Compliance with Guideline-Based Empiric Antimicrobial Therapy for Febrile Neutropenia in Adult Filipino Cancer Patients and their Effect on Outcomes

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Abstract

Introduction: Febrile neutropenia (FN) is a common complication of immunocompromised patients – whether due to infection, cancer, drug-induced, or other bone marrow failure states. With the incidence of patients with immunocompromised states on the rise, this life threatening complication is also increasing. The importance of initiating the appropriate empiric antibiotic therapy can prove to be lifesaving, thus we examined how the initial choice of antibiotics influenced patient outcomes. This study aims to determine the effect of adherence to guideline-based antimicrobial therapy for adult febrile neutropenia patients in terms of patient outcomes.

Methods: This is a 10-year cross-sectional analytical study which was conducted at the Dr. Pablo O. Torre Memorial Hospital (DPOTMH) by doing a retrospective chart review involving adult patients with FN from 2007 to 2016. We determined use of guideline-based antibiotics, examined the factors that influenced adherence, and investigated the effect of initial treatment on patient outcome.

Results: Among the 257 adult patients with FN included in the study, Infectious Diseases Society of America (IDSA) guideline-based antibiotics were administered to 65%. On multivariate analysis, the most powerful predictor of adherence to guideline-based antibiotics was the type of risk (p=0.000), with high risk patients thrice more likely to be given guideline-based antibiotics. Other predictors were physician specialty (p=0.036) and hematologic malignancy (p=0.045). This study showed that among low risk patients with FN, a trend towards patient discharge was observed (OR 1.18, CI=0.16–8.63). However overall, adherence to guideline-based empiric antibiotic in treating adult FN patients did not correlate to patient discharge (p=0.134, OR 0.557, 95% CI=0.260-1.205).

Conclusion: Our data suggest that adherence to guideline-based antibiotics in managing adult Filipino patients with febrile neutropenia does not correlate to better outcomes such as patient discharge. Significant factors associated with adherence to guideline-based antibiotics are physician specialty, hematologic malignancy, and type of risk.

Keywords: guideline, antibiotic, febrile neutropenia, Filipino, cancer, patients, outcomes

Introduction

Febrile neutropenia (FN) is diagnosed in a patient who presents with fever in a host with an Absolute Neutrophil Count (ANC) of <500. These cases are commonly found in patients with bone marrow neoplasms or those undergoing chemotherapy.[1] More than 40% of patients with solid tumors and 70% of those with hematologic cancers can develop FN.[2] Not only is it associated with significant morbidity, but studies also show that more than half of patients with FN will develop an infection (sepsis due to pneumonia, intra-abdominal infections, urinary tract infections) with a mortality rate of 5-21.5% - making it a medical emergency prompting hospitalization in the majority of cases.[3-5] With more advanced and more complicated chemotherapeutic regimens, the risk and severity of FN are increasing, resulting in more devastating complications and poorer results.[6-8]

Idiosyncratic drug-induced agranulocytosis, or severe neutropenia, is characterized by a neutrophil count under 0.5x 109/ L. Because the infections are often seen in frail patients, it is associated with an estimated mortality rate of 5% - 20%.[9,10] In Europe, the annual incidence of symptomatic idiosyncratic drug-induced agranulocytosis is between 3.4 and 5.3 cases per million people per year; while in the US, reported rates ranges from 2.4 to 15.4%.[10,11]

The standard management of patients with FN involves obtaining cultures and starting empiric antimicrobials, among others. Although the Infectious Diseases Society of America (IDSA) clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer has been revised twice since its first publication in 1997, what has not changed is the indication for immediate empirical antibiotic therapy.[7,10-12] Also, it is important to note that the

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IDSA guidelines were made in the context of North American practices.

Presently, there are no national or in-hospital clinical practice guidelines for the empiric antibiotic treatment of adult patients admitted for FN resulting to wide variations in practice patterns among clinicians. Being a developing country where most health financing come from out-of-pocket expenditure, empiric treatment with the appropriate antibiotics is not only cost-effective but life-saving.[13-16] Thus this study was done with an aim to provide data regarding compliance to the latest 2010 IDSA guidelines in the empiric antibiotic management of adult patients admitted for FN, explore the factors that influence adherence to the treatment guideline, and analyze how the use of guideline based care affect patient outcomes.

This study aims to determine the effect of adherence to guideline-based antimicrobial therapy for adult FN patients in terms of patient outcomes. More specifically, this study aims:

- To describe the demographic and clinical profile of adult patients admitted at the Dr. Pablo O. Torre Memorial Hospital (DPOTMH) for FN;
- To identify factors that influence adherence to the treatment guideline;
- To analyze how the use of guideline-based antimicrobial therapy affect patient outcomes.

Methods

This is a 10-year retrospective cross-sectional analytical study that was conducted at the DPOTMH. The study design was reviewed and approved by the hospital ethics committee. As the study does not involve any tests or interventions, the informed consent requirement was waived. Charts of patients included in the study were retrieved through the Bizbox Hospital information System using International Classification of Diseases, Tenth Revision (ICD-10) codes.

