

Evaluating and Enhancing the Current Guideline Adherence in prevention and treatment of cancer-related infections in Najaf.

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Abstract

Background: Cancer patients receiving systemic antineoplastic therapy are at risk for invasive infection. Since the magnitude of the neutrophil-mediated component of the inflammatory response may be muted in neutropenic patients, a fever may be the earliest and only sign of infection. The sign and symptom of infection are often absent or muted in the absence of neutrophil but fever remains an early but non specific sign. 50%-60% of febrile patients have an established or occult infection. The NCCN (national comprehensive cancer network) Guidelines provide a summary of infection risk categories. Poor guideline adherence may lead to inability to recognize neutropenic fever early and to initiate empiric systemic antibacterial therapy promptly in order to avoid progression to a sepsis syndrome and possibly death. On the other hand, Poor guideline adherence increases unnecessary empirical therapy.

Aim of the study:

Assessment of the current practice followed by oncologists in prevention and treatment of cancer related infections in oncology center of Najaf and evaluation of the impact of pharmacist educational intervention in improving adherence to guideline of prevention and treatment of cancer-related infections.

Methods: An educational, interventional study based on validated questionnaire was conducted at (Middle Euphrates cancer center / An-Najaf governorate/ Iraq). The questionnaires were personally delivered to all specialized (9) oncologists who were working at Middle Euphrates cancer center. A second study tool; sixty patients were included to check the existing practice of anti-infections prophylaxis, and patients' outcomes. After the study intervention, the questionnaires were redistributed to the same participants to see if there was any change regarding their knowledge about cancer related infections and its prevention. Also, another sixty patients were enrolled to analyze the change in doctors' practice toward cancer related infections prophylaxis and the possible improvements in patients' outcomes.

Results: There were 9 oncologists completed the study with 100% response rate. Significant change was noticed in the participants' knowledge toward all aspects of prevention and treatment of cancer related infections. The mean total overall knowledge scores out of (30) of all questionnaire parts increased considerably from 18.1 ± 3.2 to 24.9 ± 1.6 after intervention. Also, Overall mean total score of participants about Knowledge of Risk factors of Cancer-Related Infections with good knowledge increased from only (10.2) of participants had good overall knowledge to (11.8) after intervention. The overall rate of Prescribing antimicrobial agent for cancer-related infections increased significantly in the post intervention group, (4.9)

compared to (2.0) before intervention. Furthermore, the Proportional of overall good level of adherence in prevention and treatment of cancer-related infections to the guideline raised significantly (66.7%) before intervention vs. (100%) after intervention. In contrast, the Proportional of overall inadequate level of Adherence has been greatly reduced from 33.3% before intervention to 0.0% after intervention.

Conclusions: The clinical pharmacist's multifaceted intervention resulted in encouraging guideline implementations, as evidenced by improved knowledge about the prevention and treatment of cancer-related infections, as well as encouragement on the proper use of antimicrobial agents for cancer-related infections, according to this study.

Keywords: cancer, chemotherapy, infection, guideline, adherence, clinical pharmacist.

Introduction

Neutrophils play an important role in the host's infection protection, notably against bacterial and fungal pathogens. The risk increases for infection as the intensity and duration of neutropenia increases, with the highest risk occurring in patients who experience profound persistent neutropenia (Bow and Wingard, 2015).

In patients receiving chemotherapy for malignancy, FN is linked to a long-term increased risk of infection, and an infectious incident is linked to higher mortality that lasts up to 6 months after the infection (Nordvig et al., 2018)

Bone marrow suppression could result from cancer treatment with chemotherapy, which can hide the early signs and symptoms of an infection as well as reduce the patient's capacity to resist infections (Lyman et al., 2010).

Patients with lung cancer who develop febrile neutropenia have a tendency to mortality risk more than those with another type of cancer [8].

The NCCN Guidelines Prevention and Treatment Cancer-Related Infections identify a primary pathogen that can infect cancer patients, with an impact on the diagnosis, prevention, and treatment of infectious diseases, both common and opportunistic (Baden et al., 2016).

Patients undergoing chemotherapy for acute leukemia are suffered from FN in >80% of these patients. Despite developed diagnostic abilities in the last decade, the etiology of an infection is identified in <50% of episodes (Nesher and Rolston, 2014)(Zimmer and Freifeld, 2019).

Only 40 percent to 50 percent of NF patients have an infectious etiology, with 10 percent to 30 percent having bacteremia [6].

56% of cases were considered for Gram-negative microorganisms and gram-positive microorganisms for 43%. 3% of episodes were Candidemia and polymicrobial bacteremia expressed 11% of all cases (Martinez-Nadal et al., 2020).

The following are host factors that predisposed patients for infectious complications:

1. Immunodeficiencies in Patients with Primary Cancer.

2. Neutropenia.
3. Disruption of Mucosal Barriers.
4. Splenectomy and Functional Asplenia.
5. Corticosteroids and Other Immunosuppressive Agents.
6. Hematopoietic Cell Transplantation.
7. Chronic-graft-versus-host-disease(GVHD).

