# Appropriate Antimicrobial Therapy Reduced Mortality in Hematological Cancer Patients with Febrile Neutropenia in The Era of Multidrug Resistance

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***Objective:*** *To determine the effect of appropriate antimicrobial therapy (AAT) on mortality among Thai hematological cancer patients with febrile neutropenia (FN).*
***Material and Method:*** *A 6-year retrospective cohort study of hematological cancer patients receiving chemotherapy from January 2008 to December 2013. Risk factors associated with mortality and the effect of AAT on mortality were determined.*
***Results:*** *Of 893 chemotherapy episodes from 145 patients, FN occurred in 133 episodes (14.9%) from 67 patients. Of these 133 episodes, 61.6% were female and mean age was 47.9 years. Infections with multidrug-resistant organisms (MDROs) occurred in 18.8% and extended-spectrum-beta-lactamase (ESBL)-producing Enterobacteriaceae were the most common MDROs. Among the 133 episodes, 100 (75.2%) were given AAT. Overall mortality rate was 20.3%. No receipt of AAT [adjusted odds ratio (aOR) 9.54; p = 0.041], Multinational Association for Supportive Care in Cancer score of less than 21 points (aOR 4.37; p = 0.021), and systemic inflammatory response syndrome score of 4 (aOR 13.02; p = 0.037) were independent factors associated with mortality.*
***Conclusion:*** *AAT was associated with reduced mortality in hematological cancer patients with febrile neutropenia. Empirical antimicrobials for FN should be active against ESBL-producing bacteria in this setting where these MDROs are endemic.*

***Keywords:*** *Febrile neutropenia, Hematologic cancer, Mortality, Appropriate antimicrobials, Multidrug resistance*

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Febrile neutropenia (FN) significantly increases risk for infection and contributes to mortality among hematological cancer patients (HCPs). Incidence of FN in HCPs was reported to be higher than those with solid cancer (more than 80% vs. 10 to 50%)[1]. The higher incidence of FN is attributable to the involvement of bone marrow and immune responses of hematological cancers and the use of intensive bone marrow suppressive agents and steroid as mainstay therapy. Overall mortality rates among cancer patients with FN were reported to be 2% to 21% in previous studies[2,3]. Risk factors associated with mortality among such patients included advanced age, having lung/colorectal cancer, anemia, receipt of irradiation, having metastatic cancer and history of hospitalization prior to FN occurrence while receipt of prophylactic granulocyte colony stimulating factor (G-CSF) was a protective factor for mortality[4]. However, mortality risks have not been previously described specifically among HCPs with FN.

Initial antimicrobial therapy for FN is recommended to cover Gram-negative bacteria, especially *Pseudomonas aeruginosa* while in patients who have cellulitis, pneumonia or suspected of having intravascular catheter- or device-associated infections[5], the therapy needs to cover Gram-positive bacteria. The regimen is recommended to include bactericidal agents to treat bacteremia, which commonly occurs in FN patients. Selection of an empirical antimicrobial regimen should be based on the risk status, suspected sites of infection and the epidemiology of pathogens causing infections. Given the recent increase in incidences of infections due to multidrug-resistant organisms (MDROs) worldwide including Thailand[6], selection of appropriate

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antimicrobial therapy (AAT) has become more challenging with limited data from well-designed studies. Previous studies demonstrated the effect of antimicrobial therapy on mortality reduction in patients with bacteremia[7-16], and FN[17-19]. In addition, delayed antimicrobial administration was reported to be associated with increased risk of mortality[7,10,19,20]. However, data regarding the effect of AAT in HCPs with FN in the era of MDROs is currently limited. We performed this study to determine the effect of AAT on mortality among Thai HCPs with FN.

**Material and Method**

This retrospective cohort study was conducted at a 600-bed teaching and referral university hospital in Pathumthani, Thailand. During a 6-years period (from January 2008 to December 2013), all patients aged 15 years and older with diagnosis of hematological cancer according to the International Classification of Disease (ICD)-10 codes of C810-C969 and D45-D46, who had FN as a co-morbidity or complication (ICD-10 code of D70), were eligible for the study. The study was approved by the institutional ethics committee and conducted in accordance with the declaration of Helsinki and international conference on harmonisation guidelines for good clinical practice (ICH-GCP). Patients' informed consents were waived due to the retrospective study design.