We analyzed adult patients treated for FN from January 2007 to December 2016. The inclusion criteria (Figure 1) consisted of patients >18 years old with a suspected or documented risk factor for FN (hematologic malignancy, bone marrow failure state, or solid organ tumor after myelosuppressive chemotherapy) who developed fever (temp ≥ 38.3°C) occurring together with an episode of neutropenia (absolute neutrophil count ≤ 500). Bone marrow failure state was defined as patients who were either post-chemotherapy, on chronic steroid use (≥ 14 days), septic, or drug-induced.[17]

Although there are a number of risk stratification systems for FN attempting to use clinical parameters in identifying

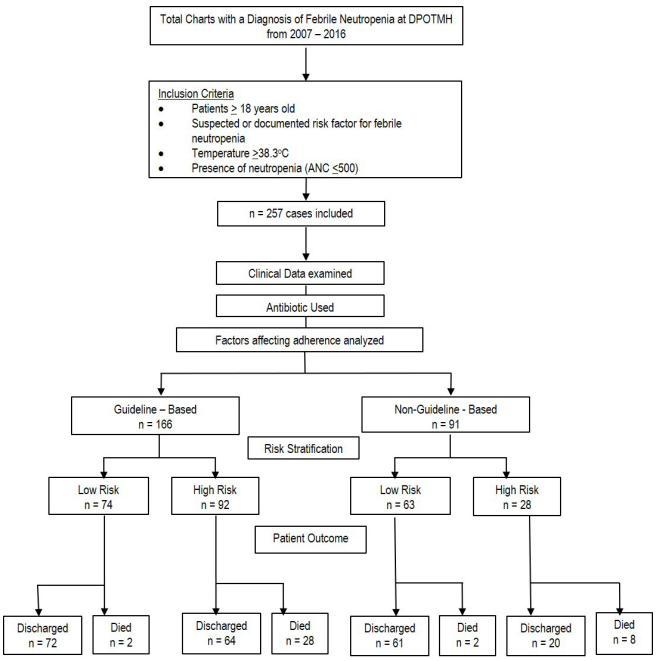

Figure 1. Study design: Inclusion criteria

patients with high-risk neutropenia, there is presently no consensus or objective system to stratify risk using population-based data. However, a multivariate regression model in one study described pneumonia, hypotension, sepsis, ICU admission, and use of mechanical ventilator to be independently associated with death.[17] Thus in this study, patients were stratified as "high risk" if they had any of these five clinical characteristics; and they were stratified into the "low risk" group if they had none of these characteristics.

For our sample size, the sample size determination using unknown proportion formula was used and resulted to a minimum sample size of 384 at 95% confidence level. Upon knowing that the overall population size was 257, it was then subjected to a finite population correction formula which yielded a final sample size of 154 at 95% level of confidence.

Clinical data analyzed included age (<60 and >60 years old), gender, marital status, and insurance status (Philippine Health Insurance Company, Private Insurance, None). Each patient's admitting physician was noted and their specialty classified as medical oncology/hematology, general internal medicine, other internal medicine subspecialties (other than oncology), or other specialties (surgery/obstetrics and gynecology). Patients were also noted if they had a known comorbidity or none.

The primary endpoint analyzed was use of guideline-based antibiotics. The outcome was based on a review of the 2010 IDSA guidelines for use of antimicrobial agents in adult patients with FN.[7] We used a definition of "guideline-based antibiotics" that included all antibiotics that were recommended. Administration of any of the following

IDSA Guidelines for INPATIENT IV ANTIBIOTICS

Empiric Antibiotic Monotherapy: Administration of any of the following antibiotics within 48 hours of hospital admission:

- Piperacillin – Tazobactam or
- Carbapenem or
- Ceftazidime or
- Cefepime

Figure 2. Study design: Inclusion criteria

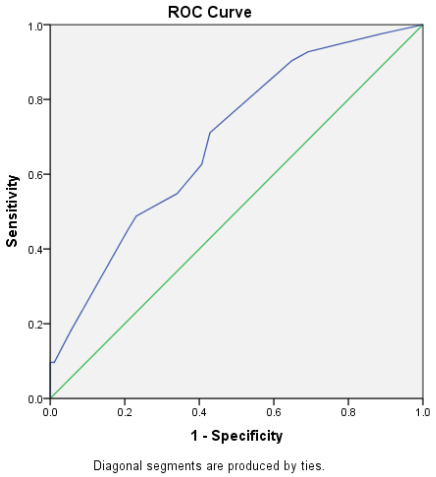

Figure 3. Hospital outcomes for low risk patients

antibiotics within 48 hours of hospital admission was considered guideline-based antibiotic therapy: ceftazidime, cefepime, piperacillin-tazobactam or carbapenems (Figure 2). We also examined how the use of guideline-based therapy influenced patient outcomes in terms of discharge or in-hospital mortality. Because of a previous study[17] showing the independent association of high risk features of adult patients with FN to mortality, a separate analysis was done between the two groups.

