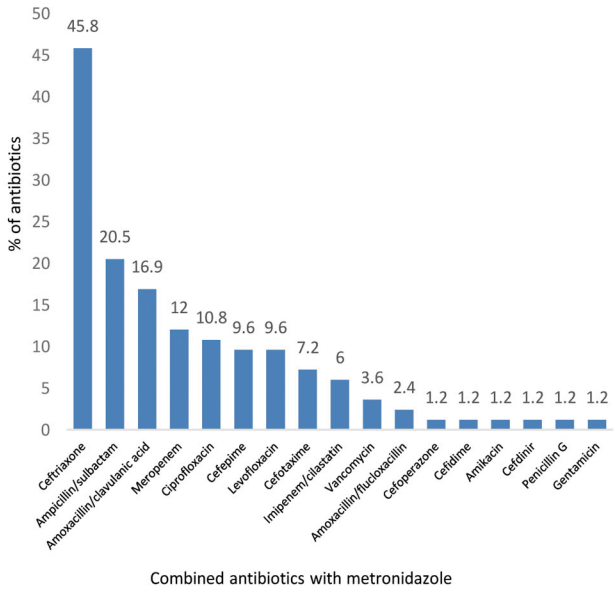

Figure 1: The percent of combined antibiotics used with metronidazole at the studied Egyptian tertiary care hospital.

Table 1: Assessment criteria for metronidazole.

Indicator	Criteria	Expected criteria threshold
Justification of Prescription	Amebiasis, anaerobic bacterial infections, bacterial septicemia, bone, and joint infections, central nervous system (CNS) infections, endocarditis, gynecologic infections, intra-abdominal infections, lower respiratory tract infections, skin and skin structure infections, surgical prophylaxis (colorectal surgery), trichomoniasis.	90%
Dosing and Frequency According to Labeled Indications	Anaerobic bacterial infections: • Loading dose: 15 mg/kg IV; not to exceed 4 g/day • Maintenance dose: 7.5 mg/kg PO/IV (over 1 h) q6hr x 7-10 days (or 2-3 weeks if severe) Intra-abdominal infection: Oral, IV: 500 mg every 8 hours as part of an appropriate combination regimen. Duration of therapy is for 4 to 7 days following adequate source control CNS infections (meningitis): IV: 7.5 mg/kg (usually 500 mg) every 6 to 8 hours for 6 to 8 weeks in combination with other appropriate antimicrobial therapy. Pelvic inflammatory disease with tubo-ovarian abscess, initial therapy (alternative regimen): IV: 500 mg every 8 hours as part of an appropriate combination regimen. Pneumonia, aspiration (alternative agent): Oral, IV: 500 mg 3 times daily in combination with an appropriate beta-lactam (e.g., oral amoxicillin, IV penicillin, or an IV third-generation cephalosporin) for 7 days Skin and soft tissue infections: • Necrotizing infections (as a component of an appropriate combination regimen) (alternative agent): IV: 500 mg every 6 hours. Continue until further debridement is not necessary, patient has clinically improved, and patient is afebrile for 48 to 72 hours. • Surgical site infections, incisional (eg, intestinal or genitourinary tract; axilla or perineum), warranting anaerobic coverage: IV: 500 mg every 8 hours in combination with other appropriate agents. Duration depends on severity. Surgical prophylaxis: IV: 500 mg within 60 minutes prior to surgical incision in combination with other antibiotics.	95%
Drug Interactions	1. Avoid	100%
	2. Therapy modification	90%
	3. Monitoring therapy	80%
Vial Storage Conditions	• Store at 20°C to 25°C (68°F to 77°F). • Protect from light. • Avoid excessive heat. • Do not refrigerate. • Do not remove the unit from overwrap until ready for use. • Discard unused solution.	100%

* IV: intravenous; PO: oral administration.

3.2. Rational Use of Metronidazole (Prescription, Dosage, and Frequency)

Overall, out of 87 patients, only 51 patients (58.6%) fulfilled the pre-specified criteria for the prescription. As illustrated in Figure 2, there was a significant difference when comparing these observed data with expected criteria threshold value (58.6% vs. 90%, respectively, with $p<0.001$). All justifications for prescribing metronidazole that was found in the patient's sheet and provided by the clinician are illustrated in Table 3.