The Prevention and the Treatment Guidelines for Cancer-Related Infections:

Several international and local societies and organizations developed clinical guidelines for the prevention and treatment of cancer-related infections like "The National Comprehensive Cancer Network" (NCCN) (Baden et al., 2016), "American Society of Clinical Oncology" (ASCO) Clinical Practice Guideline (Taplitz, Kennedy, Bow, Crews, Gleason, Hawley, Langston, Nastoupil, Rajotte and K. V Rolston, 2018) (Taplitz, Kennedy, Bow, Crews, Gleason, Hawley, Langston, Nastoupil, Rajotte and K. Rolston, 2018), "Infectious Diseases Society of America" (IDSA) guideline (Freifeld et al., 2011) and "the European Society for Medical Oncology" (ESMO) (Yates et al., 2018). The NCCN Guidelines in Oncology for the prevention and the treatment of cancer-related infections distinguish the pathogens for any patients with cancer are susceptible, it also concentrate on the prevention, the diagnosis, and the treatment of common opportunistic infectious diseases (Baden et al., 2016) (Poonacha and Go, 2011).

Risk Stratification Models

Risk stratification models depending on patient features at the outset of FN have been developed, allowing doctors to categorize patients into low- and high-risk categories. The intensity and duration of neutropenic episodes are two of the most important determinants of the outcomes of neutropenic episodes.

1. Talcott Score

At the time of presentation, patients might be categorized into four groups based on the following primary risk factors (Talcott et al., 1988):

Group 1: inpatient who had a fever.

Group 2: outpatient with concomitant comorbidities (in addition to fever and neutropenia).

Group 3: outpatient with cancer that is uncontrolled but has no associated comorbidities.

Group 4: Outpatient with NF who doesn't have any additional indicators for risk of groups 2 and 3.

2. “The Multinational Association for Supportive Care in Cancer” (MASCC)

The MASCC most widely used model for stratifying patients based on their risk of significant consequences. Since it was first published more than 15 years ago, it has been validated several times in collections from all over the world. Clinical practice recommendations from the majority of scientific organizations almost consistently support the approach [55].

Category	Weight
“The burden of illness: absent or mild symptoms”	5
“No hypotension”	5
Solid tumor or no previous invasive fungal infection	4
No COPD	4
“Outpatient status”	3
No dehydration	3
moderate symptoms (Burden of disease)	3
“Aged <60 years”	2

3.” Clinical Index of Stable Febrile Neutropenia” (CISNE) scores

In the year of 2015, researchers published the CISNE score, which showed higher specificity and positive predictive value in characterized low-risk patients with NF [58]. In ED, the CISNE score used for febrile neutropenia may be the most appropriate risk-stratification tool [59].

Prevention of Infectious Diseases:

Cancer patients who are suspected to the risk of infection, upfront prophylaxis or preemptive treatment with broad-spectrum antimicrobial medicines in opposition to the most prevalent infecting microorganism (e.g., bacterial, viral, and fungal) is recommended (Baden et al., 2016).

Prophylactic Antimicrobial is interference can lower possibilities of infection into patients who are immunocompromised, due to drug side effects, resistance to antimicrobial concerns, price issues, additionally the physiologic significance to maintaining balance in the diversity and density of the host microbiome, the decision to take prophylaxis is needs Arbitrage advantage and disadvantage (Flowers et al., 2013).

1. Antibacterial Prophylaxis
2. Pneumococcal Infection Streptococcus Prophylaxis
3. Antifungal Prophylaxis

4. Prophylaxis for Viral Infections and Preemptive Antiviral Therapy

Management of Neutropenic Patients with Fever

The selection of specific antibiotic regimens is based on an assessment of the patient's infection risk during neutropenia, which is influenced by several factors, including the depth and duration of neutropenia, cancer treatment, the underlying cancer type and status (remission, relapse, or recurrence), and comorbid medical conditions (Freifeld et al., 2011)(Network, 2020).

1. Initial Empiric Antibiotic Therapy

Avoiding sepsis syndrome as well as possibly mortality, it is crucial to diagnose NF early and begin empiric antibiotic therapy as soon as possible. In patients with neutropenic fever, it's also crucial to assess the risk of major consequences, as this will determine the course of treatment, which may include inpatient admission, intravenous antibiotics, and prolonged hospitalization (Freifeld et al., 2011).

the lack of precise tests or scoring systems that can accurately differentiate cancer patients with bacteremia from those who do not. As a result, all cancer patients should receive initial empiric therapy that must contain antibiotics against gram-negative organisms that pose the greatest harm to cancer patients (Freifeld et al., 2011). Febrile neutropenic patients should get empiric antibiotic medication within an hour of their coming and four hours of observation for at least to assess whether they are suitable for outpatient treatment or should be the hospital admitted. Unless fluoroquinolone prophylaxis was taken before the fever started, an oral fluoroquinolone plus amoxicillin/clavulanate (if penicillin-allergic receive clindamycin instead of amoxicillin/clavulanate) is indicated as empiric therapy (Flowers et al., 2013).

2. Therapy for Invasive Fungal Infections

For the empiric antifungal therapy of NF and patients with severe IFI, “amphotericin B formulations, newer triazoles (posaconazole, voriconazole, isavuconazole), and echinocandins (casposfungin, micafungin, anidulafungin)” are preferable (Rapoport et al., 2021).

Role of the Pharmacist

The oncologist pharmacist could provide patient care, where the healthcare team makes treatment decisions. In fact, they've established themselves as valuable members of the healthcare team (Holle and Boehnke Michaud, 2014). Oncology pharmacists are a crucial component of the cancer care team. They are critical in enhancing patient care (Holle, Segal and Jeffers, 2020). Oncologist pharmacists play an important role in cancer care. Those who play an important role in increasing and patient care is being improved [136] can show that using a pharmacist-led, interdisciplinary team improved symptom scores in a way that is akin to what Researchers seen in our inpatient palliative care service (Valgus et al., 2010).

