

RESEARCH COMMUNICATION

Fever/Clinical Signs and Association with Neutropenia in Solid Cancer Patients - Bacterial Infection as the Main Cause

Bassam Abdul Rasool Hassan*, Zuraidah Binti Mohd Yusoff, Saad Bin Othman

Abstract

Introduction: Neutropenia remains one of the serious side effects of chemotherapeutic drugs making cancer patients face serious risk of infections. Fever and clinical signs are considered as important indicators. The objectives of this study were to assess fever and clinical signs with neutropenia onset and/ or severity in solid cancer cases, using culture tests to determine the type of bacteria predominating, whether gram positive or gram negative. **Methods:** This observational retrospective study was conducted on files of all solid cancer patients who admitted to a general hospital between 1 January 2003 and 31 December 2006. All data were categorical and analyzed for association with neutropenia. **Results:** 117 neutropenic patients were studied, 83 (70.9%) of them suffering from fever ranging between 38.5-39 °C, with hypotension (53; 27.3%) and headache 51 (26.3%) as the most common clinical signs. Only 34 (29.1%) neutropenic patients underwent culture testing and only 14 (41.2%) showed positive growth, gram negative types predominating (9; 64.2%), mainly *Escherichia coli* (5; 35.7%), with gram positive only in 5 (35.7%). Significant associations were found for fever and clinical signs with neutropenia severity ($P<0.05$), but not neutropenia onset ($P>0.05$). Logistic regression results showed strong significant association between presence of fever ($P=0.02$, OR=1.3) (95% confidence interval (CI)) hypotension and headache ($P=0.001$, OR=1.148) (95% CI) with neutropenia severity. **Conclusion:** Fever and clinical signs specifically headache and hypotension are symptoms associated with severe neutropenia in solid cancer patients. Both may primarily result from bacterial infection, particularly gram negative forms.

Keywords: Fever - clinical signs - gram positive - gram negative - neutropenia - onset - severity

Asian Pacific J Cancer Prev, 11, 1273-1277

Introduction

Neutropenia defined as a decrease in the absolute count of neutrophils cells in the blood. Clinically neutropenia is defined as a decrease in the absolute neutrophil count (ANC) of more than two standard deviations below the normal range. So a patient is considered neutropenic when the absolute neutrophil count fall lower than the normal level of 1500 cell/ μ l. Neutropenia is mostly associated with chemotherapy regimen even though it may occur after irradiation of large parts of the body bone (Dale, 2005). While the term febrile neutropenia is used when the patient became febrile i.e. oral temperature $\geq 38.3^{\circ}\text{C}$ or $\geq 38^{\circ}\text{C}$ for more than one hour with ANC < 500 cell/ μ l or when ANC will be reduce to 500 cell/ μ l within the next 48 hours (Bledsoe et al., 2005; Dale, 2005).

Fever occurrence in neutropenic patients is an indication for the presence of infection. The infection is primarily bacteria in origin, while fungal infection which is more dangerous and occur as a second infection after bacterial infection (Flaherty, 1999). In the case of severe neutropenia patients are characterized by two main parameters, firstly fever and the second one is clinical sign

both caused by infection (Frey, 1999; Linker, 2000; Frey and Granger, 2002; Walker and Edwards, 2003). There are many studies that looked at fever occurrence and clinical signs with neutropenia such as Klastersky (2004) in Belgium which showed that 10%-50% of fever occurred with solid tumor and 80% with blood malignancy. In his study it was mentioned that fever occur as a complication of the chemotherapeutic used and required 7 to 12 days of treatment. Also neutropenic patients may suffer from several other clinical signs like abdominal pain, headache and hypotension these are caused by infection (Klastersky, 2004). While Ammann et al., (2004) carried out a retrospective study in Switzerland on 132 febrile neutropenic patients who showed the association of fever and clinical signs with neutropenia was a result of the used of chemotherapeutics drugs. In their study the incidence of fever and clinical signs was mainly caused by bacterial infections so empirical antibiotics must be used (Ammann et al., 2004). While Kern (2001) mentioned that there are several factors which can play role in case of presence of clinical signs beside infection such as old age and presence of central venous catheter (Kern, 2001). Also Munsch (2000) mentioned that it is very important for physician

*Clinical Pharmacy Discipline, School of Pharmaceutical Sciences, University of Sains Malaysia, Minden, Penang, Malaysia. *For correspondence : bassamsunny@yahoo.com*

to focus on clinical signs and symptoms. This is because when these signs occur with the presence of fever in severe neutropenic patient with absolute neutrophil count (ANC) less than 500 cell/ μ l this means that the patient required immediate hospitalization (Munsch, 2000; Rolston, 2001).