All patients who fulfilled the prescription criteria took the right dose of metronidazole. On the other hand, the frequency differed among them as follows: out of 51 patients, 42 patients (82.4%) were prescribed metronidazole with the right frequency, while nine patients (17.6%) took metronidazole with inadequate frequency. By comparing these observed data with expected dose and frequency criteria threshold value, there was no statistically significant difference regarding dosing criteria (100% vs. 95%, respectively, with $p= 0.12$). While a significant difference was found regarding frequency criteria (82.4% vs. 95%, respectively, with $p= 0.013$) as shown in Figure 2.

Table 2: Demographic data and patient characteristics at the studied Egyptian tertiary care hospital.

Number (♀/♂)	87 (36/51)
Age (years)	45.3 ± 20.8
Percent of collected prescriptions per department:	
Internal medicine department	37.9 %
ICU	33.3 %
Recovery department	11.5 %
Emergency department	5.7 %
Nephrology department	4.6 %
Gynecology department	3.4 %
Surgical department	1.1 %
Cardiology department	1.1 %
Neurosurgery department	1.1%

ICU: intensive care unit.

Table 3: Justification for Metronidazole prescription at the studied Egyptian tertiary care hospital.

Indication	No. of prescriptions	Compliance with evidence
Respiratory tract Infection: • Aspiration pneumonia • Empirical treatment for HAP	14 7 (8%) 7 (8%)	 Y N
Prophylaxis against anaerobic • RTA • Acute pancreatitis • Cholangitis • Internal bleeding • Intestinal obstruction • Chronic constipation • Intraperitoneal fluid • Intracranial hemorrhage	15 1 (1.1%) 3 (3.4%) 1 (1.1%) 3 (3.4%) 3 (3.4%) 2 (2.3%) 1 (1.1%) 1 (1.1%)	 N N Y N Y N N N
CNS infection	2 (2.3%)	Y
Prophylaxis against fungal infection	1 (1.1%)	N
Prophylaxis against hepatic complication • Hepatic encephalopathy • Variceal bleeding	7 4 (4.6%) 3 (3.4%)	N
Septicemia	3 (3.4%)	Y
Surgical prophylaxis	32 4 (4.6%) 28 (32.2%)	 N Y
Amebiasis	1 (1.1%)	Y
Acute complicated UTI	1 (1.1%)	N
Empiric for protozoal infection	1 (1.1%)	Y
Hydatid cyst	1 (1.1%)	N
Fungal sinusitis	1 (1.1%)	N
Skin infection • Bedsores + diabetic foot ulcer • Cellulitis	5 (5.7%) 2 3	 Y
Empirical treatment for diarrhea	3 (3.4%)	N

HAP: hospital-acquired pneumonia; RTA: Road traffic accident; UTI: urinary tract infection; Y: yes; N: no.

3.3. Storage of Metronidazole

The protection of metronidazole vial from light was also investigated. Overall, we reported 70.1% of metronidazole vials protected from light, while the reminders were exposed to light upon storage with a statistically significant difference (p<0.001) when compared to the expected storage criteria threshold of 100% as demonstrated in Figure 2.

3.4. Drug Interaction with Other Medications

After checking all prescriptions for drug interactions between metronidazole and other combined drugs, it was concluded that 17 prescriptions (19.5%) contained drug interactions. The action needed for these interactions were classified as 14 required monitoring, one required drug modification, and two required to avoid combination as illustrated in Table 4. Non-significant differences were observed by comparing these observed results with the expected threshold value as shown in Figure 2.

Table 4: Drug interaction between metronidazole and other combined drugs at the studied Egyptian tertiary care hospital.