Importance of guidelines adherence

Although following FN guidelines enhances the effective use of antimicrobials [139], many institutions' low rates of adherence result in poor ASP practices, higher pharmaceutical costs, and bad patient care outcomes (Wright et al., 2013)(Baugh et al., 2017). Because patients with FN are vulnerable hosts for a variety of microbial illnesses, implementing ASP for them can be difficult. Because of their continued exposure to healthcare surroundings, the risk of nosocomial pathogen colonization, and their immunosuppression, these patients may require more rigorous treatment. ASP initiatives for patients with FN, on the other hand, appear to improve mortality (Rosa, Goldani and dos Santos, 2014)(Madran et al., 2018)(Aguilar-Guisado et al., 2017). The proof that the following recommendations have a favorable influence on patient outcomes is not only important for clinical treatment, but it also reflects the competencies that a practitioner needs to effectively treat patients with such disorders (Ting et al., no date). To support successful clinical practice, the NCCN has developed evidence-based clinical guidelines. Previously, established guidelines the NCCN to prevent and treat cancer-related infections in patients with neutropenia; however, they have now extended their guidelines to include all cancer-related infections. Implementing scientific data into clinical practice is difficult and complex, and healthcare practitioners should be aware of the obstacles to a successful implementation of clinical practice recommendations (Wood and Payne, 2012).

Aim of Study

This study aims at assessing of the following:

1. The current practice followed by oncologists in the prevention as well as treatment of cancer-related infections in this oncology center from Najaf.
2. The impact of pharmacist educational intervention in improving adherence to the guideline of prevention and treatment of cancer-related infections

Method

1.Study Design and Setting

Between October 2020 and February 2021, an educational, interventional prospective pre and post-study, was conducted at (Middle Euphrates cancer center / An-Najaf governorate/ Iraq) to assess the current practice of prevention and treatment of cancer related infections prophylaxis and the impact of pharmacist educational intervention on guideline implementation. All specialized (9) oncologists who were working at Middle Euphrates cancer center during the study period were eligible for participation. After performing a pilot study that comprised (4) oncologists, a total of 9 doctors who agreed to participate in the study were included.

2. Study Tools

A- Questionnaire

Based on thorough literature review using PubMed database (Wilder-Smith, Martin and Morabia, 1997; Chandrakantan and Glass, 2011; Gan et al., 2014; Haga et al., 2014), a questionnaire was constructed to evaluate the practice implemented by doctors and pharmacists

in the setting of prevention and treatment of cancer related infections. In the observation phase, questionnaires were personally and manually delivered to (9) oncologists who were working at Middle Euphrates cancer center to identify their baseline knowledge, practice, prevention and treatment of cancer-related infections. All questionnaires were returned (response rate 100%) and the last questionnaire was received after one month. Then post-intervention the questionnaires were redistributed also by hand to the same participants to see if there was any change regarding their baseline knowledge, practice, prevention and treatment of cancer-related infections.

B- Patients part

For further evaluation, (60) patients' cases were taken both 'before and after' pharmacist intervention to compare the prescribing pattern of the prophylactic antimicrobial (antibacterials, antifungals or antiviral) and the incidence of infection between the pre- and post-interventional phases of the study.

After that, the study intervention was implemented in which the clinical pharmacist performed an intense educational program over a 3-months period to create awareness about cancer-related infection problem and the guideline recommendations according to the NCCN guideline for prevention and treatment of cancer related infection. This program involved: (a) lecture presentation in the weekly meeting of each specialty including the clinical pharmacists (b) distribution of booklets to each participant. (c) in addition to activation the role of a clinical pharmacist to participate in the regulation dose and working as a team and to create awareness of the clinical pharmacist in the ward about cancer-related infection problem.

Results

Part I: Patients' data before and after intervention

There were 60 patients with different types of cancers enrolled in this study before intervention program, similar number of patients was enrolled after intervention. Both patients' groups were not significantly different in their baseline demographic characteristics regarding, types of cancers or mode of treatment, in all comparisons, P. value > 0.05, not significant. As shown in table 1.1, according to patients' medical records, prescription of Antibacterial agent and Antifungal agent rates increased significantly after intervention, reflected optimization of treatment and prevention of cancer related infection according to guideline, (P<0.05, significant). Prescription of Antiviral agent were also increased but did not reach the statistical significance, (P>0.05)

Table 1.1. Cancer-related infection prophylaxis or treatment received (according to Patient's medical record)

Item	Patients group				P. value
	Before intervention		After intervention		
	No.	%	No.	%	

Antibacterial agent	Yes	41	68.3	51	85.0	0.035
	No	19	31.7	9	15.0	sig
Antiviral agent	Yes	5	8.3	9	15.0	0.255
	No	55	91.7	51	85.0	ns
Antifungal agent	Yes	14	23.3	40	66.7	< 0.001
	No	46	76.7	20	33.3	sig
*Chi-square test used in all comparison, sig: significant, ns: not significant						

The evaluation of and decision about adherence to guideline before and after intervention according to patient's medical records revealed that reporting of risk factors was good before intervention where in a rate of 86.7%, however, it increased significantly to 96.7% after intervention, ($P < 0.05$). Similarly, a significant optimization was reported after intervention program in prescription of cancer-related infection prophylaxis according to guideline, Type and dose of cancer-related infection prophylaxis and proper duration of cancer-related infection prophylaxis, ($P < 0.05$), (Table 1.2)