Percentage and frequency distribution was used to determine the profile of respondents according to demographic variables and clinical outcomes. Chi-square was used to determine the association of the variables, hospital outcomes, and adherence to the use of guideline-based antibiotic therapy. Multivariate logistic regression analysis was used to determine the factors associated with use of guideline-based antibiotics. Using the Risk Operating Curve (ROC, Figure 3) which is a measure of the ability of the model to discriminate the adherence and non-adherence of subjects to guideline-based antibiotics, the model is an acceptable fit if it has an Area Under the Curve (AUC) of ≥0.7. In this study, the area under the ROC is 0.691 which is near the cut-off value and is still acceptable. All analyses were performed using SPSS, version 22.

Results

This study reviewed a total of 257 charts of patients with FN that met our inclusion criteria (Figure 1). Majority of our subjects were less than 60 years old (n=160, 62.3%). Among them, 59.5% were female (n=153) and 76.3% were married (n=196). Insurance status revealed that almost half of the subjects (n=113, 44%) have PHIC, more than a quarter (n=100, 38.9%) had no insurance and the remainder had private insurances (n=44, 17.1%). Majority of the patients (n=162, 63%) had underlying comorbidities. More than half (n=141, 54.9%) of the subjects were admitted under the service of medical oncology/hematology, followed by more than a quarter (n=79, 30.7%) under other internal medicine (IM) subspecialties while the remaining minority were admitted under general IM service (n=15, 5.8%) and other specialties such as surgery or obstetrics and gynecology (n=22, 8.6%). The most common primary solid tumor site identified in this study was breast cancer comprising 23.7% of the subjects (n=61), followed by tumors clumped under one group designated as "others" (gastric=8, nasopharyngeal=7, laryngeal=6, ovarian=6, endometrial=5, prostate=4, esophageal=4, urinary bladder=2, testicular=2, cervical=2) comprising 18.7% (n=46), while colorectal (n=20) and lung (n=18) cancer lagged behind with only 7.8% and 7% in frequency respectively. Among hematologic malignancies, acute leukemia was diagnosed in 11.3% (n=29) of the subjects while lymphoma was seen in only 8.6% (n=22), and a subset of hematologic conditions grouped as "others" composed 6.2% (n=16) (multiple myeloma=8, aplastic anemia=7, polycythemia vera=5, myelodysplastic syndrome=2). Almost three quarters (n=189) of the subjects had a level of neutropenia between 100-500 while only 26.5% (n=68) were found to have levels less than 100. Almost half of the bone marrow failure states is secondary to chemotherapy (n=118), 18.3% were drug induced (n=47, propylthiouracil 27, methimazole 20) particularly from anti-thyroid medications, 10.5% from sepsis (n=27) while 3.1% were secondary to radiotherapy (n=8) and 2.3% were from prolonged steroid use (n=6). According to our data, more than half (n=166, 64.6%) adhered to guideline-based empiric antibiotics and majority (n=136, 84.4%) of these patients were discharged from the hospital. (Table I)

Patients who are male (OR, 1.25; 95% CI, 0.90-1.31), married (1.5, 0.83-2.70), with comorbidities (1.1, 0.53-1.54), managed by medical oncologists/hematologists (3.86, 1.51–9.87), those with very severe neutropenia with ANC <100 (1.18, 0.70-1.97), those with high risk features (2.79, 1.63–4.80), and those who have prolonged steroid use (1.81, 0.25-13.32) were more likely to receive guideline-based antibiotics. In contrast, younger patients <60 years old (OR 0.58, 95% CI 0.34–0.99), those with private insurance (0.68, 0.33-1.42), those admitted under general internists (0.11, 0.03-0.36), patients with colorectal (0.88, 0.29-2.63), lung cancer (0.59, 0.17-2.01), acute leukemia (0.89, 0.30-2.61), sepsis (0.49, 0.22-1.08), and those with drug-induced FN (0.48, 0.15-1.55) were less likely to receive guideline-based antibiotics. Results of the univariate analysis are displayed in Table II, and it can be inferred that although the previously mentioned associations

Table I. Clinical and demographic characteristics

Variable	Classification	N (%)
Age (years)	< 60 ≥ 60	160 (62.3) 97 (37.7)
Sex	Male Female	104 (40.5) 153 (59.5)
Marital status	Married Single / separated / widow(er)	196 (76.3) 61 (23.7)
Insurance status	Philhealth Private None	113 (44) 44 (17.1) 100 (38.9)
Co-morbidities	Present[a] None	162 (63) 95 (37)
Physician specialty	Medical oncology / hematology General internal medicine (IM) Other IM subspecialties Others[b]	141 (54.9) 15 (5.8) 79 (30.7) 22 (8.6)
Primary tumor site	Breast Colorectal Lung Others[c]	61 (23.7) 20 (7.8) 18 (7.0) 46 (18.7)
Hematologic malignancy	Acute leukemia Lymphoma Others[d]	29 (11.3) 22 (8.6) 16 (6.2)
Level of neutropenia	100-500 <100	189 (73.5) 68 (26.5)
Bone marrow failure states	Post-chemotherapy Post-radiotherapy Prolonged steroid use Drug-induced[e] Sepsis	118 (45.9) 8 (3.1) 6 (2.3) 47 (18.3) 27 (10.5)
Antibiotics used	Guideline-based Non-guideline-based	166 (64.6) 91 (35.4)
Patient outcome	Discharge Died	217 (84.4) 40 (15.6)

