

Use of Antibiotics in a Haematology Ward – An Audit[†]

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Abstract

Introduction: Rising rates of antibiotic resistance prompted a review of antibiotic use policies hospitalwide. The Department of Haematology established a new set of consensus guidelines in 2002 for antibiotic use in febrile neutropenia. The aim of our study was to audit adherence to the guidelines established for febrile neutropenia in patients treated for haematologic malignancies. **Materials and Methods:** An antibiotic escalation pathway was developed by haematologists and infectious disease physicians. Adherence to the guidelines was audited. Patients with acute myeloid leukaemia (AML) or acute lymphocytic leukaemia (ALL) who had febrile neutropenia after chemotherapy were reviewed. The audit was performed by a retrospective review of casenotes. **Results:** Forty patients with 100 episodes of febrile neutropenia were surveyed. Thirty-two had AML, 7 had ALL and 1 had undifferentiated leukaemia. In 76% of episodes, fever developed within the first 14 days of neutropenia. In 31 episodes, cefepime was started as the first-line agent; hence, compliance with the first-line agent was 31%. Fever defervesced in 13 episodes. The most common reason for switching antibiotics was persistent fever. There were clinical indications for non-compliance with the use of the first-line agent in all cases. There were 3 deaths – none related to non-compliance with or strict adherence to the guidelines. Four patients had proven fungal infections. **Conclusions:** Given the complex nature of the cases, compliance was reasonable, as there were valid reasons in all cases where the guidelines were not adhered to. Based on our findings, the guidelines could be simplified.

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Key words: Adherence, Chemotherapy, Febrile neutropenia, Leukaemia, Resistance

Introduction

Rising rates of antibiotic resistance prompted a review of antibiotic use policies hospitalwide. The Department of Haematology established a new set of consensus guidelines in 2002 for antibiotic use in febrile neutropenia. We were tasked by the hospital's Pharmacy and Therapeutics Committee to audit adherence to the guidelines. We report our findings in this article.

Materials and Methods

A new antibiotic escalation pathway (Fig. 1) was drafted by the authors based on IDSA/EORTC¹ guidelines. The guidelines did not cover bacterial and fungal prophylaxis, nor did it cover the use of granulocyte-colony-stimulating factor (G-CSF). The use of these agents was at the discretion of the managing physicians. This was discussed at a

meeting with the senior haematologists and infectious disease (ID) physicians. After a consensus was established, the guidelines were disseminated through e-mail to all haematologists and ID physicians. The guidelines were also incorporated into handbooks for medical officers attached to the Department of Haematology. Adherence to the guidelines was audited.

Although the guidelines applied to any neutropenic sepsis, the decision was taken to review only patients with acute myeloid leukaemia (AML) or acute lymphocytic leukaemia (ALL) who became febrile while neutropenic after curative chemotherapy. AML and ALL patients form the majority of inpatients receiving chemotherapy. Only the largest Haematology ward was audited. This ward did not house patients undergoing haematopoietic stem cell transplantation. As this was an audit ordered by a hospital

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committee, there was no need for patient consent. The period of review was June 2002 to April 2004. Patient recruitment was closed when 100 patient-episodes were reached. From March 2003 to August 2003, Singapore was affected by the severe acute respiratory syndrome (SARS) and patient admissions fell drastically.² During the SARS period, malignancies were generally managed with oral chemotherapeutic agents as patients preferred to stay away from inpatient care. Some patients defaulted completely.

The audit was performed by a retrospective review of casenotes by the authors within 2 months of patients' discharge. The following data were collected: patient demographics, types of chemotherapy, duration of neutropenia, use of antibiotic and antifungal prophylaxis, microbiological data, nephrotoxicity and hepatotoxicity, antibiotics and antifungals used, and clinical outcome.