Patients' information collected was epidemiological data [age, sex, diagnosis, staging, the eastern cooperative oncology group (ECOG) performance status, international prognostic index (IPI) score and other comorbidities], baseline laboratory data [complete blood count (CBC), chemistry, creatinine, liver function test and lactate dehydrogenase (LDH)], treatment received, CBC on the day of chemotherapy, the use of G-CSF prophylaxis, date of FN occurrence, parameters in multinational association for supportive care in cancer (MASCC) score[21], systemic inflammatory response syndrome (SIRS) score, laboratory results, antimicrobial agents used, time to antimicrobial therapy, definite microbiological diagnosis, and outcomes. All data was retrieved from patient medical records. Patients could be re-entered into the study only if the subsequent FN episode occurred more than 30 days apart from previous FN occurrences. Patients were excluded if their medical records could not be retrieved. Identification and antibiotic susceptibilities of causative pathogens determined by the minimum inhibitory concentration breakpoints for resistance were according to Clinical Laboratory Standards Institute criteria.

Febrile neutropenia was defined as a single oral temperature measurement of more than 38.3°C or a temperature of more than 38.0°C sustained over a 1-hour period in patients with an absolute neutrophil count less than 500 cells/uL or expected to be less than 500 cells/uL within 48 hours[5]. Invasive pulmonary aspergillosis was diagnosed using proven (positive *Aspergillus* spp. culture from sterile site or compatible histopathological findings of infected tissue) or probable criteria (positive culture in non-sterile site or positive serum galactomannan antigen along with compatible clinical and radiological signs)[22]. Candidiasis was diagnosed based on positive culture from infected sites. Current practice in Thailand was partially according to the Infectious Disease Society of America guideline on FN[5], with exception of antibacterial prophylaxis due to resource constraint. Patients in the present study received no antimicrobial prophylaxis. Empirical antimicrobial therapy (eAT) was defined as antimicrobial given prior to availability of microbiological results while definitive antimicrobial therapy (dAT) was defined as antimicrobial treatments given after organism identification and susceptibility were known. Appropriate antimicrobial therapy was defined as the use of correct dose and interval of antimicrobial agents that were active against the identified causative organisms. In cases of FN without an identifiable causative organism, appropriate antimicrobial therapy was defined as receiving antimicrobial therapy with *Pseudomonas aeruginosa* coverage according to clinical practice guideline[5]. Time to antimicrobial therapy was defined as the time since FN episodes were suspected or diagnosed to the time the particular antimicrobial therapy was given. MDROs were defined as causative pathogens that were resistant or intermediately susceptible to $\geq$3 of the antimicrobial categories used to treat infections due to such pathogens[23]. The primary outcomes of the study were factors associated with 30-day all-cause mortality, including the effect of AAT while the secondary outcome was the effect of AAT on event-free survival, which was defined as the time from FN diagnosis to relapse, death or loss to follow-up.

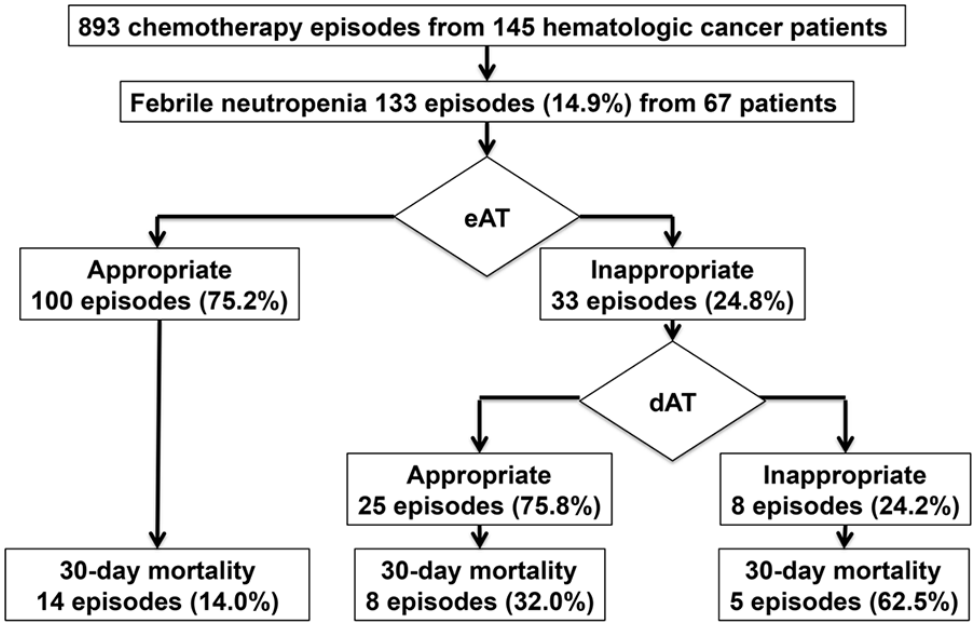
Statistical analyses were performed using STATA software, version 12.0 (Stata Corp, Texas, USA). Categorical variables were compared using the Pearson Chi-square or Fisher's exact test, as appropriate. Continuous variables were compared by the Mann-Whitney-U test. Univariable and multivariable regression analyses were performed using mixed effect