Interacting drugs	No. of prescriptions	Action needed	Notes about drug interaction
Metronidazole + Ondansetron	4	Monitoring	Ventricular arrhythmias
Metronidazole + Phenytoin	2	Monitoring	Toxicity of phenytoin & decrease metronidazole efficacy
Metronidazole + Levofloxacin	2	Monitoring	Ventricular arrhythmias
Metronidazole + Ciprofloxacin	5	Monitoring	Ventricular arrhythmias
Metronidazole + Warfarin	1	Modification	Need decrease dose of warfarin
Metronidazole + Mebendazole	1	Avoiding	Associated with Stevens Johnsons syndrome (mebendazole increase the toxic effect of metronidazole)
Metronidazole + diazepam	1	Avoiding (injectable and rectal dosage forms of diazepam) Monitoring (all dosage forms of diazepam)	Disulfiram - like reaction, use diazepam (containing propylene glycol) after three days of stopping metronidazole
Metronidazole + atorvastatin	1	Monitoring	Peripheral neuropathy (a potential side effect of both medication)

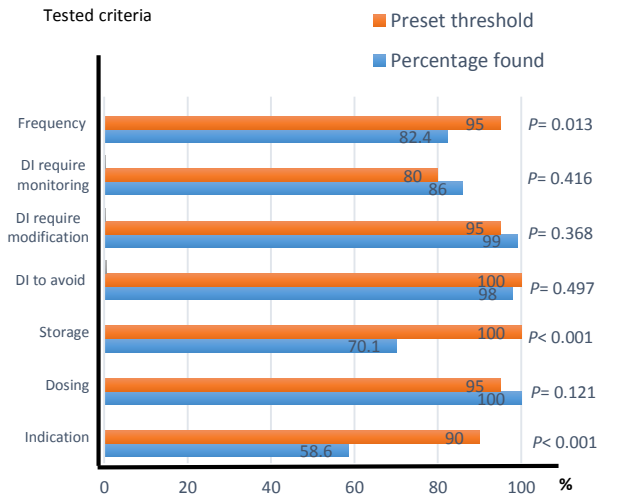

Figure 2: Expected criteria threshold versus observed data at the studied Egyptian tertiary care hospital.
DI: drug interaction.

Although metronidazole is a widely used antimicrobial agent, its reconsidered safety data in addition to the global antibiotic resistance crisis opened the window for the ultimate need for evaluating its use. This study illustrated that metronidazole is usually used at this studied Egyptian tertiary care hospital for any suspected and documented anaerobic infection. Only 58.6% of the utilization patterns reported here are in agreement with medical guidelines and literature.

At this hospital, 8% of cases received empiric treatment of metronidazole for managing hospital-acquired pneumonia (HAP). Inconsistence with this finding, 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society of clinically suspected HAP. These guidelines offer other antibiotics with activity against Staphylococcus aureus, Pseudomonas aeruginosa, or other gram-negative bacilli after assessing mortality risk and factors increasing the likelihood of methicillin-resistant Staphylococcus aureus (MRSA).[11]

In disagreement with medical guidelines, metronidazole was used for prophylaxis against anaerobic infections (12.6%) rather than intestinal obstruction and cholangitis cases. Metronidazole is originally indicated for the management of anaerobic infections caused by Bacteroides species but not for prophylaxis.[12] From these cases, intravenous metronidazole was used as a prophylactic antibiotic for acute pancreatitis. In contrast, the American College Guidelines for Gastroenterology[13] and a multicenter, prospective, double-blind, placebo-controlled randomized study,[14] demonstrated that routine use of antibiotics for prophylaxis in patients with severe acute pancreatitis and/or sterile necrosis is not recommended.

While the use of prophylactic antibiotics for decreasing incidence of infected pancreatic necrosis (IPN) should be preferably done based on presence or absence of risk factors for infection & following of monitoring parameters (e.g., blood urea nitrogen, procalcitonin level, and C-reactive protein) to previously predict the occurrence of infection. In the case of infected necrosis, antibiotics with good penetrating ability to pancreatic tissues such as carbapenem and quinolones are useful in decreasing morbidity and mortality rates. Although metronidazole possess a good penetrating ability, it was found that metronidazole may be a leading cause of pancreatitis although the mechanism is not exactly known.[15]

As well, metronidazole was prescribed in the studied hospital for prophylaxis against fungal infections while there is no evidence supported this use for metronidazole. The most commonly used agents for fungal infection prophylaxis are posaconazole, fluconazole, voriconazole, itraconazole, micafungin, and other antifungal agents.[16, 17]

At this studied hospital, 4.6% of cases received metronidazole for prophylaxis against hepatic encephalopathy (HE). The use of antibiotics for prophylaxis against HE has been discouraged mainly due to adverse effects reported with their long term use. In contrast, lactulose is effective for preventing the recurrence of HE in cirrhotic patients.