[a] *Hypertension, diabetes mellitus, chronic kidney disease*
[b] *Surgery, obstetrics and gynecology*
[c] *Gastric, nasopharyngeal, laryngeal, ovarian, endometrial, prostate, esophageal, urinary bladder, testicular, cervical)*
[d] *Multiple myeloma, aplastic anemia, polycythemia vera, myelodysplastic syndrome*
[e] *Drugs other than cytotoxic chemotherapeutic agents (propylthiouracyl, methimazole)*

showed the trends as discussed, only age (p=0.048) and type of risk (p=0.000) as a variable were found to be statistically significant.

On the other hand, results of the multivariate analysis showed that the statistically significant variables for adherence to guideline-based antibiotics are physician specialty (p=0.036), whether the patient has a hematologic malignancy (p=0.045) and the type of risk (p=0.000), as depicted in Table III. For physician specialty, the reference group is "other specialties" such as surgery or obstetrics and gynecology. The results showed that patients who were admitted under a medical oncologist/hematologist (OR 3.186, 95% CI 1.199-8.466), a general internist (6.482, 1.407-33.265), or an internist with a subspecialty other than oncology (2.069, 0.726-5.899) were thrice, six times, and twice more likely to receive guideline-based antibiotics compared to patients admitted under the service of "other specialties" such as surgery or obstetrics and gynecology respectively. Furthermore, those with no hematologic malignancies (0.502, 0.256-0.985) and those who have low risk features (0.3485, 0.198-0.603) are less likely to be given guideline-based antibiotics. (Table III)

There was no significant statistical association between adherence to guideline-based treatment and patient outcomes (p-value of 0.134 at 5% level of significance). Furthermore, a trend towards being discharged was also not observed if a patient was managed using guideline based antibiotic (OR=0.56, 95% CI=0.26–1.21). However, when the patients were divided into low risk and high-risk groups, a trend towards patient discharge was noted in the low risk group with adherence to guideline-based antibiotic (OR=1.18, CI=0.16–8.63). On the other hand, no significant association towards patient discharge was noted in the high risk group (OR=0.91, CI=0.36–2.32). (Table IV)

Discussion

This is the first Filipino study investigating adherence to guideline-based antibiotics in patients with FN and their effect on outcomes. Our study evaluated adherence to guideline-based empiric antimicrobial therapy based on the IDSA Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients 2010 update, and their effects on patient outcome at a tertiary hospital in Negros Occidental, Philippines.

Our data shows that by using univariate analysis, age (p=0.048) and type of risk (p=0.000) as a variable were found to be statistically significant – similar with the significant variables identified on a previous study by Wright et al. in 2013.[17] However in contrast to the findings of that study, our data showed that patients <60 years old (OR 0.58, 95% CI 0.34–0.99) were less likely to be given guideline-based antibiotics. On the other hand, similar findings were noted in terms of type of risk wherein those with high risk features (2.79, 1.630–4.801) were also more likely to be given guideline-based antibiotics.

The significance of patient characteristics such as sex, age and insurance status were proven to influence the management of FN in a number of studies.[17-18,19] In this study, our data noted three factors which had statistical significance in predicting adherence: physician specialty (p=0.036), presence of hematologic malignancy (p=0.045) and the type of risk (p=0.000). In terms of physician specialty, our study showed that admission under the service of a medical oncologist/hematologist, a general medical internist, or an IM subspecialist were significant predictors of adherence to guideline-based antibiotics, in contrast to a previous study where results did not show significant association.[17]

Table II. Univariate analysis of factors associated with use of guideline – based antibiotics