multi-level model due to the repeated nature of FN occurrence. Factors with *p*-value <0.2 from Chi-square or Fisher's exact test were included in univariable analysis and those with *p*-value <0.1 from univariable analysis were included in multivariable analysis. Survival analysis was done using Kaplan-Meier survival analysis. The effect of appropriate antimicrobial therapy and were compared using Cox's proportional hazard ratios adjusted to factors with *p*-value <0.05 from multivariable regression. In the case of higher early mortality, Wilcoxon-Breslow method was used for comparison of survival-time curve. All stated *p*-values were 2-sided and were considered significant if the value is less than 0.05. Given that mortality rates in hematological cancer patients with FN and *Pseudomonas aeruginosa* bacteremia were reported to be 21.0% and 80.0% in those receiving AAT and those not receiving AAT, respectively[19] and the ratio of AAT to no AAT in the mentioned study was 16.8, this study required 94 and 6 FN episodes with AAT and without AAT, respectively to have 90% power to detect the difference in the mortality rates at 5% significance level.

## Results

### *Characteristics of FN episodes and infectious causes*

Eight hundred and ninety three chemotherapy episodes from 145 HCP medical records were reviewed. A total of 133 FN episodes (14.9%) from 67 HCPs who received chemotherapy were included in the final analysis. The study flow categorizing types of antimicrobial therapy and mortality rates is shown in Fig. 1. Mortality within 30 days of FN occurred in 27 FN episodes (20.3%). Appropriate eAT was given in 100 FN episodes (75.2%) which resulted in 14% 30-day mortality rate while the mortality rate of HCPs receiving inappropriate eAT depended on subsequent definitive antimicrobial therapy (dAT) (Fig. 1). The characteristics of each FN episodes are shown in Table 1. Significant variables at FN onset that were associated with 30-day mortality included advanced age, higher SIRS score and MASCC scores, hypotension, vasopressor requirement, intubation, lower platelet level, lower creatinine clearance, lower level of albumin, and higher level of total bilirubin, direct bilirubin and aspartate aminotransferase. Treatments of FN and infectious sources are shown in Table 2. Respiratory tract infection, urinary tract infection, bacteremia, and inappropriate eAT were significantly associated with 30-day mortality. The etiologic organisms could be identified in 77 FN episodes (57.9%) and are shown in Fig. 2. The three most common causative organisms were Enterobacteriaceae (32.5%), *Aspergillus* spp. (24.7%) and extended-spectrum beta-lactamase (ESBL)-




eAT = empirical antimicrobial therapy; dAT = definite antimicrobial therapy

**Fig. 1** Study flow.

**Table 1.** Baseline characteristics and laboratory data of each FN episodes

| Parameter | Outcome of FN episodes | | *p*-value |
|---|---|---|---|
| | Recovery (n = 106) | Dead in 30 days (n = 27) | |
| Female sex | 68 (64.2) | 14 (51.9) | 0.241 |
| Mean age at FN (years) (SD) | 46.2 (16.3) | 54.6 (18.9) | 0.023 |
| Age at FN >60 years | 19 (17.9) | 13 (48.2) | 0.001 |
| Chemotherapy given | | | 0.257 |
| CHOP | 20 (18.9) | 6 (22.2) | |
| CVP | 2 (1.9) | 1 (3.7) | |
| ABVD | 1 (0.9) | 1 (3.7) | |
| Other salvage lymphoma | 12 (11.3) | 7 (25.9) | |
| ALL protocols | 14 (13.2) | 2 (7.4) | |
| AML type regimen | 57 (53.8) | 10 (37.0) | |
| Prophylactic G-CSF given | 61 (57.6) | 16 (59.3) | 0.872 |
| Recent admission with infection | 20 (18.9) | 9 (33.3) | 0.104 |
| SIRS score | | | 0.011 |
| 2 | 15 (14.2) | 2 (7.4) | |
| 3 | 86 (81.1) | 19 (70.4) | |
| 4 | 5 (4.7) | 6 (22.2) | |
| Mean MASCC score (points) (SD) | 21.0 (2.2) | 19.0 (3.3) | <0.001 |
| Hypotension | 3 (2.8) | 7 (25.9) | <0.001 |
| Vasopressor needed | 4 (3.8) | 11 (40.7) | <0.001 |
| Intubation needed | 2 (1.9) | 12 (44.4) | <0.001 |
| Mucositis | 14 (13.2) | 3 (11.1) | 0.771 |
| Mean Hb at FN (g/dL) (SD) | 8.7 (1.4) | 8.2 (1.7) | 0.128 |
| Median ANC at FN (cells/uL) (IQR) | 90 (30 to 292) | 102 (26 to 243) | 0.392 |
| Median platelet at FN (x10^3/uL) (IQR) | 25 (12 to 82) | 17 (6 to 36) | 0.032 |
| Mean CrCl at FN (mL/min/1.73 $m^2$) (SD) | 100.9 (30.2) | 70.4 (37.2) | <0.001 |
| Mean albumin at FN (g/dL) (SD) | 3.0 (0.6) | 2.5 (0.6) | <0.001 |
| Mean globulin at FN (g/dL) (SD) | 3.6 (1.0) | 3.6 (0.9) | 0.717 |
| Median TB at FN (mg/dL) (IQR) | 0.7 (0.4 to 0.9) | 1.0 (0.5 to 1.4) | 0.036 |
| Median DB at FN (mg/dL) (IQR) | 0.2 (0.1 to 0.3) | 0.4 (0.2 to 0.7) | 0.003 |
| Median AST at FN (U/L) (IQR) | 25 (17 to 38) | 31 (22 to 63) | 0.032 |
| Median ALT at FN (U/L) (IQR) | 41 (31 to 58) | 44 (32 to 62) | 0.363 |
| Median ALP at FN (U/L) (IQR) | 110 (82 to 153) | 119 (69 to 173) | 0.962 |