Table 1.2. Evaluation Decision about adherence to guideline before and after intervention according to patients' medical records

	Patients group				P. value
	Before intervention		After intervention		
	No.	%	No.	%	
Reporting Risk factors of Cancer-Related Infections	51	85	58	96.7	0.027 sig
Cancer-related infection prophylaxis prescribed according to guideline	52	86.7	58	96.7	0.048 sig
Type and dose of cancer-related infection prophylaxis	48	80.0	57	95.0	0.013 sig
Proper duration of cancer-related infection prophylaxis	44	73.3	55	91.7	0.008 sig

Regarding the reasons for non-adherence to guideline in some patients, all Oncologists reported that the high cost is the main reason, followed by shortage in resources and facilities in the center (66.7%), Concern about adverse effects (55.6%), inconvenient to use in our patients

(33.3%), and the least frequent reason was Disagreement between guidelines and clinical practice and experience (11.1%), (Table 1.3)

Table 1.3. Reasons for Under-Use of or Noncompliance with Guideline for prevention and treatment of cancer-related infections according to Oncologists' opinion

Reason	No.	%
Increased costs	9	100.0
Shortage in resources or facilities in the center	6	66.7
Concern about adverse effects	5	55.6
Guidelines are difficult or inconvenient to use in our patients	3	33.3
Disagreement between guidelines and clinical practice and experience	1	11.1

Part II: Oncologist's Questionnaire

The participant oncologists were 9, with a mean age of 43.3 (range 34 – 66) years and a duration in practice ranged 1 – 28 years. They were 7 males and 2 females. Five Oncologists with Board graduation and 4 with high diploma or Master degree.

However, when the mean total score for each domain compared before and after intervention it showed a statistically significant increase in all domains; Knowledge about Risk factors of Cancer-Related Infections, Assessment of risk, Prescribing antimicrobial agent for Cancer-Related Infections, and the overall total score for all domains, (Table 1.4 and Figures 1.1, 1.2, 1.3 & 1.4).

Despite good proportion of Oncologist (66.7%), had good adherence to guideline, however, after intervention none had inadequate adherence, the good adherence rate was 100% after intervention, (Figure 1.5).

Table 1.4. Mean total scores of Oncologists about prevention and treatment of Cancer-Related Infections before and after intervention

	Before intervention		After intervention		P. value*
	Mean	SD	Mean	SD	
Total score for Knowledge about risk factors 14 items	10.2	1.5	11.8	1.1	0.023 sig
Total score for Assessment of risk factors 10 items	5.9	1.8	8.2	1.2	0.018 sig

Total score for prescribing antimicrobial agent 6 items	2.0	1.2	4.9	0.9	0.007 sig
Overall Total Score 30 Items	18.1	3.2	24.9	1.6	0.007 sig
* Wilcoxon test used in all comparison					
** SD: standard deviation, ns: not significant, sig : significant					

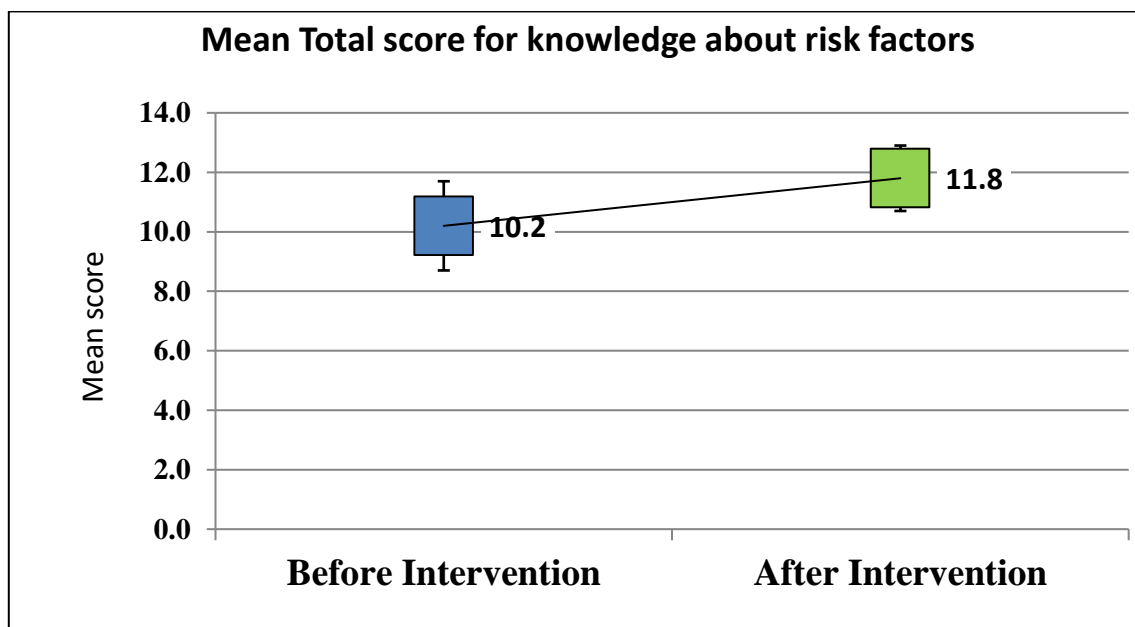


Figure1.1. Modified Box-plot showing the significant increase in Mean Total score for knowledge of Oncologist about cancer-related-infection risk factors