Furthermore, adding rifaximin to lactulose become the best-documented option to maintain remission in patients with one or more bouts of overt HE while on lactulose treatment.[18-20]

In this study, intravenous metronidazole was used as a prophylactic antibiotic in variceal hemorrhage, but no evidence supports this use. Patients with cirrhosis presenting with GI hemorrhage are at a high risk of developing bacterial infections. According to the updated 2016 American Association for the Study of Liver Diseases (AASLD) practice guidance, intravenous ceftriaxone is the prophylactic antibiotic of choice in most centers, not metronidazole.[21]

Regarding the use of metronidazole for surgical prophylaxis observed in the current study, most of the cases received this antimicrobial agent in agreement with previous literature mainly in colon surgical prophylaxis cases. It was observed that metronidazole was used as a prophylactic antimicrobial agent after tonsillectomy.

The use of antibiotics for this purpose is not well suggested by strong evidence.[22] However, antibiotics suggested for prophylaxis in head & neck surgeries including tonsillectomy were cefazolin, clindamycin, and amoxicillin-clavulanate. Cefazolin was the antibiotic of choice due to many factors such as cost-effectiveness, fewer side effects. Therefore, using metronidazole as a prophylactic antibiotic for tonsillectomy is not supported.[23]

Moreover, our results showed that one case received metronidazole combined with ampicillin/sulbactam for the management of complicated urinary tract infections (UTIs). This finding was in disagreement with the 2018 European Association of Urology guidelines. These guidelines recommended mainly in the case of hospitalized patients with complicated UTIs the use of an aminoglycoside with or without amoxicillin or a 2nd or 3rd generation cephalosporin or extended-spectrum penicillin with or without an aminoglycoside. It is reasonable to assess the resistance percentages of causative micro-organisms for selecting a suitable antimicrobial regimen.[24]

There is no evidence supported using metronidazole as an anti-infective agent in the management of hydatid cyst observed in the current study. Human infection with Echinococcus granulosus leads to the development of one or more hydatid cysts located most often in the liver and lungs. For alveolar echinococcosis, albendazole is considered the key element of anti-infective prophylaxis.[25] Furthermore, Albendazole and mebendazole are the only anthelmintics effective against cystic echinococcosis. Albendazole is the drug of choice against this disease because its degree of systemic absorption and penetration into hydatid cysts is superior to that of mebendazole.[26] Previous study showed that metronidazole could also be used while with a similar effect of hypertonic saline on the membrane of hydatid cyst during puncture treatment.[27] For the previous reasons, metronidazole is misused for managing the hydatid cyst as an antibacterial agent.

In addition, data from the current study revealed that intravenous metronidazole was used as an empiric treatment in acute diarrhea. However, the evidence does not support empiric anti-microbial therapy for routine acute diarrheal infection, except for traveler's diarrhea (TD) where the probability of bacterial pathogens is high enough to justify the

potential use of antibiotics with their expected side effects. The first step for managing acute diarrhea is rehydration, preferably oral rehydration.[28, 29] Using probiotics, in this case, is not recommended, except in cases of post-antibiotic-associated illness. Non-antibiotic therapies like bismuth subsalicylates (BSSs) or zinc can be administered in mild to moderate diarrhea.[28] Combined loperamide/simethicone may exhibit faster and more complete relief of acute nonspecific diarrhea and gas-related discomfort compared to either medication alone.[30] Testing for Clostridium difficile toxins A and B is recommended for patients who develop unexplained diarrhea after three days of hospitalization. In such a case where Clostridium difficile is documented, we can consider using metronidazole for the treatment of diarrhea.[28]