Fifty years ago febrile neutropenia is highly associated with mortality that is more than 80%, while now days the mortality is lower than 20%. Again the mortality is due to bacterial or fungal infection. Severity of febrile neutropenia increase with more aggressive chemotherapy employed (Kern, 2005). When neutropenia or febrile neutropenia occur the patient will be under the risk of infection either with gram-positive or gram-negative bacterial, fungal or even viral infection (Linker, 2000). The sources of the bacterial infection in neutropenic patients vary according to the neutropenia levels. In the first week of neutropenia occurrence (day 0-7) the primary source is from the gastro intestinal tract (GIT) and skin and the usual bacterial infection from these sites is the gram-negative bacteria (Greene, 2004). While in the second period (day 7-14) the infection also originate from the GIT, however now the main infections involve the aerobic gram-negative and positive bacteria. During this period besides bacterial infection, fungal infection especially *Candida albicans* could also take place. Neutropenia exceeding 14 days is the most critical period because the source of infection has increased from GIT to skin and respiratory tract (Greene, 2004). In addition exogenous infection resulting from contact with hospital members and from its environment are also majors factors of infection. In this period beside bacterial and fungal infection the patient is also exposed to viral infection such as *Herpes simplex virus*, *varicella zoster*, *BK virus* and *Adenovirus* (Jenson, 2003; Greene, 2004). In 1960s and 1970s majority of the infections were caused by gram-negative bacteria especially bacilli. However over 25 years it was observed that there was a change in the type of bacteria involve in febrile neutropenic that is from gram-negative to gram-positive bacteria.

The common types of the gram-positive bacteria were *Coagulase-negative staphylococci* and *Staphylococcus aureus*. The explanation for this change was not clear but some hypotheses were put forward: Firstly the mandatory techniques decrease the gram-negative bacterial infection. Also the use of low contaminated foods and oral quinolones play a role in changing the pattern from gram-negative to gram-positive bacteria. These changes in type of bacteria causing infection emphasized or high lights the importance and necessity for performing the culture and sensitivity test due to the high mortality rate of the gram-negative bacteria (Schimpff, 2001). Clinically identification of the causative organism of infection is very important so it is necessary to perform two blood cultures that is one for bacteria and the other for fungal infection (Flaherty, 1999). These blood cultures should be taken from central venous catheter and from peripheral vein (Mitchell, 1999; Wade, 2001). Bone aspiration and biopsy should also be taken in order to ascertain the main cause of the infection (Mitchell, 1999).

Materials and Methods

Data source

Ethical approval letter for conducting this study was obtained and granted from the clinical research center (CRC) of the hospital which is followed the declaration of Helsinki 1964. This is an observational retrospective study was conducted on files of solid cancer patients treated in this hospital. This study retrospectively covered the period between the period 1 January 2003 and 31 December 2006. A total of 117 patients fulfilling the inclusion criteria were selected from the total number of 4503 solid cancer patients. All of 117 patients suffered from neutropenia cancer after chemotherapy treatment. The neutropenic patients in this hospital were considered as having febrile neutropenia when their body temperature $\geq 38.5^{\circ}\text{C}$ and the ANC < 500 cell/ μ l.

Inclusion and exclusion criteria of the study

The inclusion criteria for this study were the patients must suffer from solid cancer, male or female adult ≥ 18 years old, treated with chemotherapy, their files must be found in the oncology clinic and record office of the hospital and must be admitted to ward C19. While the exclusion criteria were all the pediatric patients will excluded, all the patients who suffer from neutropenia as a result from hematological diseases not caused by chemotherapy, all the patients who treated with radiotherapy and as a result of that they suffer from neutropenia and all the patients who did not admitted to ward C19.

Data collection

All the data collected was retrospectively from the patients files which were found in the oncology clinic and the record office of the hospital. These data were collected by the uses of a special data form sheet which was already design for this study. So all the patients who admitted to the hospital between 1 January 2003 and 31 December 2006 files were retrospectively reviewed. After that all the clinical information obtained were keyed into SPSS[®] software program, which by it all the statistical analysis to find if there is an association between neutropenia onset and severity on one side and with types of chemotherapeutics drugs or regimens and their schedule of administration on the other side.