Definitions

Fever was defined as a single oral temperature $\geq 38.5^{\circ}\text{C}$ or a temperature $\geq 38^{\circ}\text{C}$ persisting for ≥ 1 hour. Neutropenia was defined as an absolute neutrophil count (ANC) < 500 cells/ mm^3 . A patient-episode was defined as fever occurring during neutropenia. Each patient was allowed to have more than 1 "patient-episode" in the neutropenic phase following a single course of chemotherapy. Hence, if fever recurred after at least 48 afebrile hours during an episode of neutropenia, that was counted as a separate episode. Fungal infections were defined according to guidelines issued by the MSG/EORTC.¹

Results

Forty patients who had a total of 100 episodes of febrile neutropenia (FN) were surveyed. Their ages ranged from 17 to 71 years, with a median of 44.5 years. Eighteen were male. There were 32 patients with AML and 7 patients with ALL. One patient had undifferentiated acute leukaemia.

The types of chemotherapy administered are shown in Table 1. The majority of the patients received high-dose

Table 1. Types of Chemotherapy Administered and Number of Febrile Episodes

Chemotherapy administered	No. of febrile episodes
IA 3+7	31
IA 2+7	10
HIDAC	11
HCVAD	8
Others	40

IA: idarubicin, Ara-C (cytarabine); HIDAC: high-dose Ara-C; HCVAD: hyper-fractionated cyclophosphamide, vincristine, adriamycin, dexamethasone; Others: etoposide, cytarabine, fludarabine, mitoxantrone

chemotherapy. The absolute neutrophil count (ANC) at diagnosis is shown in Table 2. Ciprofloxacin prophylaxis was used in 43 episodes and antifungal prophylaxis was used in 65 episodes. In 94 of the episodes, subcutaneous G-CSF 300 μg was administered. The duration of neutropenia varied according to the chemotherapy, as shown in Table 3.

Onset of Febrile Neutropenia in Relation to Chemotherapy

The majority of neutropenic episodes eligible for evaluation occurred within the first 14 days of chemotherapy. Details are given in Table 4. Neutropenia was not always associated with the start of fever. In 76% of the episodes, fever developed within the first 14 days of neutropenia.

Allergies

Five patients had antibiotic allergies. Two patients developed an allergy to cefepime (CEF). In one of them, the subsequent first-line agent was piperacillin-tazobactam (TAZ). This was the only episode of deviation from the guidelines that could be attributed to a pre-existing allergy. Two other patients had allergies to trimethoprim-sulfamethoxazole, and 1 patient developed a vancomycin (VAN) allergy.

Table 2. Absolute Neutrophil Count at Diagnosis

ANC at diagnosis (cells/ mm^3)	No. of patient/episodes
< 500	16
501-999	29
> 1000	55

ANC: absolute neutrophil count

Table 3. Duration of Neutropenia

Duration of neutropenia	Chemotherapy			
	IA 3 + 7	IA 2 + 7	HIDAC	HCVAD
Range (days)	11-63	6-29	7-43	6-20
Median (days)	20	13	22	11.5

IA: idarubicin, Ara-C (cytarabine); HIDAC: high-dose Ara-C; HCVAD: hyper-fractionated cyclophosphamide, vincristine, adriamycin, dexamethasone

Table 4. Onset of Febrile Neutropenia in Relation to Start of Chemotherapy

Onset of febrile neutropenia	No. of episodes
D1-7	32
D8-14	45
D15-28	20
$> D29$	3

D: day

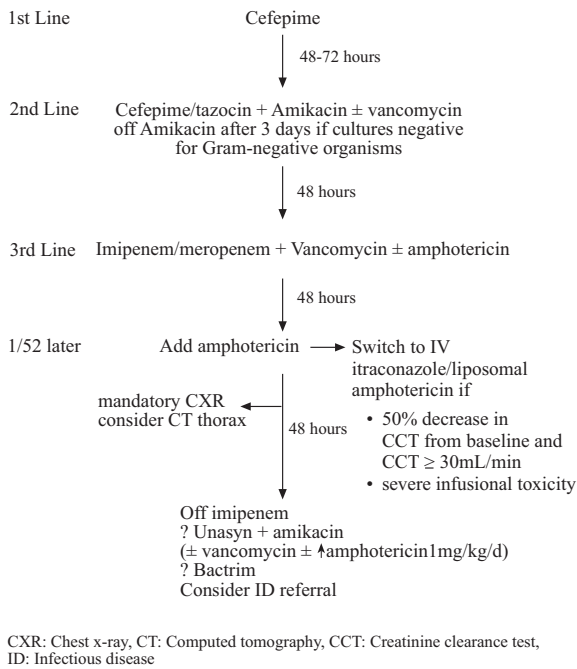


Fig. 1. Treatment guidelines for febrile neutropenia.