Data in table is presented as n (%) unless indicated otherwise.
ABVD = adriamycin/bleomycin/vinblastine/dacarbazine; ALL = acute lymphoblastic leukemia; ALP = alkaline phosphatase; ALT = alanine transferase; AML = acute myeloid leukemia; ANC = absolute neutrophil count; AST = aspartate transferase; ATB = antibiotics; CHOP = cyclophospha mide/doxorubicin/vincristine/prednisolone; CrCl = creatinine clearance by CKD-EPI equation; CVP = cyclophosphamide/vincristine/prednisolone; DB = direct bilirubin; FN = febrile neutropenia; Hb = hemoglobin; IQR = interquartile range; MASCC = multinational association for supportive care in cancer; TB = total bilirubin

producing Enterobacteriaceae (23.4%). Infections with MDROs occurred in 18.8%. Extended-spectrum-beta-lactamase (ESBL)-producing Enterobacteriaceae were the most common MDROs (13.5%), followed by multidrug-resistant (MDR) *Acinetobacter baumannii* (3.8%), methicillin-resistant *Staphylococcus aureus* (1.5%) and MDR *Pseudomonas aeruginosa* (0.8%).

***Analysis of factors associated with 30-day mortality***

Mixed effect, multilevel regression analysis was performed and the results in univariable and multivariable analyses are shown in Table 3. Independent factors associated with 30-day mortality were inappropriate eAT and dAT, SIRS score of 4 points, and MASCC score less than 21 points. There was a

**Table 2.** Treatments and infectious foci of FN episodes

| Parameter | Outcome of FN episodes | | *p*-value |
|---|---|---|---|
| | Recovery (n = 106) | Dead in 30 days (n = 27) | |
| Appropriate empirical antimicrobial therapy | 86 (81.1) | 14 (51.9) | 0.002 |
| Mean time to eAT (hours) (SD) | 2.3 (2.0) | 2.7 (1.8) | 0.343 |
| Time to eAT of more than 2 hours[a] | 27 (25.5) | 11 (40.7) | 0.117 |
| Appropriate dAT if eAT inappropriate | 17/20 (85.0) | 8/13 (61.5) | 0.124 |
| Therapeutic G-CSF given | 78 (73.6) | 17 (63.0) | 0.275 |
| Positive culture | 52 (49.1) | 25 (92.6) | <0.001 |
| Sources: | | | |
| Respiratory tract | 27 (25.5) | 13 (48.2) | 0.022 |
| Urinary tract infection | 20 (18.9) | 13 (48.2) | 0.002 |
| Diarrhea | 26 (24.5) | 9 (33.3) | 0.354 |
| Skin and soft tissue infection | 15 (14.2) | 5 (18.5) | 0.571 |
| Bacteremia | 30 (28.3) | 17 (63.0) | 0.001 |
| Multi-drug resistant organisms | 17 (16.0) | 8 (29.6) | 0.107 |
| Fungal infection | 21 (19.8) | 9 (33.3) | 0.133 |
| *Candida* spp. | 6 (5.66) | 5 (18.52) | |
| *Aspergillous* spp. | 15 (14.15) | 4 (14.81) | |
| Antimicrobial therapy given: | | | |
| Ceftazidime | 28 (26.4) | 3 (11.1) | 0.130 |
| Appropriate to organism identified | 26/28 (92.9) | 1/3 (33.3) | 0.037 |
| Beta-lactam with beta-lactamase inhibitors | 50 (47.2) | 16 (59.3) | 0.050 |
| Appropriate to organism identified | 45/50 (86.5) | 9/16 (52.9) | 0.004 |
| Carbapenems | 21 (19.8) | 5 (18.5) | 0.880 |
| Appropriate to organism identified | 15/21 (71.4) | 3/5 (60.0) | 0.628 |
| Addition of amikacin | 14 (13.2) | 1 (3.7) | 0.163 |
| Addition of fluoroquinolones | 1 (0.9) | 0 | 0.612 |
| Addition of vancomycin | 7 (6.6) | 4 (14.8) | 0.167 |
| Addition of mold active agents | 9 (8.5) | 3 (11.1) | 0.671 |