Statistical analysis

The power of this study according to its sample size was more than 87.5% i.e., since the power of the study > 80 then the results of this study can be dependable. The type of the data collected were a categorical data which included whether they suffer from fever or not (YES or NO), the patient will consider he is feverish when his body temperature $\geq 38.5^{\circ}\text{C}$. About the clinical signs it have been collected by recording their occurrence within those patients i.e., recording their frequency of occurrence within the patients. About culture test pattern by recording those who culture test done for them then by recording who has been given a positive growth of bacteria. After that the focus change on which is the type of the bacteria that has been detected here whether it is

gram positive or negative and what is its type. While on the other side it include neutropenia onset depend on the time when its start after chemotherapy administration and its classified as the following within the first week after receiving chemotherapy ≤ 7 days, within two weeks after chemotherapy administration 8-13 days and more than or after two weeks ≥ 14 days) and neutropenia severity which classified according to absolute neutrophil count (ANC) which include (Mild when ANC < 1500 cell/ μ L and > 1000 cell/ μ L, Moderate when ANC < 1000 cell/ μ L and > 500 cell/ μ L, Severe when ANC ≤ 500 cell/ μ L). These data are not normally distributed this has been confirm after the uses of the SPSS® program since the ($P=0.003$, Kolmogorov-Smirnov test). Since the main objective for this observational study is the looking for association and risk factors and since the data was categorical then the main statistical test which is suitable is Chi-square test and significance was set at P value < 0.05 . The confidence interval for this test is 95%. All information related with presence of fever and clinical signs within those solid cancer patients were collected in prepared data sheet. The data were then analyzed by using SPSS® version 15 program to see the association between these chemotherapeutics and neutropenia onset and severity. While the data related with pattern of culture test and type of bacteria responsible for infection it will be clarify descriptively.

Results

One hundred and seventeen neutropenic patients were involved in this study, the main result that concern with the presence or absence of fever among neutropenic patients is shown in Table 1.

Even though most of the neutropenic patients suffered from fever ($n= 83$; 70.9%) with temperature range between 38.5°C-39°C but only a small number of them were considered having febrile neutropenia. This is because only a small proportion ($n= 33$; 28.2%) of them have an ANC value ≤ 500 cell/ μ L to be considered as febrile neutropenic. While about clinical signs a total frequency of 194 clinical signs were observed among the major proportion of those neutropenic patients 96 (82.1%). Very few proportion do not show clinical signs they represent 17.9% of the total population of this study. Hypotension was the most common clinical sign associated with neutropenia that is 27.3% of the clinical signs, headache (26.3%) is the second most common clinical sign observed. This is followed by hypertension (12.9%), mucositis (10.8%), diarrhea (8.2%), urinary tract infection (7.7%) and chest infection (5.7%).

Table 1. Occurrence of Fever Among Patients With Neutropenia (n=117)

Presence of Fever	Number of Patients	Percentage
Yes	83	70.9
No	34	29.1
Total	117	100

Table 2. Different types of Clinical Signs Observed in Neutropenic Patients in Penang Hospital (n=194)

Clinical Signs	Frequency	Percentage
1 Hypotension	53	27.3
2 Headache	51	26.3
3 Hypertension	25	12.9
4 Mucositis	21	10.8
5 Diarrhea	16	8.2
6 Urinary tract infection	15	7.7
7 Chest infection	11	5.7
8 Kidney infection	1	0.5
9 Liver infection	1	0.5
Total	194	100

The least common clinical signs observed among these patients were kidney infection (0.5%) and liver infection (0.5%) these results will be clear through Table 2. About culture test result very few ($n=34$; 29.1%) of patients culture test was done, while majority of them culture test dose not done. Only 14 (41.2%) of those patients show positive growth while 20 (58.8%) show negative growth. For those who showed positive growth gram negative ($n=9$; 64.2%) was the predominant type of bacteria which responsible for infection, while gram positive was represent ($n=5$; 35.7%). *Escherichia coli* 5 (35.7%) was the predominance followed by *Klebsiella pneumonia* 3 (21.4%) then *Pseudomonas aeruginosa* 1 (7.1%) these represent gram negative. While *Coagulase-negative staphylococcus* 3 (21.4%) represent the predominant gram positive bacteria followed by *Staphylococcus aureus* 2 (14.3%), these results will be clear in Table 3. About statistical analysis by using Chi-square and Fisher's Exact tests to find the association of fever and clinical signs with onset and severity of neutropenia. The results showed that neither fever nor clinical signs both have a significant association with neutropenia onset since P values for both the Chi-square and Fisher's Exact tests are > 0.05 . While with neutropenia severity both are showed significant association since the P values for both the Chi-square and Fisher's Exact were < 0.05 at a confidence interval of 95% these results will clear through Table 3. Logistic Regression test was then use for significant associated variables to obtain the variable with