1st Line	CEF	31/100 (31%)
	CEF + VAN or AMK	51/100 (51%) No change 13/51 (25.5%)
2nd line	TAZ	17/38 (44.7%)
	Add VAN	9/38 (23.7%)

Fig. 2. Compliance with guideline (for commencing with CEF as first-line therapy)

Compliance with First-line Agents

In 51 episodes, CEF, with or without another agent, was used as a first-line agent. CEF was used as a single agent in 31 episodes. This gives a compliance rate of 31%. In 20 of the episodes, physicians started with TAZ. In 19 of the episodes, a carbapenem was used as a first-line agent. In the remaining 10 episodes, various regimens were adopted. These were primarily directed against skin and soft-tissue infections and *Clostridium difficile* diarrhoea.

Use of cefepime as a first-line agent: In 31 of the episodes, CEF monotherapy was used as a first-line agent. The median duration of CEF therapy was 3 days (range, 1 to 15). In another 20 episodes, CEF plus another agent [amikacin (AMK) or VAN] was used. Of these 51 episodes, fever defervesced without the need for any change in antibiotics in 13 (25.5%). The mean duration of antibiotic use without change was 6 days (range, 3 to 15). In the 38 episodes in which physicians changed to another antibiotic, TAZ was selected in 17 (44.7%) instances; in 9 (23.7%) instances VAN was added. The median duration of TAZ

Table 5. Number of Patient-episodes with Positive Blood Culture Results

Organism	No. of episodes
Coagulase-negative <i>Staphylococcus</i>	5
<i>E. coli</i>	3
<i>Pseudomonas aeruginosa</i>	3
<i>Stenotrophomonas maltophilia</i>	2
<i>Enterococcus</i>	2
Polymicrobial	3

There was 1 episode each of MRSA, Candida, Enterobacter, Campylobacter fetus, *S. mitis* and Bacillus.

use was 5.5 days. These data are illustrated in Figure 2. The most common reason for switching from TAZ was persistent fever. In 7 (18.5%) instances, change was culture-directed.

Use of piperacillin-tazobactam (TAZ) as a first-line agent: In 20 of the episodes, physicians started with TAZ. The most common reason for starting with TAZ was prior use of broad-spectrum antibiotics. These patients were not on other antibiotics at the time of commencement of TAZ. Fifteen (75%) of the instances were not first-episode neutropenic fevers, i.e., the patients had received antibiotics for previous episodes of neutropenic fever but had recovered from those episodes. The 5 patients who received TAZ for first-episode neutropenic fever received it because all of them had had fever at diagnosis (only 1 of them was neutropenic at diagnosis) and had received CEF before. There were no instances of defervescence without a change in antibiotics. The median duration of TAZ use as a first-line agent was 3 days (range, 1 to 8). In 13 (65%) instances, physicians switched to a carbapenem with or without VAN. The most common reason for switching was persistent fever. Only 2 changes were directed by blood cultures.

Use of a carbapenem as a first-line agent: In 19 episodes, a carbapenem was used as a first-line agent. These patients were not on other antibiotics at the time of commencement of a carbapenem. Both imipenem (IMI) and meropenem (MER) are available at our institution and physicians may select 1 of them at their discretion. Sixteen (84.2%) of the instances where carbapenems were used were not first-episode neutropenic fevers, i.e., the patients had received antibiotics for previous neutropenic fever but had recovered from those episodes. The 3 patients who received a carbapenem in their first episode of neutropenic fever received it for the following reasons: 1 patient had an abnormal chest X-ray prior to commencement of chemotherapy and received CEF for presumed pneumonia; the second patient had fever at the time of diagnosis and received CEF and AMK prior to chemotherapy; the third patient, who had AML M3, developed ATRA (all-trans retinoic acid) syndrome and received CEF for broad-spectrum antibiotic coverage for lung infiltrates prior to

neutropenia. The median duration of use of a carbapenem was 4 days (range, 1 to 9). Of the 19 episodes in which a carbapenem was used as a first-line antibiotic, there was no change in 4 episodes. One of them died in the Medical Intensive Care Unit (MICU) shortly after the institution of IMI. In another 4, antibiotics were changed but these were de-escalation of therapy, as follows. In 1 patient, VAN was stopped; in another a positive culture for methicillin-resistant *Staphylococcus aureus* (MRSA) led to the discontinuation of all antibiotics except VAN; in the third patient, concomitant ampicillin-sulbactam was stopped and in the fourth patient, concomitant metronidazole was stopped.