Data in table is presented as n (%) unless indicated otherwise.
dAT = definitive antimicrobial therapy; eAT = empirical antimicrobial therapy; FN = febrile neutropenia; G-CSF = granulocyte colony stimulating factor
[a] Time to antimicrobial therapy was controlled under the hospital FN fast track scheme, which required time to eAT to be less than 120 minutes

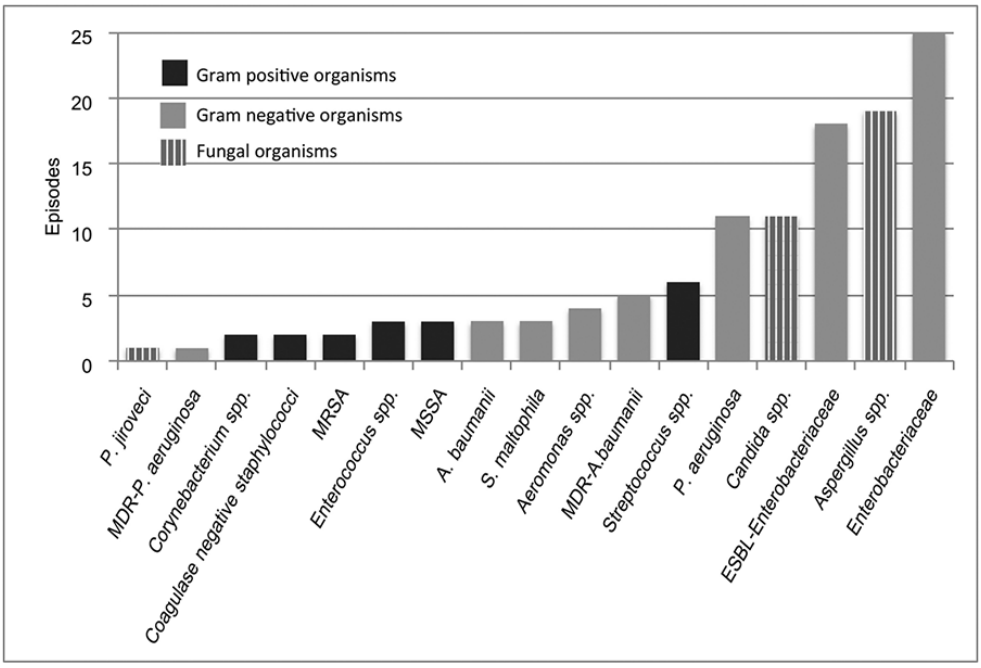
trend toward significant mortality associated with serum albumin less than 3.0 g/dL.

### *Effect of appropriate antimicrobial therapy on event-free survival after FN*

The effect of antimicrobial therapy on event-free survival from the onset of FN is shown in Fig. 3. After adjusted for SIRS score, MASCC score and serum albumin level, the adjusted hazard ratios (aHR) for inappropriate eAT and dAT and inappropriate eAT but appropriate dAT were 3.31 (95% CI 1.09 to 10.06; *p*-value = 0.035) and 1.60 (95% confidence interval (CI) 0.71 to 3.61; *p*-value = 0.252), respectively compared to receipt of appropriate eAT and dAT. Wilcoxon-Breslow's analysis of event-free survival showed that patients who received inappropriate eAT regardless of dAT appropriateness had significantly worse outcome during the early course of FN compared to those receiving appropriate eAT (*p*-value = 0.005).