Table 3. Types of the Bacteria Isolated from Culture Growth of Neutropenic Patients in Penang Hospital (n=14)

Bacteria Group	Bacteria Isolated	Number of Bacteria Growth	Percentage
1 Gram negative type	<i>Escherichia coli</i>	5	35.7
	<i>Klebsiella pneumonia</i>	3	21.4
	<i>Pseudomonas aeruginosa</i>	1	7.1
	Subtotal	$n=9$	64.2
2 Gram positive type	<i>Coagulase-negative staphylococcus</i>	3	21.4
	<i>Staphylococcus aureus</i>	2	14.3
	Subtotal	$n=5$	35.7
Total		$n= 14$	100

the greater association. The results of Logistic Regression showed the presence of fever had a significant association ($P=0.02$) with the highest Odd Ratio (OR)=1.3 and confidence interval (CI)=95% compare with insignificant association of no fever ($P=0.845$). For this reason fever was considered as a main risk factor for neutropenia severity that mean as the severity increases the incidence of fever will also increase. While about the clinical signs the result of Logistic Regression show that the two clinical signs i.e., hypotension and headache both show significant association with P value =0.001 and OR=1.148 with CI=95%. While others clinical signs show insignificant association $P>0.05$, so both hypotension and headache both consider as a risk factors for neutropenia severity.

Discussion

As shown in Table 1, 83 (70.9%) patients developed fever with the range from 38.5°C - 39°C. However, not all of them were diagnosed as being febrile neutropenic because their ANC was not below 500 cell/ μ l on admission and also did not decrease to 500 cell/ μ l in the next 48 hours. The explanation for fever being considered as the risk factor for neutropenia severity is because patient who suffered from severe neutropenia, will have the risk of fever rising by 10% each day as long as ANC remain \leq 500 cell/ μ l. In addition, severe neutropenic patients will be under serious risk of infection i.e. bacterial as a primary infection or secondarily by fungal infection which lead to fever higher than 38.3°C (Dale, 2005). It is known that solid cancer patients are under the risk of microbiological infection by 50%-60% hence will result in the occurrence of fever. So as the severity of neutropenia increase, patients immunity will decrease and thus the severity of infection will also increase which will lead to fever. Also the most common characteristic obtained during severe neutropenia is fever and the presence of abdominal pain or mucositis or pneumonia (Frey, 1999; Munshi, 2000; Dale, 2005). So all these explanations shows that fever is one of the main risk factors associated with severe neutropenia, but not with onset of it. The explanation for the insignificant association of fever with onset is that when neutropenia happens the ANC requires a certain period of time to be reduced. It has been mentioned that when ANC remain higher or equal to 1000 cell/ μ l it will be enough to protect the body from any infection which is the main factor that lead to occurrence of fever (Frey, 1999, Frey and Granger, 2002; Dale, 2005). Also severe neutropenic patient is a candidate with high risk in developing periodontal diseases, mouth and rectal ulcer and also bacterial pneumonia (Frey, 1999). The cause for hypotension which is the most frequent clinical signs observed in this study was given by Nuver and his colleagues that is the chemotherapy drugs could cause cardiovascular changes and could effect the carotid arteries thickness which could lead to the effect on the systolic and diastolic blood pressure. Hence this would result in high incidence of hypotension and a lower incidence of hypertension (Nuver et al., 2005). Also diarrhea, renal problem and fever experienced by cancer patients could lead to dehydration and therefore causing hypotension. Headache the