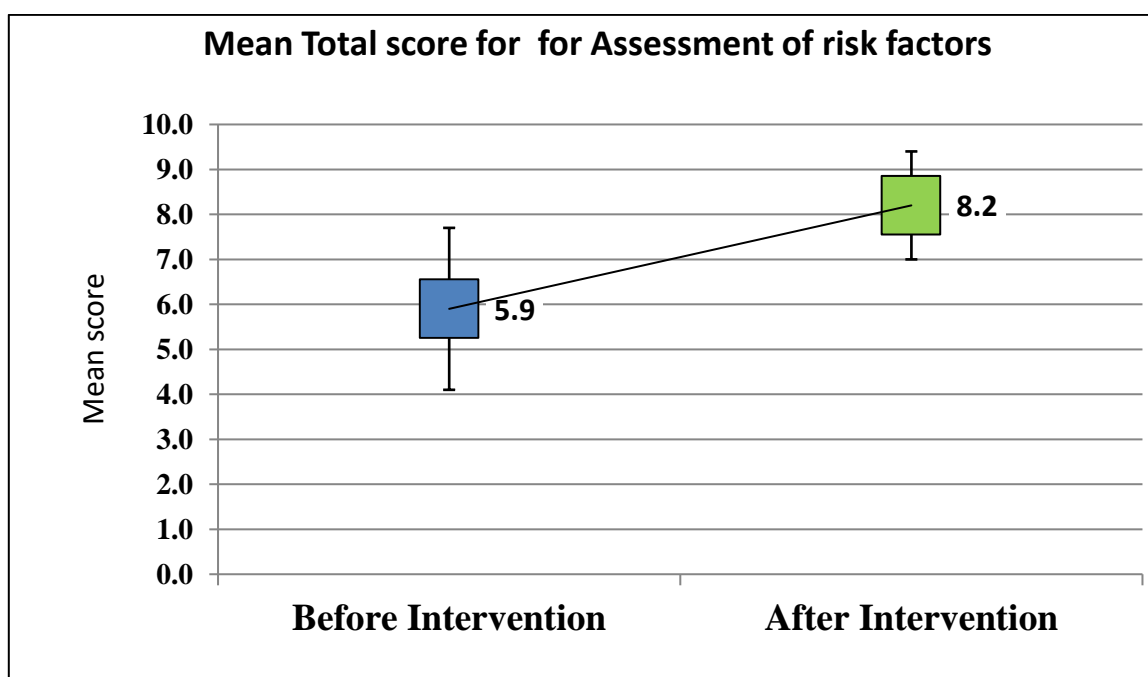


Figure 1.2. Modified Box-plot showing the significant increase in Mean Total score for knowledge of Oncologist in assessment of cancer related-infection risk factors

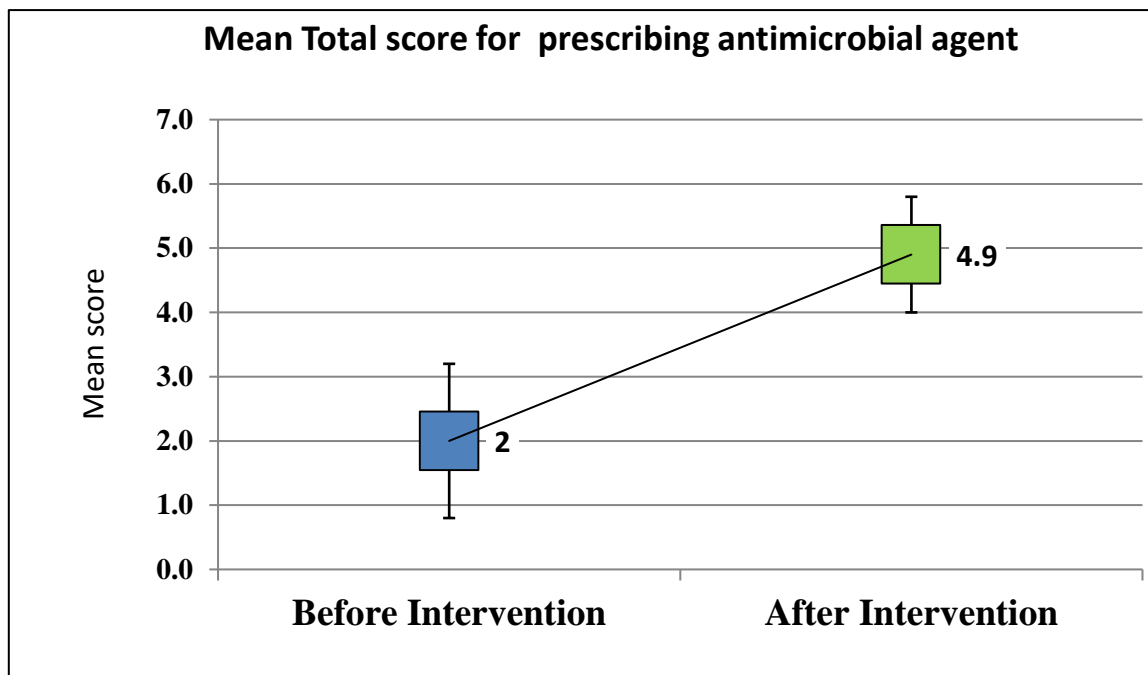


Figure 1.3. Modified Box-plot showing the significant increase in Mean Total score of Oncologist in prescribing of antimicrobial agent for treatment and prevention of cancer related-infection