## Discussion

The effect of AAT on mortality among HCPs with FN was demonstrated in this study. First, appropriate eAT was associated with decreased 30-day mortality compared to inappropriate eAT. Second, inappropriate eAT and dAT was identified as an




ESBL = extended-spectrum beta-lactamase; MDR = multidrug-resistant; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*

**Fig. 2** Causative infectious organisms detected.

independent predictor for 30-day mortality in the multi-level mixed effect (adjustment for shared frailty due to repetitive nature of FN occurrence) multivariable analysis (adjusted for age, MASCC scorem SIRS score, platelet level, renal function, liver function and infectious origin). Lastly, inappropriate eAT only and both inappropriate eAT and dAT were associated with lower event-free survival compared to both appropriate eAT and dAT. These benefits of AAT were consistent with previously reports among HCPs with FN[18,19,24].

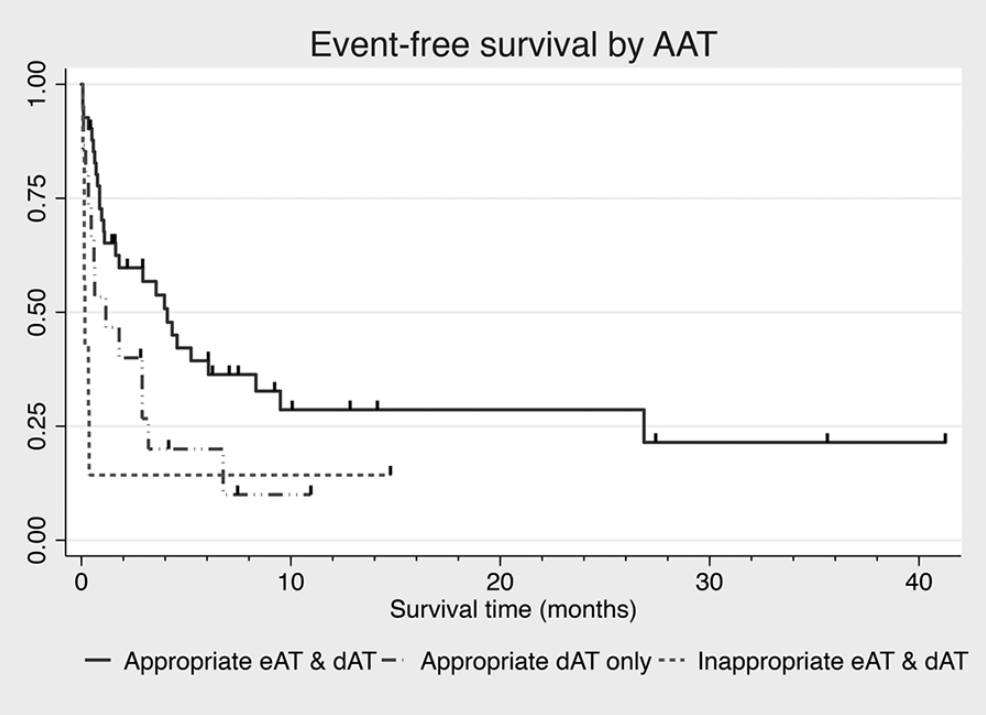
The rate of AAT prescription in this study was 75%, which was comparable to previous published studies[12,13], but higher than other studies[7,16,24]. All of the aforementioned studies contain a significant portion of patients with hematological cancer. The higher rate of inappropriate antimicrobial prescription in those studies compared to the present study may be due to the inclusion of non-neutropenic febrile patients, in whom there was no specific recommendation regarding antimicrobial choices. Our study demonstrated that ESBL-producing Enterobacteriaceae were the most common MDROs causing FN in HCPs consistent with the high prevalence of ESBL-producing Enterobacteriaceae-associated infections in Thailand[25]. Given that some of the empirical antimicrobial agents for FN recommended in the IDSA[5] and our guidelines, including cefoperazone-sulbactam and cefepime, were considered inactive against ESBL-producing enterobacteriaceae, prescribing such antimicrobial agents according to the guidelines could explain the inappropriate eAT observed in this study. Thus, in regions where ESBL-producing pathogens were endemic, eAT for FN should be broad-spectrum antimicrobials that have activity against *P. aeruginosa* and ESBL-producing pathogens. These antimicrobials include group 2 carbapenems, such as imipenem, meropenem, and doripenem or a beta-lactam/beta-lactamase inhibitor, such as piperacillin-tazobactam if the pathogens are susceptible and the infections are not severe[26,27]. In addition, FN patients with risk factors associated with acquisition of ESBL-producing pathogens including prior administration of the 3rd generation cephalosporins, previous colonization with ESBL-producing pathogens, presence of central venous or arterial catheters, a urinary catheter and ventilator assistance[26] should be empirically treated with these antimicrobials. It should be noted that the high prevalence of aspergillosis among our HCPs with FN and its delayed diagnosis inevitably precluded appropriate eAT and dAT. These