secondary most frequent sign observed in this study has been shown to be highly associated with chemotherapeutics given intrathecally that will lead to increase in the intra cranial pressure (Howland and Mycek, 2006). The hypertension observed could result from renal damage because of the intensive chemotherapeutics drugs leading to electrolyte lost and problem with blood pressure ending with hypertension (20). Mucositis occurred as a result of damages occurring in the mouth and oropharynx because of intensive chemotherapy effect (Talcott and Rubenstein, 2001). The injury to the mucosal barrier of the gastro intestinal tract can lead to diarrhea as well as urinary tract infection (UTI) that results from severe gram-negative infection which occur because of the chemotherapy beside the damage that occur to the kidneys (Talcott and Rubenstein, 2001). Chest infection in neutropenic patients are characterized by sputum production and cough (Talcott and Rubenstein, 2001). Bacterial and fungal infection of the liver are due to neutropenia as well as the effect of chemotherapeutic drugs on the liver leading to elevation in the alkaline phosphatase, transaminases, bilirubin and amylase/ lipase. Then as the severity of neutropenia increases the bacterial and fungal infection would result in these above mentioned signs and symptoms (Talcott and Rubenstein, 2001). Schimpff (2001) concluded that clinical signs are associated with the severity of neutropenia and the grading of infection and lesion correlate with neutrophil count. Both of fever and clinical signs when present especially within severe neutropenic patients mostly they caused by infection specifically by bacterial infection (Flaherty, 1999; Mitchell, 1999; Schimpff, 2001; Wade, 2001). So it is very important to do culture test especially for neutropenic patients who suffer from fever but this study as we notice culture test was done only for few patients. The main explanation for the low number of those who culture and sensitivity done for them. This is because culture and sensitivity even its results are very important and required but it is very costly so it is not always done for the patients (Wade, 2001). Also the culture done only for those patients who suffered from fever and those who the antibiotics did not have a beneficial effect for this reason culture done for them to know what the main risk factor for this fever is. Even so the number of those who culture and sensitivity test was done for them the number of those who show growth was very low. The explanation it is known that some of the bacteria need more than 3 days to grow so it is very important to repeat the test (Hughes et al., 2002; Lyman and Wilmot, 2006). However the culture and sensitivity test still need to be performed because it is very important to determine if there is infection or not this is because during neutropenia the presence of fever mean that there is an infection. The National Comprehensive Cancer Network (NCCN[®]) guide lines mentioned that efforts must be focused to determining the causative organisms and the site of infection. Sample of specimens and blood for culture be of adequate volume that is 20-40 ml and two blood sampling must be taken one sample from the peripheral site and other from the central venous catheter (Wade, 2001). This will help to identify and differentiate between infection and contaminated microorganisms.

Many cancer centers take only one sample from the patient's vascular catheter so from this because of the complex situation which occur as a result of difficulty to identify the cause of infection. So it is a very important to do cultures and biopsy for the neutropenic patients since the occurrence of infection by bacteria or other things is inversely proportional with the ANC (Wade, 2001). There are reports showed that the most common bacteria causing infection in neutropenic patients is the gram-positive bacteria which approximately 85%. However in this study show changes since gram-negative bacterial infection is more than the gram-positive infection (i.e., dangerous change in the causative type of bacteria) (Wade, 2001). This might be due to the severity of infection and neutropenia in the patients since this will cause shifting of the normal flora of the oropharyngeal toward the predominant gram-negative because of the acute of illness (i.e., the severity of neutropenia). Since severity of illness (i.e., severity of neutropenia) will considered as the major factor for perturb of the indigenous flora (Wade, 2001). Also the severe illness will cause change of the oropharyngeal flora toward gram-negative bacilli. Then by the aspiration of these gram-negative bacilli from the oropharyngeal this will lead to respiratory infection with pneumonia (Wade, 2001). Other important risk factor due to the excessive use of the antimicrobial agents which lead to rapid and radical changes of the indigenous flora. Beside these factors other important sources of gram-negative bacterial infection are the hospital environment and hands of the medical staff (Wade, 2001). Another explanation about the emerging of gram-negative bacterial type infection is that neutropenic patients are predisposed to infection by the organisms which are normally found on the patient body surface. These organisms included *Staphylococcus aureus*, *Streptococcus species* and gram-negative bacilli entering from gastrointestinal tract (Dale, 2005). So all these could help to explain the predominantly gram-negative infections observed in the neutropenic patients studied.

In conclusion, fever, hypotension and headache were major and important risk factors associated with severe neutropenia. Fever and clinical signs incidence increase with the increase in neutropenia severity and the main cause for them is infection due to reduce in patient's immunity. So it is very important to focus on culture test to get the main cause for this fever and clinical signs. On the other hand fever and clinical signs has no association with neutropenia onset thus cancer patients may experience neutropenia without the presence of fever.