Variable	Classification	Guideline-based antibiotics	Non-guideline-based antibiotics	*p*-value	Odds ratio
Age (years)	< 60 ≥ 60	96 70	64 27	0.048	0.58 (0.335 – 0.998)
Sex	Male Female	102 64	51 40	0.399	1.25 (0.897 – 1.308)
Marital status	Married Single / Separated / Widow(er)	131 35	65 26	0.177	1.5 (0.831 – 2.696)
Insurance status	Philhealth Private None	30 67 69	14 46 31	0.289	1 [Reference] 0.68 (0.325 – 1.421) 1.04 (0.484 – 2.228)
Co-morbidities	Present[a] None	106 60	56 35	0.713	1.10 (0.534 – 1.535)
Physician specialty	Med Onco / Hema General internal medicine Other IM subspecialties Others[b]	97 61 49 8	44 3 30 14	0.15	1 [Reference] 0.11 (0.032 – 0.3645) 1.35 (0.758 – 2.404) 3.86 (1.508 – 9.865)
Primary tumor site	Breast Colorectal Lung Others[c]	41 14 14 24	20 6 4 22	0.2139	1 [Reference] 0.88 (0.293 – 2.628) 0.59 (0.171 – 2.010) 1.88 (0.855 – 4.131)
Hematologic malignancy	Acute leukemia Lymphoma	30 30	9 8	0.823	0.89 (0.302 – 2.614)
Level of neutropenia	<100 100 – 500	76 90	38 53	0.535	1.18 (0.703 – 1.974)
Type of risk	High risk[d] Low risk	92 74	28 63	0.000	2.79 (1.630 -4.801)
Bone marrow failure states	Post-chemotherapy Post-radiotherapy Prolonged steroid use Sepsis Drug-induced[e]	76 6 2 37 15	42 0 2 10 4	0.1104	1 [Reference] 0 (N/A) 1.81 (0.246 – 13.316) 0.49 (0.221 – 1.082) 0.48 (0.150 – 1.548)

[a] Hypertension, Diabetes Mellitus, Chronic Kidney Disease
[b] Surgery, Obstetrics and Gynecology
[c] Gastric, nasopharyngeal, laryngeal, ovarian, endometrial, prostate, esophageal, urinary bladder, testicular, cervical)
[d] Presence of pneumonia, hypotension, sepsis, ICU admission, and use of mechanical ventilator
[e] Drugs other than cytotoxic chemotherapeutic agents (Propylthiouracyl, methimazole)

Table III. Multivariate analysis of significant variables to the adherence of use of guideline-based antibiotics

Variables	Coefficients	*p*-value	Odds ratio
Physician specialty		0.036	
Med onco / hema versus other specialties[a]	1.159	0.020	3.186 (1.199– 8.466)
Internal medicine versus other specialties[a]	1.923	0.017	6.482 (1.407– 33.265)
Other IM sub-specialty versus other specialties[a]	0.727	0.174	2.069 (0.726 – 5.899)
Hematologic malignancy (1 – no, 0 – yes)	-0.689	0.045	0.502 (0.256 – 0.985)
Type of risk (1 –low risk, 0 –high risk[b])	-1.063	0.000	0.3485 (0.198– 0.603)

[a]Surgery, Obstetrics and Gynecology
[b]Presence of pneumonia, hypotension, sepsis, ICU admission, and use of mechanical ventilator

Table IV. Association of adherence to guideline-based antimicrobial therapy in adult febrile neutropenia patients to hospital outcomes

Variable	Classification	Hospital discharge	Death	*p*-value	Odds ratio (95% CI)
Adherence	Guideline-based antibiotics[a]	136	30	0.134	0.557 (0.260-1.205)
	Non-guideline-based antibiotics	81	10		

[a] Any of the following: Piperacillin-Tazobactam, Carbapenem, Ceftaidime, or Cefepime

An observed variability in terms of distribution of care for patients with FN was noted in our study – consistent with the results of a study done by Freifeld et al. in 2006, which revealed that management of patients with FN was not congruent with the standards set by guideline-based protocols. In the same study they have also concluded that patients who were categorized as belonging to the group with high risk features had no direct correlation between antibiotic adherence[18], again contrasting the findings of our study which showed that patients with low risk features were less likely to be given guideline-based antibiotics (*p*=0.000, OR 0.3485, 95% CI 0.198-0.603). Additionally, it can be inferred that those who have high risk features (pneumonia, hypotension, sepsis, ICU admission, and use of mechanical ventilator) were thrice more likely to receive guideline-based antibiotics.

The evidence that adherence to guidelines significantly impacts patient outcomes in a positive way is not only vital for clinical care but is also reflective of the competencies that a practitioner must possess to adequately manage patients with such conditions. Our data showed that 64.6% of patients were given guideline-based antibiotic – a figure not far from the results of previous studies where reported