**Table 3.** Univariable and multivariable analysis of factors associated with 30-day mortality

| Parameters | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% CI | *p*-value | Adjusted odds ratio | 95% CI | *p*-value |
| Age at FN more than 60 years | 4.25 | 1.72 to 10.49 | 0.002 | 0.87 | 0.20 to 3.79 | NS |
| SIRS score: | | | | | | |
| 2 | Reference | | | Reference | | |
| 3 | 1.79 | 0.33 to 9.65 | 0.498 | - | - | - |
| 4 | 11.10 | 1.14 to 108.47 | 0.039 | 13.02 | 1.17 to 144.54 | 0.037 |
| MASCC score less than 21 points | 6.27 | 2.11 to 18.69 | 0.001 | 4.37 | 1.25 to 15.30 | 0.021 |
| Hypotension* | 12.02 | 2.86 to 50.46 | 0.001 | | | |
| Vasopressor needed* | 17.53 | 4.97 to 61.80 | <0.001 | | | |
| Intubation needed* | 41.60 | 8.47 to 204.37 | <0.001 | | | |
| Laboratory at FN onset: | | | | | | |
| Platelet less than 10,000/uL | 3.12 | 1.08 to 9.01 | 0.036 | 1.57 | 0.37 to 6.70 | NS |
| CrCl less than 60 mL/min | 4.39 | 1.48 to 13.01 | 0.008 | 1.73 | 0.43 to 6.91 | NS |
| Albumin less than 3 g/dL | 4.87 | 1.58 to 15.01 | 0.006 | 3.51 | 0.95 to 13.04 | 0.060 |
| Total bilirubin more than 1 mg/dL | 3.55 | 1.46 to 8.62 | 0.005 | 2.07 | 0.45 to 9.41 | NS |
| Direct bilirubin more than 0.5 mg/dL | 3.08 | 1.03 to 9.17 | 0.043 | 0.42 | 0.06 to 2.89 | NS |
| AST more than 30 U/L | 2.50 | 0.93 to 6.72 | 0.068 | 1.28 | 0.35 to 4.64 | NS |
| Infectious sources: | | | | | | |
| Respiratory tract | 2.72 | 1.12 to 6.60 | 0.027 | 1.86 | 0.49 to 7.06 | NS |
| Urinary tract | 4.19 | 1.52 to 11.54 | 0.006 | 3.50 | 0.83 to 14.83 | NS |
| Bacteremia | 4.75 | 1.64 to 13.82 | 0.004 | 2.01 | 0.57 to 7.05 | NS |
| Effect of antimicrobial therapy: | | | | | | |
| Appropriate eAT and dAT | Reference | | | Reference | | |
| Inappropriate eAT but appropriate dAT | 2.98 | 0.98 to 9.03 | 0.054 | 1.59 | 0.33 to 7.65 | NS |
| Inappropriate eAT and dAT | 13.24 | 1.90 to 92.33 | 0.009 | 9.54 | 1.09 to 83.27 | 0.041 |

* These parameters were omitted in multivariable model due to redundancy and collinearity.

AST = aspartate aminotransferase; CI = confidence interval; CrCl = creatinine clearance by CKD-EPI equation; dAT = definite antimicrobial therapy; eAT = empirical antimicrobial therapy; FN = febrile neutropenia; MASCC = multinational association for supportive care in cancer; SIRS = systemic inflammatory response syndrome




AAT = appropriate antimicrobial therapy; dAT = definitive antimicrobial therapy; eAT = empirical antimicrobial therapy

**Fig. 3** Event-free survivals after FN occurrence, stratified by antimicrobial appropriateness.

findings underlie the essential of knowledge about local epidemiology and prevalence of drug resistance of FN causative organisms and clinical risk factors for each pathogen in guiding selection of AAT.

The strengths of this study were the inclusion of FN episodes among HCPs receiving chemotherapy, which were at highest risk of mortality and the long follow-up time which allowed for analyses of event-free survival after FN occurrence while study limitations included inherited misclassification and information biases from a retrospective study design and limited generalizability due to data from a single institution and its small sample size. Given that all HCPs with FN in this study received antimicrobial therapy within 2 hours after the FN diagnosis as a result from the "fast-track febrile neutropenia" clinical practice guidelines in our hospital, the effect of timing of antimicrobial administration on mortality could not be assessed.

## Conclusion

Febrile neutropenia was a significant cause of mortality among HCPs in our setting. Appropriate empirical and definitive antimicrobial therapy is a key factor associated with reduced mortality. Selection of AAT should be based on local epidemiology and prevalence of drug resistance of causative pathogens derived from locally conducted studies. In the era of multidrug resistant infections, ESBL-producing Enterobacteriaceae have emerged as important MDROs causing FN in HCPs. Empirical antimicrobial therapy for FN needs to have additional activity against these organisms in endemic settings.