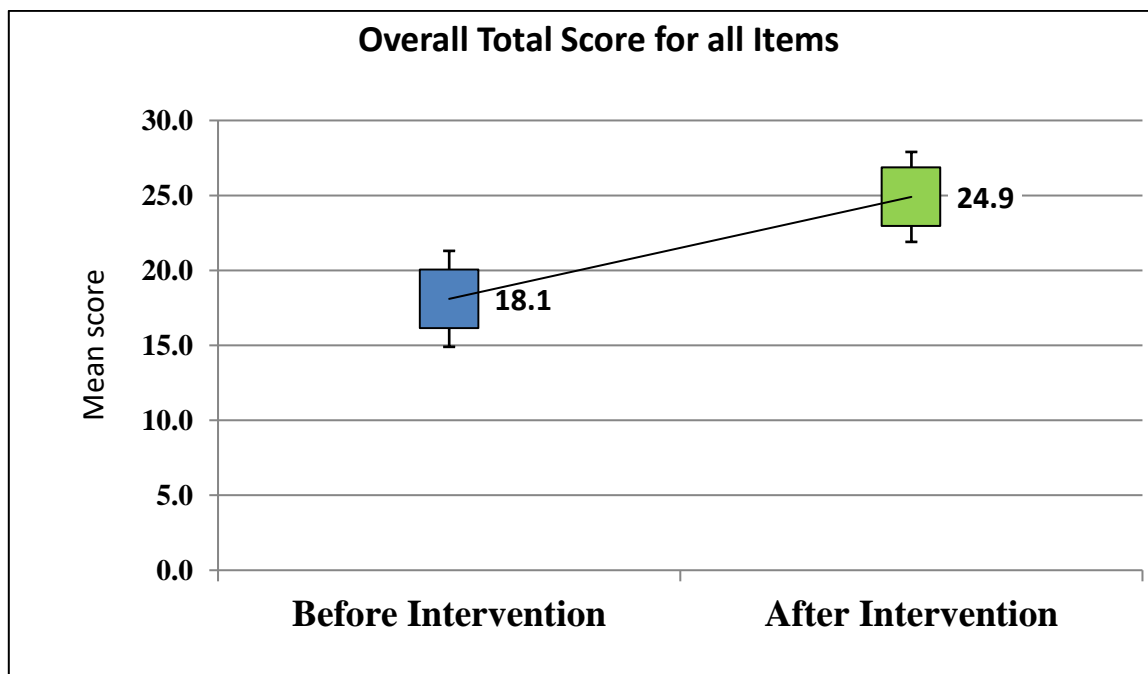


Figure 1.4. Modified Box-plot showing the significant increase in overall mean total score of Oncologist for treatment and prevention of cancer related-infection

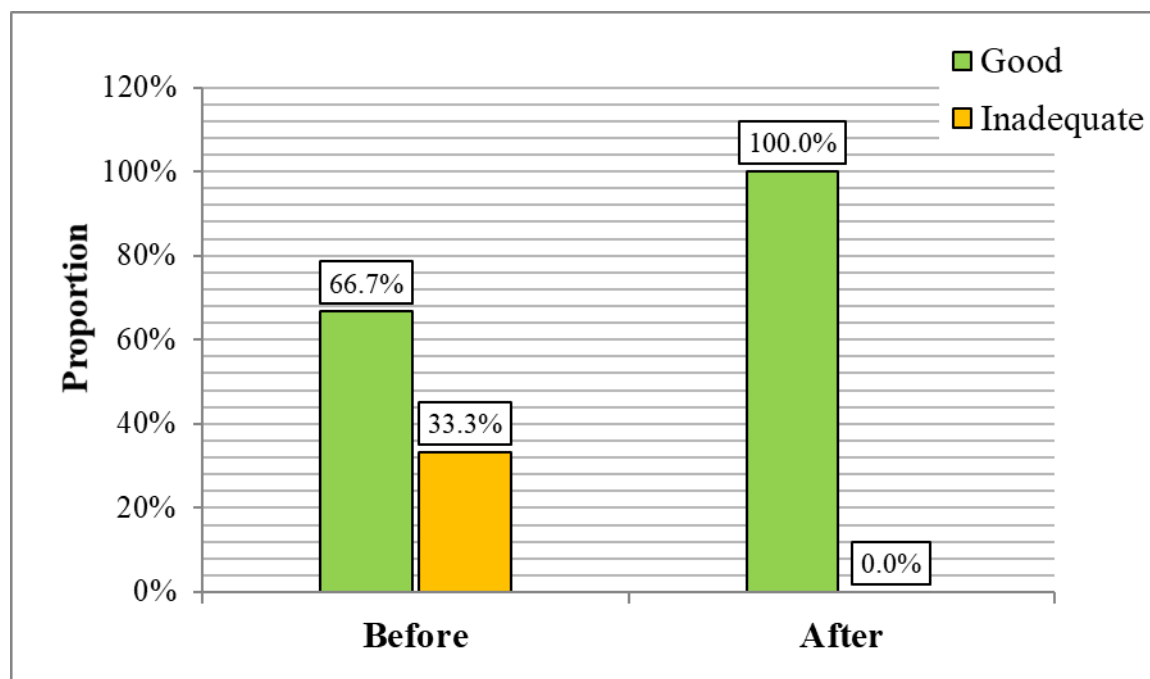


Figure 1.5. Proportional distribution of overall good and inadequate level of Adherence in prevention and treatment of cancer-related infections before and after intervention.