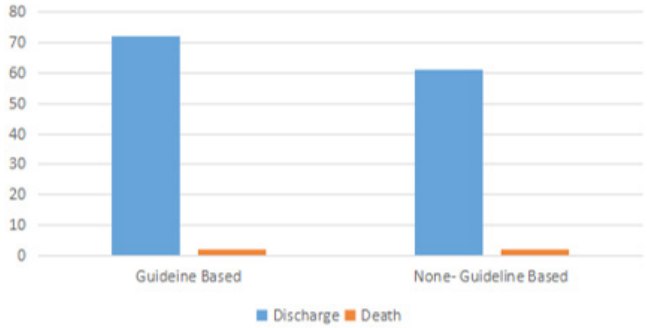

Figure 4. Hospital outcomes for low risk patients

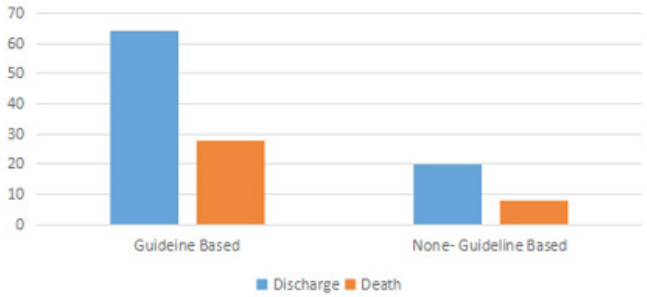

Figure 5. Hospital outcomes for high risk patients

guideline-based antibiotic adherence was at 56% by Jin. et al. in 2010,[20] 78.9% in a study done by Wright et al. in 2013[17], and 53% by Rosa et al. in 2014.[21] In the study done by Wright et al., guideline-based antibiotics were utilized in 77.8% of low-risk and 82.7% (p<0.0001) of high-risk patients in comparison to the data gathered from our study that showed guideline-based antibiotics utilized in 54% of low risk patients and in 76.7% of high-risk patients.

In 2015, a study done by Akalin et al. showed that compliance to guideline-based antibiotics in the management of adult patients with FN did not affect clinical outcomes (p=0.648).[22] Similar statistical results were produced in our study which showed that adherence did not statistically predict patient outcomes (p=0.134), and patients who were managed using guideline-based antibiotics did not show a trend towards being discharged (OR 0.56, 95% CI 0.260-1.205). These results are in contrast to a study done by Rosa et al. where hospitalized FN cases treated using guideline-based recommendations had a relative risk reduction in 28-day mortality of 64% compared to cases receiving antimicrobial treatment non-adherent to the recommendations.[21] However, upon dividing the patients into low risk and high-risk groups (Figures 4 and 5), a trend towards patient discharge was noted in the low risk FN group with adherence to guideline-based antibiotic (OR 1.18, CI = 0.16–8.63) – similar to the findings of a previous study by Wright et al.[17]

While our study benefits from the inclusion of all patients diagnosed with FN admitted in our institution from 2007 to 2016, we identified some critical limitations. The current ICD-10 coding is deficient of an exact code for FN. Previous reports have utilized a number of classification schema including assortment of patients with neutropenia or fever or other related combinations. Although the above-mentioned selection criteria exhibited good validity, we opted for a more precise designation to include only adult patients admitted with FN as the primary diagnosis. Although this may have narrowed our sample size, we deemed it prudent to do so as to truthfully represent those patients whose primary diagnosis was FN and to gauge initial decision-making.

Lastly, the study was limited by involvement of only one tertiary medical center and hence may have led to underestimation or overestimation of projections.

Recommendations

Results of this study can provide future researchers with an overview of the current status of the local clinical practice in terms of adherence, or the lack thereof, to guideline-based antibiotics in managing adult patients with FN. However, a similar but larger scale study to determine adherence to guideline-based antibiotics and their effect on outcome is recommended to be done among the different tertiary hospitals in Negros Occidental.

A study on the adherence to guideline based antibiotic management among patients with FN at the emergency room level can also be done since there are studies[23] stating that a delay of antibiotic initiation of more than one hour adversely affects patient outcome. One parameter to be measured may include whether the initial antibiotic was continued (a parameter of clinical improvement) or was shifted to a broader spectrum antibiotic 72 hours after initiation.

It has been common practice to use Granulocyte Colony Stimulating Factor (G-CSF) among clinicians in the management of FN where previous studies stated that although it decreases the length of hospital stay, its use had no effect on mortality.[24-28] A local in-hospital study is thus recommended assessing these variables in relation to patient outcomes in terms not only of discharge versus death, but also improvement of hematologic parameters and / or clinical characteristics.

Lastly, the variability in practice patterns for FN suggest that initiatives to improve outcomes and reduce medical expenditures are urgently needed. For many inpatient settings, validated protocols in writing physician orders have led to improved outcomes.[19,29-34] Similarly, computerized guides to direct management have been effectively observed to influence the use of evidence-based treatments in some settings.[22,35] These initiatives provide further opportunities to promote more effective and less costly care for cancer patients with FN and are therefore recommended.

Conclusion

This study showed that most adult patients admitted at our institution for FN were females, <60 years old, married, were insured under PHIC, had comorbidities, and were managed under the service of a medical oncologist/ hematologist. The most common primary tumor site was breast cancer, most had an absolute neutrophil count between 100-500, and most were post-chemotherapy.

In summary, although a trend towards patient discharge was observed among low risk patients with FN, our data suggest that adherence to guideline-based antibiotics in managing adult Filipino patients with FN did not correlate with patient discharge. Significant factors associated with adherence to use of guideline-based antibiotics are physician specialty, hematologic malignancy, and type of risk.

Acknowledgements

The authors are indebted to all members of the Riverside Medical Center (RMC) Department of Internal Medicine most especially to its Research Committee. The authors especially thank Dr. Andrew Mallen and Dr. Jeanette Umali for the expert review and guidance of the paper, and for Mr. John Michael Gabriel Zaragoza and Dr. Cherie Grace Quingking for their statistical expertise. This study was supported by the RMC Department of Internal Medicine research fund.