## What is already known on this topic?

Hematological cancer patients are at highest risk for febrile neutropenia and severe life-threatening infections. Appropriate and timely antimicrobial therapy has been shown to reduce mortality in bacteremic patients, patients with severe pneumonia and also patients with cancer, including hematological cancer. Multiple studies in Thailand focus on epidemiology of febrile neutropenia as a whole group (solid and hematological cancer) and emphasize on microbial etiology. Recent articles reported higher incidence of resistance organisms in febrile neutropenia. Mortality rates in this group of patients varied by cancer type, with hematological cancer being the highest risk group.

**What this study adds?**

This study showed that survival of hematological cancer patients with febrile neutropenia was affected by appropriate antimicrobial therapy. Appropriate definitive therapy strongly reduced the risk of death, while appropriate empirical treatment had a trend toward significance to reduce mortality. Resistance bacteria were increasingly shown to be growing challenges in choosing appropriate empirical treatment. In settings where ESBL-producing Enterobacteriaceae are endemic, empirical antibiotics with activity against these bacteria should be considered among hematological cancer patients with febrile neutropenia.

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**Potential conflicts of interests**

None.

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## *การใช้ยาปฏิชีวนะที่เหมาะสมและผลต่ออัตราการตายในผู้ป่วยมะเร็งโลหิตวิทยาที่มีภาวะไข้ร่วมกับเม็ดเลือดขาวต่ำในยุคของเชื้อดื้อยา*

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***วัตถุประสงค์:*** *เพื่อศึกษาผลของการใช้ยาปฏิชีวนะที่เหมาะสมต่ออัตราการตายของผู้ป่วยโรคมะเร็งโลหิตวิทยาที่ได้รับยาเคมีบำบัด*

***วัสดุและวิธีการ:*** *การทบทวนแฟ้มเวชระเบียนผู้ป่วยโรคมะเร็งโลหิตวิทยาที่ได้รับยาเคมีบำบัดในระยะเวลา 6 ปี ตั้งแต่ เดือนมกราคม พ.ศ. 2551 ถึง เดือนธันวาคม พ.ศ. 2556 เพื่อหาผลของการรักษาด้วยยาปฏิชีวนะที่เหมาะสมต่ออัตราการตายรวมทั้งปัจจัยเสี่ยงที่เกี่ยวข้อง*

***ผลการศึกษา:*** *การศึกษานี้รวบรวมแฟ้มผู้ป่วยจากการให้ยาเคมีบำบัดทั้งหมด 893 ครั้งในผู้ป่วย 145 ราย เกิดภาวะไข้ร่วมกับเม็ดเลือดขาวต่ำทั้งหมด 133 ครั้ง (ร้อยละ 14.9) ในผู้ป่วย 67 ราย ในจำนวนครั้งของเหตุการณ์ทั้งหมดร้อยละ 61.6 เป็นเพศหญิงและอายุเฉลี่ย 47.9 ปี พบการติดเชื้อดื้อยาร้อยละ 18.8 โดยพบว่าในกลุ่มเชื้อดื้อยาเป็นเชื้อ Enterobacteriaceae ที่ผลิต extended spectrum beta-lactamase มากที่สุดจากจำนวนเหตุการณ์ทั้งหมด ผู้ป่วย 100 ราย (ร้อยละ 75.2) ได้รับยาปฏิชีวนะที่เหมาะสมอัตราการตายโดยรวมของการศึกษานี้ร้อยละ 20.3 ปัจจัยที่มีผลเพิ่มอัตราการตายได้แก่ การไม่ได้รับยาปฏิชีวนะที่เหมาะสมภายหลังทราบผลเพาะเชื้อ (adjusted odds ratio 9.54, p-value = 0.041) การมีคะแนน MASCC น้อยกว่า 21 (adjusted odds ratio 4.37, p-value = 0.021) และการมีคะแนน SIRS 4 คะแนน (adjusted odds ratio 13.02, p-value = 0.037)*

***สรุป:*** *การได้รับยาปฏิชีวนะที่เหมาะสม สามารถช่วยลดอัตราการตายในผู้ป่วยโรคมะเร็งโลหิตวิทยาที่มีภาวะไข้ร่วมกับเม็ดเลือดขาวต่ำได้ควรพิจารณาให้ยาปฏิชีวนะที่เหมาะสมที่ครอบคลุมกลุ่มเชื้อ Enterobacteriaceae ที่ผลิต extended spectrum beta-lactamase ในถิ่นที่มีความชุกของเชื้อดื้อยานี้สูง*