Discussion

The use of Cancer-related infection prophylaxis during the neutropenia period is an important topic in Several international and local societies and organizations that developed clinical guidelines for the prevention and treatment of cancer-related infections for using the correct prophylactic agent, timing, and dosing that interfere significantly with the outcome of the patients with cancer ([14] [27] [49] [50] [51]). This study provides a novel description of Evaluating and enhancing the Current Guideline Adherence in prevention and treatment of cancer-related infections, the present study is the first study in Iraq that attempted to explore the impact of clinical pharmacist educational intervention on the knowledge among providers and on improving adherence to NCCN guideline for prevention and treatment of Cancer-Related Infections prophylaxis guideline. Hence, a total number of 9 oncologists were included in the research. Regarding to knowledge of participant doctors toward NCCN guideline for prevention and treatment of Cancer-Related infections prophylaxis guideline we found that mean total scores of Oncologists about prevention and treatment of Cancer-Related Infections increased after the clinical pharmacist intervention particularly in the questions concerned with the significant knowledge of Oncologist about cancer-related-infection risk factors, This is due to the fact that before intervention(10.2) of doctors had a good level of knowledge about this part compared to (11.8) after intervention Similarly, the educational intervention performed by the clinical pharmacist resulted in considerable improvement in the knowledge of Oncologist in the assessment of cancer related-infection risk factors, where the majority of participants after intervention correctly responded to the most items about risk assessment of Cancer-Related Infections. This is revealed by the finding that the proportion of doctors with good knowledge after the intervention was (8.2) versus (5.9) before the intervention, ($P < 0.05$). The knowledge enhancement among the enrolled doctors in the current study could be attributed to

the clinical pharmacist educational program via a 30-minute presentation lecture (displaying cancer-related infection condition in terms of definition, incidence, complications, risk factors, risk predicting method, and suitable prophylactic approaches based on the NCCN guideline recommendations); booklets distribution; as well as joining with morning tour of the doctors.

Guidelines are difficult or inconvenient to use in our patients, it also be considered as barrier to the oncologist in the center to applied the recommendation of the guideline to some of their patients, This is similar to a study that show This incompatibility of guidelines and practice is likely multifaceted, owing in part to a lack of familiarity of the guidelines, their complexities, and the fact that the MASCC score has a low predictive value for consequences in only 83 percent of patients and is thus untrustworthy (Bitar, 2015) (Baugh et al., 2016). In another survey, Questionnaires were sent to oncologists across the UK to discover how they treat FN on a regular basis. A number of oncologists also commented on the practical difficulties in assessing and managing low-risk FN. Several respondents mentioned challenges with junior staff's capacity to estimate risk, such as "junior employees play it safe" and "(difficulty in identifying whether) the nadir is gone or coming." (Innes et al., 2005). So it is necessary to develop our specific country guideline many factors, including regional microbial epidemiological and antimicrobial resistance, the presence of timely reporting of microbiological data, expertise in infectious illness management, and past antibiotic prescribing habits, all contribute to this guideline. (Gyssens, Kern and Livermore, 2013), Also be appropriate to our environment and our patient economic condition because although differing from one another. This approach similar to a recent study that conclude Clinical practice guidelines for febrile neutropenia in adult cancer patients received a moderate rating, with 37.5 percent being recommended to be used in practice. In the creation and reporting procedures, guideline developers should concentrate on increasing the applicability and rigor of clinical practice guidelines. Prior to implementation in clinical settings, critical evaluation of guidelines should become normal practice (Nasr et al., 2018) To achieve compliance, a strategy for incorporating guidelines into standard care must be devised, with frequent reevaluation.

There are some limitations in our research: First, it was a single-center study, only Middle Euphrates cancer center / An-Najaf governorate/ Iraq, due to restrictions in time and short durations to follow up a single center study design. which limits generalizability in other Oncology centers in Iraq. However, this initial work is an important first step toward evaluating and enhancing the Current Guideline Adherence in prevention and treatment of cancer-related infections. Second, the use of paper medical records and incomplete medical documentation also posed a challenge since all microbiology results were It is in the patient's hand or their relative and is not placed in the patient's file, and antibiotic administration was inconsistently documented, some of the data obtained, particularly the objective elements of the MASCC score, could be incompletely documented. Third, we did not power this study to detect differences in clinical outcomes between risk groups.

References

1. Aguilar-Guisado, M. et al. (2017) 'Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial', *The Lancet Haematology*, 4(12), pp. e573–e583.