Concerning to drug-drug interactions occurred while using metronidazole concomitantly with other drugs, we found two major interactions that require avoiding concomitant use. First: the interaction between metronidazole and mebendazole which is associated with Stevens Johnson's syndrome as mebendazole increases the toxic effect of metronidazole.[31, 32] Second: concomitant use of metronidazole with diazepam containing propylene glycol can lead to a disulfiram-like reaction; limited to injectable and rectal dosage forms of diazepam. Diazepam should be used after three days of metronidazole discontinuation.[8,33] Furthermore, Metronidazole increases the effect of diazepam by inhibiting CYP3A4, close monitoring is required.[10] When using metronidazole with warfarin, the dose of warfarin should be decreased to avoid the increase in warfarin serum concentration. As metronidazole is a weak inhibitor of CYP2C9, the primary enzyme responsible for S-warfarin metabolism.[34]

Some drug-drug interactions were recognized form collected prescriptions needed monitoring such as interactions between metronidazole and ondansetron, ciprofloxacin, or levofloxacin. Despite this interaction is rare but its incidence considered life-threatening. Theoretically, concurrent use of two or more drugs that can cause QT interval prolongation may result in additive effects and increased risk of ventricular arrhythmias including torsade de pointes and sudden death. Caution and clinical monitoring are recommended if these agents are prescribed with metronidazole. Patients should be advised to seek prompt medical attention if they experience symptoms such as dizziness, lightheadedness, fainting, palpitation, irregular heart rhythm, shortness of breath, or syncope.[9]

Metronidazole may inhibit one or more of the enzymes responsible for phenytoin metabolism and phenytoin may induce the enzyme(s) responsible for metronidazole metabolism. This interaction requires monitoring as phenytoin may decrease the effect of metronidazole and metronidazole may increase the toxicity of phenytoin.[8,35] Using metronidazole together with atorvastatin may increase the risk of nerve damage, which is a potential side effect of both medications.[9] Furthermore, metronidazole will increase the level of atorvastatin by inhibiting its metabolism. Therefore, close monitoring is required.[10] Although all these interactions with its three action needed categories (avoid, need modification, and monitoring) showed no statistically significant differences when compared with the expected threshold values, while the outcome of these interactions is clinically significant.

In our study, we concluded 70.1% of total cases with proper storage conditions for metronidazole which showed a statistically significant difference when compared to the expected threshold value. As reported in previous literature and metronidazole monograph, excessive heat and light lead to the degradation of metronidazole and this diminishes its stability upon storage under these conditions. Dark containers and storage at 20-25°C are the optimum storage conditions for metronidazole and wrap shouldn't be removed until it is ready for use. Some studies revealed that the effect of heat is more pronounced than the effect of light on the stability and the exposure of metronidazole to oxidizing agents can exaggerate the effect of light on degradation. So, for safe and effective therapy, optimum storage conditions should be strictly followed.[5,7,36,37]

Finally and regarding the pharmacoeconomics, inappropriate use of metronidazole seen in our study including overprescribing of combined antibiotics, unnecessary use of metronidazole in such cases, drug interactions, and inappropriate storage conditions may lead to further undesirable sequences. It could be associated with the increased need for laboratory monitoring, decreased treatment adherence, prescribing other medications to overcome patients' complaints and complications resulted from inappropriate use, decreased quality of life, and increasing the length of hospital stay. All these features may contribute to rising the economic burden of the individual and to the health system.

4. CONCLUSION

In conclusion, metronidazole was overprescribed at this studied Egyptian tertiary care hospital, the rationalization for prescription section showed that there is a need for the change in the policy of prescribing metronidazole to limit its use to cases where there are no other available alternatives. Recommendations with proper use, proper storage, drug interactions of metronidazole, and the need for comprehensive written prescriptions must be sent to the hospital management system. The prospective DUE program on metronidazole will be conducted again at this hospital after the announcement of these recommendations.

STUDY LIMITATION

The major study limitations are small sample size in addition to the lack of recording the actual duration of metronidazole therapy in our investigations that resulted from improper completion of patients' prescriptions in such cases.

ETHICAL APPROVAL

The study was approved on 25th August 2016 by the Research Ethics Committee, Faculty of Pharmacy, Tanta University (REC-TP) with ethical approval number CP0004. The study was carried out in accordance with the 1964 Helsinki

declaration and its later amendments or comparable ethical standards. Collected data were gathered after verbal consent from the patients or their family relatives. Also, verbal consent was obtained from the head of the tertiary care hospital to permit checking up the prescriptions.

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest.

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