Bacteraemia: Twenty-four episodes were associated with a positive blood culture. They are shown in Table 5. Bacteraemia-directed changes in antibiotics occurred in 19 instances of antibiotic changes.

Deaths: Three deaths were recorded during the period. The first mortality was a 53-year-old Chinese woman with AML who had been treated for T-cell lymphoma in 1989 and was in remission from her lymphoma. She had undergone a splenectomy in 1993 for thrombocytopenic purpura. In 2002, she was diagnosed with AML and was given IA 3 + 7 but did not go into complete remission and was therefore re-induced with IA 3 + 7. She developed neutropenia on D6 chemotherapy and fever on D9. She remained neutropenic until death. She had a complicated clinical course, with rash, critical illness polyneuropathy and persistent fever. A large number of antibiotics was used. She developed bleeding from the gastro-intestinal tract and hypotension on D60 chemotherapy and was sent to the MICU, where she died after 3 days. There were no positive blood cultures.

The second mortality was a 42-year-old Chinese woman who died after consolidation chemotherapy for AML M2. She was discharged on D7 chemotherapy but was admitted 3 days later for hypophosphatemia and thrombocytopenia. She was sent home after 3 days, i.e., D13 chemotherapy. On D16 chemotherapy she was admitted for fever of 2 days' duration. The white cell count was 100 cells/mm³ and she was hypotensive on admission. She was admitted directly to the MICU and required 3 vasopressors. She was started on IMI but died the next day. Blood cultures were positive for *E. coli*, susceptible to amoxicillin-clavulanate, TAZ, ceftriaxone and gentamicin.

The third mortality was a 71-year-old Chinese man who died after induction chemotherapy (IA 3 + 7) for AML M1. He was neutropenic at diagnosis and remained neutropenic until his death. He received CEF prior to chemotherapy and was one of the patients who received TAZ as a first-line antibiotic when fever developed post-chemotherapy. He had watery diarrhoea and went into shock and acute renal

failure. Chest X-ray showed right lower lobe consolidation. Blood cultures were initially negative, but a repeat blood culture, drawn on D13 chemotherapy, yielded *Enterococcus*, resistant to ampicillin but susceptible to VAN. Stools sent for *Clostridium difficile* toxin tests were negative. A CT scan of the abdomen, done on D11, showed pancolitis. After surgical review, the decision was for conservative management in view of the poor blood counts and the patient's advanced age. The patient was brought to the MICU but perished on D14 despite full support. The patient did not receive amphotericin.

It is possible to argue that the institution of amphotericin might have helped in the case of the third mortality, but it is doubtful if death could have been prevented.

Probable and proven fungal infections: Four patients had proven fungal infections. The first patient was a 41-year-old Chinese man with AML M2, diagnosed in April 2002. He was not neutropenic at diagnosis. He received induction and consolidation chemotherapy and was admitted for mobilisation chemotherapy (etoposide/cytarabine). He was not on itraconazole prophylaxis. He developed fever on D9 and was severely neutropenic with total white cell count (TWC) of 60 cells/mm³. He was on various antibiotics, including IMI, VAN and trimethoprim-sulfamethosazole (TMP-SMX). Septic spots were noted on the lower limbs on D15. Blood cultures on D15 showed *Candida tropicalis*. Amphotericin (AmB) was started on D16. Skin biopsy showed vasculitis consistent with septicaemia. Cultures from skin biopsy were negative. All other cultures were negative. CT abdomen and pelvis showed mildly enlarged spleen with minute hypodense foci, consistent with hepatosplenic candidiasis. He was discharged with fluconazole. AmB was given for subsequent courses of chemotherapy, with documented improvement in hepatosplenic lesions.