2. Baden, L. R. et al. (2016) 'Prevention and treatment of cancer-related infections, version 2.2016, NCCN clinical practice guidelines in oncology', *Journal of the National Comprehensive Cancer Network*, 14(7), pp. 882–913.
3. Baugh, C. W. et al. (2016) 'Provider familiarity with specialty society guidelines for risk stratification and management of patients with febrile neutropenia.', *The American journal of emergency medicine*, 34(8), pp. 1704–1705.
4. Baugh, C. W. et al. (2017) 'Emergency department management of patients with febrile neutropenia: guideline concordant or overly aggressive?', *Academic Emergency Medicine*, 24(1), pp. 83–91.
5. Bitar, R. A. (2015) 'Utility of the Multinational Association for Supportive Care in Cancer (MASCC) risk index score as a criterion for nonadmission in febrile neutropenic patients with solid tumors', *The Permanente journal*, 19(3), p. 37.
6. Bow, E. and Wingard, J. R. (2015) 'Overview of neutropenic fever syndromes', *UpToDate* (pristupljeno 18.05. 2017) Dostupno na: <http://www.uptodate.com>.
7. Flowers, C. R. et al. (2013) 'Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline', *J Clin Oncol*, 31(6), pp. 794–810.
8. Freifeld, A. G. et al. (2011) 'Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America', *Clinical infectious diseases*, 52(4), pp. e56–e93.
9. Gyssens, I. C., Kern, W. V and Livermore, D. M. (2013) 'The role of antibiotic stewardship in limiting antibacterial resistance among hematology patients', *haematologica*, 98(12), p. 1821.
10. Holle, L. M. and Boehnke Michaud, L. (2014) 'Oncology pharmacists in health care delivery: vital members of the cancer care team', *Journal of oncology practice*, 10(3), pp. e142–e145.
11. Holle, L. M., Segal, E. M. and Jeffers, K. D. (2020) 'The expanding role of the oncology pharmacist'. *Multidisciplinary Digital Publishing Institute*.
12. Innes, H. et al. (2005) 'Management of febrile neutropenia in the United Kingdom: time for a national trial?', *British journal of cancer*, 93(12), pp. 1324–1328.
13. Lyman, G. H. et al. (2010) 'Risk of mortality in patients with cancer who experience febrile neutropenia', *Cancer*, 116(23), pp. 5555–5563.
14. Madran, B. et al. (2018) 'Implementation of an antimicrobial stewardship program for patients with febrile neutropenia', *American journal of infection control*, 46(4), pp. 420–424.
15. Martinez-Nadal, G. et al. (2020) 'Inappropriate empirical antibiotic treatment in high-risk neutropenic patients with bacteremia in the era of multidrug resistance', *Clinical Infectious Diseases*, 70(6), pp. 1068–1074.
16. Nasr, Z. G. et al. (2018) 'Critical appraisal of clinical practice guidelines for adult cancer patients with febrile neutropenia', *International Journal of Pharmacy Practice*, 26(1), pp. 49–54.
17. Nesher, L. and Rolston, K. V. I. (2014) 'The current spectrum of infection in cancer patients with chemotherapy related neutropenia', *Infection*, 42(1), pp. 5–13.
18. Network, N. C. C. (2020) 'NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Prevention and Treatment of Cancer-Related Infections. Version 2.2020. June 5, 2020'.
19. Nordvig, J. et al. (2018) 'Febrile neutropenia and long-term risk of infection among patients treated with chemotherapy for malignant diseases', in *Open forum infectious diseases*. Oxford University Press US, p. ofy255.
20. Poonacha, T. K. and Go, R. S. (2011) 'Level of scientific evidence underlying recommendations arising from the National Comprehensive Cancer Network clinical practice guidelines', *Journal of clinical oncology*, 29(2), pp. 186–191.
21. Rapoport, B. L. et al. (2021) 'Treatment of infections in cancer patients: an update from the

- neutropenia, infection and myelosuppression study group of the Multinational Association for Supportive Care in Cancer (MASCC)', *Expert Review of Clinical Pharmacology*, 14(3), pp. 295–313.
22. Rosa, R. G., Goldani, L. Z. and dos Santos, R. P. (2014) 'Association between adherence to an antimicrobial stewardship program and mortality among hospitalised cancer patients with febrile neutropenia: a prospective cohort study', *BMC infectious diseases*, 14(1), pp. 1–8.
 23. Talcott, J. A. et al. (1988) 'The medical course of cancer patients with fever and neutropenia: clinical identification of a low-risk subgroup at presentation', *Archives of internal medicine*, 148(12), pp. 2561–2568.
 24. Taplitz, R. A., Kennedy, E. B., Bow, E. J., Crews, J., Gleason, C., Hawley, D. K., Langston, A. A., Nastoupil, L. J., Rajotte, M. and Rolston, K. V (2018) 'Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update', *Journal of Clinical Oncology*, 36(30), pp. 3043–3054.
 25. Taplitz, R. A., Kennedy, E. B., Bow, E. J., Crews, J., Gleason, C., Hawley, D. K., Langston, A. A., Nastoupil, L. J., Rajotte, M. and Rolston, K. (2018) 'Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update', *J Clin Oncol*, 36(14), pp. 1443–1453.
 26. Ting, F. I. L. et al. (no date) 'Compliance with Guideline-Based Empiric Antimicrobial Therapy for Febrile Neutropenia in Adult Filipino Cancer Patients and their Effect on Outcomes'.
 27. Valgus, J. et al. (2010) 'Pharmacist-led, interdisciplinary model for delivery of supportive care in the ambulatory cancer clinic setting', *Journal of oncology practice*, 6(6), pp. e1–e4.
 28. Wood, S. K. and Payne, J. K. (2012) 'Implementation of national comprehensive cancer network evidence-based guidelines to prevent and treat cancer-related infections.', *Clinical journal of oncology nursing*, 16(3).
 29. Wright, J. D. et al. (2013) 'Deviations from guideline-based therapy for febrile neutropenia in cancer patients and their effect on outcomes', *JAMA internal medicine*, 173(7), pp. 559–568.
 30. Yates, L. R. et al. (2018) 'The European society for medical oncology (ESMO) precision medicine glossary', *Annals of Oncology*, 29(1), pp. 30–35.
 31. Zimmer, A. J. and Freifeld, A. G. (2019) 'Optimal management of neutropenic fever in patients with cancer', *Journal of oncology practice*, 15(1), pp. 19–24.