Acknowledgments

We like to thank all the hospital staff for their cooperation and their efforts to help us for doing this study. Also we like to thank all the staff in the oncology clinic and the record office of the hospital for their efforts by helping us to get the patients files that stored their.

Part of this work was presented as a poster at the 4th Asian Association of School of Pharmacy-9th Malaysian Pharmaceutical Society Scientific Conference 2009 10-13th June 2009.

References

- Ammann RA, Aebi C, Hirt A, et al (2004). Fever in neutropenia in children and adolescents: evolution over time of main characteristics in a single center, 1993-2001. *Support Care Cancer*, **12**, 826-32.
- Bledsoe BE, Kufs D, Soltis CA (2005). Hematology. In: Bledsoe BE, Porter RS, Cherry RA, eds. *Paramedic care principles and practice*. New Jersey: Pearson Prentice Hall, 458-289.
- Dale DC (2005). Neutropenia. In: Herman NW, ed. *Encyclopedia of Life Sciences*. Chichester: John Wiley & Son's, Ltd., 147-63.
- Flaherty J (1999). Infectious complications of oncology therapy. In: Vokes EE, Golomb HM, editors. *Oncologic Therapies*. Berlin: Springer, 228-44.
- Frey RJ (1999). Neutropenia. In: Donna O, Christine J, Karen B, eds. *The Gale Encyclopedia of Medicine*. Farmington Hills: Gale Research, An International Thomson Company, 2057-9.
- Frey R, Granger J (2002). Neutropenia. In: Thackery E, ed. *The Gale Encyclopedia of Cancer*. Detroit: Gale Group, 770-773.
- Greene NG (2004). Composition of the normal microbial flora. In: Greene NG, ed. *Infections in cancer patients*. New York: Marcel Dekker, INC, 15-21.
- Hughes WT, Armstrong D, Bodey GP, et al (2002). Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis*, **34**, 730-51.
- Howland RD, Mycek MJ (2006). Pharmacology. Lippincott Williams & Wilkins, Philadelphia.
- Jenson B (2003). Fever and neutropenia. *Shiraz E-Medical J*, **4**, 1-16.
- Klastersky J (2004). Management of fever in neutropenic patients with different risks of complications. *Clin Infect Dis*, **39**, 32-7.
- Kern WV (2005). Current epidemiology of infections in neutropenic cancer patients. In: Rolston KVI, Rubenstein EB, eds. *Textbook of febrile neutropenia*. London: Martin Dunitz, 57-90.
- Linker CA (2000). Blood. In: Tierney LM, McPhee SJ, Ppatakis MA, eds. *Current Medical Diagnosis and Treatment*. New York: Appleton & Lange, 499-551.
- Lyman GH, Wilmot JP (2006). Risks and consequence of chemotherapy-induced neutropenia, *Clinical Cornerstone*, **8**, 12-8.
- Mitchell D (1999). Infections in cancer patients. In: Bishop JF, ed. *Cancer Facts*. Australia: Harwood Academic, 361-4.
- Munshi HG (2000). Severe neutropenia: a diagnostic approach. *Western j med*, **172**, 248-52.
- Nuver J, Smit AJ, Van Der Meer J, et al (2005). Acute chemotherapy-induced cardiovascular changes in patients with testicular cancer. *Clin Oncol*, **23**, 9130-7.
- Rolston KVI (2001). Infections in patients with solid tumors. In: Rolston KVI, Rubenstein EB, eds. *Text Book of Febrile Neutropenia*. London: Martin Dunitz, Ltd., 91-109.
- Schimpff SC (2001). Fever and neutropenia: an historical perspective. In: Rolston KVI, Rubenstein EB, eds. *Text book of febrile neutropenia*. London: Martin Dunitz, Ltd, 1-26.
- Talcott JA, Rubenstein EB (2001). Initial clinical evaluation and risk assessment of the febrile neutropenic cancer patient. In: Rolston KVI, Rubenstein EB, eds. *Text book of febrile neutropenia*. London: Martin Dunitz Ltd., 50-165.
- Wade JC (2001). Evaluation and management of fever in the neutropenic hematopoietic stem cell transplant patient. In: Rolston KVI, Rubenstein EB, eds. *Text book of febrile neutropenia*. London: Martin Dunitz, Ltd, 125-49.
- Walker R, Edwards C (2003). Laboratory data. In: Wynne HA, Edward C, eds. *Clinical Pharmacy & Therapeutics*. New York: Churchill Livingstone, 47-65.