References

1. **Braunwald E, Fauci AS, Kasper DL, et al. (2015),** Harrison's Principles of Internal Medicine, McGraw-Hill, 19th edition.
2. **Dale DC (2004),** "Chemotherapy-induced neutropenia," Cancer, vol. 100, no. 2, pp. 228–237.
3. **Billote K, Mendoza M, and Baylon H (1997),** "Infections in febrile neutropenia and possible prognostic factors associated with mortality," Philippine Journal of Microbiology and Infectious Diseases, vol. 26, no. 2, pp. 55–59.
4. **Kuderer NM, Dale DC, Crawford J, Cosler LE, and Lyman GE (2006),** "Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients," Cancer, vol. 106, no. 10, pp. 2258–2266.
5. **Lyman GH, Michels SL, Reynolds MW, Barron R, Tomic KS, and Yu J (2010)**, "Risk of mortality in patients with cancer who experience febrile neutropenia," Cancer, vol. 116, no. 23, pp. 5555–5563.
6. **Lyman GH, Kuderer NM (2003).** Epidemiology of febrile neutropenia. Support Cancer Ther.;1(1):23-35.
7. **Freifeld A, Bow E, Sepkowitz K, 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 Oxford Journal.
8. **National Comprehensive Cancer Network.** Prevention and treatment of cancer- related infections; (2009). http://www.nccn.org/ professionals/ physicians_gls/pdf/infections.pdf.
9. **Strom BL, Carson JL, Schinnar R, Snyder ES, Shaw M.(1992).** Descriptive epidemiology of agranulocytosis. Arch Intern Med 152:1475-1480.
10. **Andres E, Cottet-Mourot R, Keller O, Serraj K, Vogel T (2015),** "Clinical Articularities of Drug – Induced Agranuloctosis or Severe Neutropenia in Elderly Patients," Journal of Hematology and Thromboembolic Disease, Volume 4, Issue 2.
11. **Wisplinghoff H, Seifert H, Wenzel RP, and Edmond MB (2003),** "Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States," Clinical Infectious Diseases, vol. 36, no. 9, pp. 1103–1110.
12. **Hiransuthikul N, Tantawichien T, Suwangool P, and Nuchprayoon T (1996),** "Febrile neutropenia in Chulalongkorn Hospital during 1994-1995," Chulalongkorn Medical Journal, vol. 40, pp. 781–799.
13. **Caggiano V, Weiss RV, Rickert TS, Linde-Zwirble WT (2005).** Incidence, cost, and mor- tality of neutropenia hospitalization associated with chemotherapy. Cancer.; 103(9):1916-1924.
14. **Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH (2006).** Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer. 106(10):2258-2266.
15. **Weycker D, Malin J, Edelsberg J, Glass A, Gokhale M, Oster G (2008).** Cost of neutro- penic complications of chemotherapy. Ann Oncol;19(3):454-460.
16. **Elting LS, Lu C, Escalante CP, et al (2008).** Outcomes and cost of outpatient or inpatient management of 712 patients with febrile neutropenia. J Clin Oncol;26 (4):606-611.
17. **Wright J, Neugut AI, Ananth CV, et al (2013).** Deviations from Guideline-Based Therapy for Febrile Neutropenia in Cancer Patients and Their Effect on Outcomes. JAMA Intern Med; 173(7):559-568
18. **Freifeld A, Sankaranarayanan J, Ullrich F, Sun J (2008).** Clinical practice patterns of managing low-risk adult febrile neutropenia during cancer chemotherapy in the USA. Support Care Cancer; 16:181–191.
19. **Perrone J, Hollander JE, Datner EM (2004).** Emergency Department evaluation of patients with fever and chemo-therapy-induced neutropenia. J Emerg Med; 27: 115-9
20. **Jin J, Lee YM, Ding Y, Koh LP, Lim SE, Lim R, Tambyah PA, Hsu LY (2010).** Prospective audit of febrile neu-tropenia management at a tertiary university hospital in Singapore. Ann Acad Med Singapore, 39:453–599.
21. **Regis GR, Luciano Z, Goldani RP (2014).** Association between adherence to an antimicrobial stewardship program and mortality among hospitalised cancer patients with febrile neutropaenia: a prospective cohort study. BMC Infec-tious Diseases, 14:286.
22. **Akalin E, Yaka E, Yilmaz S, et al (2015).** Compliance with the IDSA Guidelines for Emergency Management of Febrile Neutropenia in Cancer Patients. Acta Medica mediterranea,31:785.
23. **Rhodes A, Evans L, Alhazzani W, et al (2016).** Surviving Sepsis Campaign: International Guidelines for Manage-ment of Sepsis and Septic Shock: Society of Critical Care Medicine Journal, 2017.
24. **Cosler LE, Eldar-Lissai A, Culakova E, et al (2007).** Therapeutic Use of Granulocyte Colony-Stimulating Factors for established febrile neutropenia: effect on costs from a hospital perspective. Pubmed.gov. Pharmacoeconomics; 25(4):343-51.
25. **Kelly S and Wheatley D (2009).** Prevention of febrile neutropenia: use of Granulocyte Colony-Stimulating Factors. Br J Cancer; 101(Suppl 1): S6-S10.
26. **Rocio GC, Jose I, Mayordomo MV, Tornamira ML, et al (2001).** Granulocyte Colony-Stimulating Factor in the Treatment of High-Risk Febrile Neutropenia: a Multicenter Randomized Trial. Journal of the National Cancer Institute, Volume 93, Issue 1, 3, Pages 31-38.
27. **Smith TJ, Bohlke K, Lyman G, Carson KR, et al (2015).** Recommendations for the Use of WBC Growth Factors: American Society

of Clinical Oncology Clinical Practice Guideline Update. Journal of Clinical Oncology 33, no. 28 3199-3212.