The second patient was a 15-year-old Malay boy diagnosed with AML M1. He was not neutropenic on diagnosis and did not receive itraconazole prophylaxis. On D14 induction chemotherapy with IA 3+7, he spiked a fever. ANC was then <500 cells/mm³. As he had already received TAZ and AMK for an earlier fever, he was started on IMI, TMP-SMX and AmB. Blood cultures taken on days 14, 15 and 17 chemotherapy grew *Candida tropicalis*. He received 3 weeks of AmB and was discharged with fluconazole.

The third patient was a 59-year-old Chinese man with hypertension, hyperlipidaemia, gout and Type II diabetes mellitus. He was diagnosed with AML M1 and was started on induction chemotherapy. Itraconazole prophylaxis was started as well. He was neutropenic (ANC <500 cells/mm³) on diagnosis. He developed fever on D15, with TWC of 290 cells/mm³. Blood cultures taken from the Hickman line

on D15 grew *Trichosporon*. He was started on AmB and the Hickman line was removed. AmB was continued throughout his hospitalisation and continued through further courses of chemotherapy.

The fourth patient was a 50-year-old Chinese woman diagnosed with ALL in July 2002. She was neutropenic at diagnosis. Induction chemotherapy with HCVAD #1A was started. Itraconazole prophylaxis was commenced. She developed fever on D6. Broad-spectrum antibiotics were started. AmB was empirically added on D8 as she was still febrile. Blood cultures, including fungal cultures, were negative. She subsequently developed symptoms of a lower respiratory tract infection. Chest X-ray showed bilateral lobar consolidation. Computed tomography (CT) thorax showed extensive consolidation in both lungs, particularly within the upper lobes. Ground glass changes were also noted in addition to areas of consolidation. Bilateral pleural effusions were present. Bronchial alveolar lavage (BAL) grew *Aspergillus flavus*. AmB-induced renal impairment was noted and Abelcet was subsequently given to a cumulative dose of 2250 mg. Caspofungin was also given for 10 days. Repeat CT scan 3 weeks later showed marked improvement in the lung lesions. However, wedge-shaped densities and cavitating nodules within the upper lobes, representing residual areas of fungal infection, were still present. She continued to receive outpatient conventional AmB 3X a week while not on chemotherapy.

Discussion

These guidelines were modelled on those issued by the Infectious Diseases Society of America in 2002.³ Other authorities have published along similar lines.³⁻⁶ The major difference between our guidelines and the others was to allow a switch to other β -lactam agents when fever persisted after 48 to 72 hours, in the absence of microbiologically documented infection or a change in the patient's clinical status.

In the IDSA publication, if the patient's physical examination remained unchanged, and if there were no positive cultures, persisting with the same antibiotic was an option.³ Our guidelines were based on a consensus of all senior staff in the department at that time, several of whom had anecdotally seen catastrophic infections with gram-negatives that produced extended-spectrum β -lactamases.

The authors recognised that TAZ and CEF have an almost similar spectrum of action, and that there were publications in which CEF's performance against difficult gram-negatives might even be interpreted as superior to TAZ's.⁷ At the time when consensus was sought among haematologists, no head-to-head comparison of CEF and TAZ had been published. The authors were aware of one publication in which CEF was comparable to piperacillin-

gentamicin in febrile neutropenia.⁸ Soon after our audit started, a paper documenting comparability between CEF-AMK and TAZ-AMK was published.⁹ It is important to point out that in the Yamamura et al⁸ study, the mean duration of neutropenia was 9 days in both arms, and in the Sanz et al⁹ study, the median duration of neutropenia was 4 days. Both studies included patients with lymphoma, and the Sanz study also included patients with solid tumours. Our cohort had a median duration of neutropenia ranging from 11.5 to 22 days, depending on the type of chemotherapy.

In our study, the use of TAZ as a first-line antibiotic in febrile neutropenia was not associated with defervescence without a change in antibiotics. The likely explanation is that all 20 patients who received this as first-line actually had been exposed to broad-spectrum agents before.