28. **Yu MG, Villalobos RE, et al (2015).** Predictors of Outcome and Severity in Adult Filipino Patients with Febrile Neutropenia. Advances in Hematology, Article ID 920838.
29. **Stulberg JJ, Delaney CP, Neuhauser DV, Aron DC, Fu P (2010),** Koroukian SM. Adherence to surgical care improvement project measures and the association with postoperative infections. Jama; 303:2479–2485.
30. **Lindenauer PK, Remus D, Roman S, et al (2007).** Public reporting and pay for performance in hospital quality improvement. N Engl J Med; 356:486–496.
31. **Campion FX, Larson LR, Kadlubek PJ, Earle CC, Neuss MN (2011).** Advancing performance measurement in oncology: quality oncology practice initiative participation and quality outcomes. J Oncol Pract.; 7:31s–35s.
32. **Zuckermann J, Moreira LB, Stoll P, Moreira LM, Kuchenbecker RS, Polanczyk CA (2008).** Compliance with a criticalpathway for the management of febrile neutropenia and impact on clinical outcomes. Ann Hematol; 87: 139-45
33. **Debey C, Meert AP, Berghmans T, Thomas JM, Sculier JP (2011).** Febrile neutropenia at the emergency department of a cancer hospital. Rev Med Brux; 32: 74-82.
34. **Iting LS, Lu C, Escalante CP, Giordano SH, Trent JC, et al (2008).** Outcomes and cost of outpatient or inpatient management of 712 patients with febrile neutropenia. J Clin Oncol; 26: 606-11.
35. **Courtney DM, Aldeen AZ, Gorman SM, Handler JA, Trifilio SM, et al (2007).** Cancer associated neutropenic fever: clinical outcome and economic costs of emergency department care. Oncologist; 12: 1019-26

Appendices

SPSS Tables

Age		Frequency	Percent	Valid percent	Cumulative percent
Valid	Less than 60 years old	97	37.7	37.7	37.7
	60 years old and above	160	62.3	62.3	100.0
	Total	257	100.0	100.0	

Gender		Frequency	Percent	Valid percent	Cumulative percent
Valid	Female	153	59.5	59.5	59.5
	Male	104	40.5	40.5	100.0
	Total	257	100.0	100.0	

Marital status		Frequency	Percent	Valid percent	Cumulative percent
Valid	Single, widower, separated	61	23.7	23.7	23.7
	Married	196	76.3	76.3	100.0
	Total	257	100.0	100.0	

Insurance status		Frequency	Percent	Valid percent	Cumulative percent
Valid	None	100	38.9	38.9	38.9
	Private	44	17.1	17.1	56.0
	PHIC	113	44.0	44.0	100.0
	Total	257	100.0	100.0	

Co-morbidities		Frequency	Percent	Valid percent	Cumulative percent
Valid	No co-morbidity	95	37.0	37.0	37.0
	With co-morbidity	162	63.0	63.0	100.0
	Total	257	100.0	100.0	

Physician specialty		Frequency	Percent	Valid percent	Cumulative percent
Valid	Medical oncology	141	54.9	54.9	54.9
	Internal Medicine	15	5.8	5.8	60.7
	IM subspecialty	79	30.7	30.7	91.4
	others	22	8.6	8.6	100.0
	Total	257	100.0	100.0	

Neutropenia		Frequency	Percent	Valid percent	Cumulative percent
Valid	Less than 100	114	44.4	44.4	44.4
	101-500	143	55.6	55.6	100.0
	Total	257	100.0	100.0	

Multivariate analysis of significant variables to the adherence of use of guideline-based antibiotics	B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I.for EXP(B)	
							Lower	Upper
Medical oncology			8.537	3	.036			
Internal medicine	1.159	.499	5.404	1	.020	3.186	1.199	8.466
Other IM subspecialties	1.923	.807	5.680	1	.017	6.842	1.407	33.265
Other specialties	.727	.534	1.852	1	.174	2.069	.726	5.899
Hematologic malignancy	-.689	.344	4.020	1	.045	.502	.256	.985
Type of risk	-1.063	.284	13.959	1	.000	.345	.198	.603
Constant	.775	.603	1.649	1	.199	2.171		

Area	Std. error[a]	Asymptotic sig.[b]	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
.691	.035	.000	.623	.759