The authors also recognised that many authorities favour introducing or discontinuing a glycopeptide, or introducing an antifungal agent at the 72- or 96-hour mark, if fever persists.^{5,6} It has been emphasised that "juggling antibiotics" is not helpful.⁵ Nevertheless, a survey of haematology units in the UK found that when response to initial empirical therapy did not occur after 24 to 48 hours, 31% of physicians changed to a carbapenem.¹⁰ Similarly, Chamberlain et al¹¹ found, in a survey of paediatric oncologists, that a small percentage switched from some other β -lactam to MER when the patient did not defervesce. The practice in our hospital seems consistent with clinical practice elsewhere, though admittedly, the data supporting this are scarce – only 1 (small) study had shown that IMI was used successfully as salvage therapy.¹²

In this audit, the median duration of CEF use was 3 days, and in the patients in whom CEF was switched to TAZ, the median duration of TAZ use was 5.5 days. The median duration of CEF use in febrile neutropenia is longer in the literature. In a series of 98 adults with febrile neutropenia (median duration 14 days) treated empirically with CEF, Jandula et al¹³ used CEF for a median of 9 days. The death rate was 10% but none was attributed to a bacterial infection. Cordonnier et al¹⁴ studied a CEF-AMK combination against ceftazidime-AMK in febrile neutropenia. The median duration of neutropenia was 23 days in the CEF arm and 19 days in the ceftazidime arm. The median duration of CEF use was 13 ± 7 days. Of the deaths in the CEF arm, 2 patients developed shock within 2 days and had their antibiotics changed, while the rest died of non-infectious causes.¹⁴ In our audit, the median duration of CEF use was 3 days and the median duration of TAZ use following CEF was 5.5 days. As CEF and TAZ are almost similar in their spectrum, a similar result would probably have been obtained had the physicians not switched from CEF to TAZ. Hence in our revised guidelines, we shall no longer advocate a CEF-TAZ switch.

Our audit showed that compliance with CEF alone as a first-line agent was 31%. All instances in which TAZ, or IMI or MER were used as first-line agents were reviewed in detail. In all cases, the reasons were easy to understand. In the majority of instances, the patient, though experiencing the “first” febrile episode in neutropenia, had been treated previously with antibiotics. This group included those who were not undergoing induction chemotherapy for the first time. It also included those undergoing induction chemotherapy for the first time, but who, because of prolonged neutropenia, had had more than one bout of fever. There were also patients experiencing febrile neutropenia for the first time after receiving induction chemotherapy – these deviations, too, were thought to be forgivable as these patients had been febrile prior to chemotherapy and had received CEF then. The literature provides no data to support or refute these practices. A huge number of publications exist that merely inform us about the non-inferiority of 1 combination of antibiotics when compared against another – these are reviewed in the international guidelines.²⁻⁴

Guidelines can only serve as guidelines. Doctors should use their discretion when initiating treatment for a condition for which a guideline exists. In the management of immunocompromised patients, in particular, clinical judgement should always be exercised. If we exclude cases in which there were valid reasons for deviating from the guidelines, then the actual compliance would be better.

It is quite clear that patients experiencing febrile neutropenia are a heterogeneous group, even within a defined population (in this case, only those with acute leukaemias). Hence, clinical judgement should also be exercised in situations where guidelines exist. Although we are not able to find an audit like ours in the literature, we have found other audits of febrile neutropenia. Innes et al¹⁵ performed a questionnaire survey of 128 clinicians in 50 cancer departments in the UK, and found surprisingly low rates of compliance with or adherence to published guidelines. They found, for example, that only 38% of the clinicians surveyed stratified patients according to risk, and with “substantial variation” in the definition of “low-risk”. Chamberlain et al¹¹ noted that 18 different antibiotic regimens were implemented as first-line therapy in 127 episodes of febrile neutropenia in 114 patients over a 2-month period in 12 paediatric oncology centres. They also found that the physicians changed antibiotics more frequently than was recommended in the literature. Our finding of a 31% compliance appears reasonable, given that there were valid reasons for not adhering to guidelines in the other episodes.

Based on the findings of this audit, we are revising our guidelines. The major change will be that, should fever persist at 48 hours with no positive microbiology, the option to change to TAZ will be omitted. Options at this stage will reflect IDSA recommendations, such as the initiation or discontinuation of VAN, as the case may be.

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