

Improving the emergency department management of post-chemotherapy sepsis in haematological malignancy patients

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ABSTRACT

Objective: To review the result of the implementation of treatment protocol for post-chemotherapy sepsis in haematological malignancy patients.

Design: Case series with internal comparison.

Setting: Accident and Emergency Department, Queen Elizabeth Hospital, Hong Kong.

Patients: Febrile patients presenting to the Accident and Emergency Department with underlying haematological malignancy and receiving chemotherapy within 1 month of Accident and Emergency Department visit between June 2011 and July 2012. Similar cases between June 2010 and May 2011 served as historical referents.

Main outcome measures: The compliance rate among emergency physicians, the door-to-antibiotic time before and after implementation of the protocol, and the impact of the protocol on Accident and Emergency Department and hospital service.

Results: A total of 69 patients were enrolled in the study. Of these, 50 were managed with the treatment protocol while 19 patients were historical referents. Acute myeloid leukaemia was the most commonly encountered malignancy. Overall, 88% of the patients presented with sepsis syndrome. The mean door-to-antibiotic time of those managed with the treatment protocol was 47 minutes versus 300 minutes in the referent group. Overall, 86%

of patients in the treatment group met the target door-to-antibiotic time of less than 1 hour. The mean lengths of stay in the emergency department (76 minutes vs 105 minutes) and hospital (11 days vs 15 days) were shorter in those managed with the treatment protocol versus the historical referents.

Conclusion: Implementation of the protocol can effectively shorten the door-to-antibiotic time to meet the international standard of care in neutropenic sepsis patients. The compliance rate was also high. We proved that effective implementation of the protocol is feasible in a busy emergency department through excellent teamwork between nurses, pharmacists, and emergency physicians.

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New knowledge added by this study

- A well-written, easily available treatment protocol together with stocking of antibiotics in the emergency department can effectively shorten the door-to-antibiotic (DTA) time from 300 minutes to 47 minutes.
- In this study, 86% of patients met the target DTA time of less than 1 hour.

Implications for clinical practice or policy

- Orchestrated efforts between nurses, pharmacists, and physicians are crucial for implementation of the protocol in one of the busiest emergency departments in the region.

Introduction

Cancer patients receiving chemotherapy sufficient to cause myelosuppression and adverse effects on the integrity of gastro-intestinal mucosa are at high risk of invasive infections. Patients with profound, prolonged neutropenia are at particularly high risk of serious infections. Prolonged neutropenia is most likely to occur in patients undergoing induction chemotherapy for acute leukaemia. More than 80% of

those with haematological malignancies will develop fever during more than one chemotherapy cycle.¹ Since neutropenic patients are unable to mount a strong inflammatory response to infections, fever may be the only sign. Infection in neutropenic patients can progress rapidly, leading to serious complications and even death with a mortality rate ranging from 2% to 21%.^{2,3} It is critical to recognise neutropenic fever patients early and initiate empirical, broad-

spectrum antibiotics. Major international guidelines advocate early administration of empirical antibiotics within 1 hour of emergency department (ED) presentation, sometimes even without cytological proof of neutropenia.^{4,7} However, management of febrile neutropenic patients varies across different EDs, and even among different physicians. A recent audit performed in the EDs of the United Kingdom showed that only 26% of the audited patients received intravenous antibiotics within the target time of 1 hour.⁸ Another study in French EDs showed that management of febrile neutropenia was inadequate and severity was under-evaluated in the critically ill.⁹ In order to improve and standardise the care of post-chemotherapy sepsis in haematological malignancy patients, the Accident and Emergency Department (A&E) and Department of Medicine of Queen Elizabeth Hospital (QEH) initiated a treatment protocol in 2011. This is the first hospital in Hong Kong to implement such a treatment protocol. It included febrile patients with haematological malignancy who had received chemotherapy within 1 month of ED visit. These patients were identified at triage station and provided with a fast-track consultation. The ED physician would verify the history and perform a thorough physical examination and targeted investigations. Empirical antibiotics were administered after taking appropriate culture samples aiming at a door-to-antibiotic (DTA) time of less than 1 hour (Fig).

Local publication on post-chemotherapy patients mainly focused on solid tumour patients, in-patient management and their outcomes.¹⁰ There is a paucity of literature concerning the initial ED management of haematological malignancy patients. The objective of this study was to examine the protocol compliance rate among ED physicians, the DTA time before and after implementation of the protocol, and the impact of the protocol on A&E and hospital services. It also serves to provide invaluable epidemiological data regarding the haematological malignancy patients in Hong Kong.

Methods

This is a before-and-after study of the impact of a protocol on the management of post-chemotherapy sepsis in haematological malignancy patients. A 2-year retrospective chart review was conducted. The first chart review was performed from June 2010 to May 2011. These patients were admitted through ED to the haematological ward prior to implementation of the protocol and served as historical referents. Data were retrieved from the admission book of the haematology ward. A diagnosis of post-chemotherapy fever or neutropenic fever was shortlisted. Cases that were admitted through ED were analysed. The second year started from June 2011. The intervention group included patients

改善急症室對血癌病人化療後敗血病的治療

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目的：探討針對血癌病人化療後敗血病的治療方案的成效。

設計：內部比較的病例回顧。

安排：香港伊利沙伯醫院急症室。

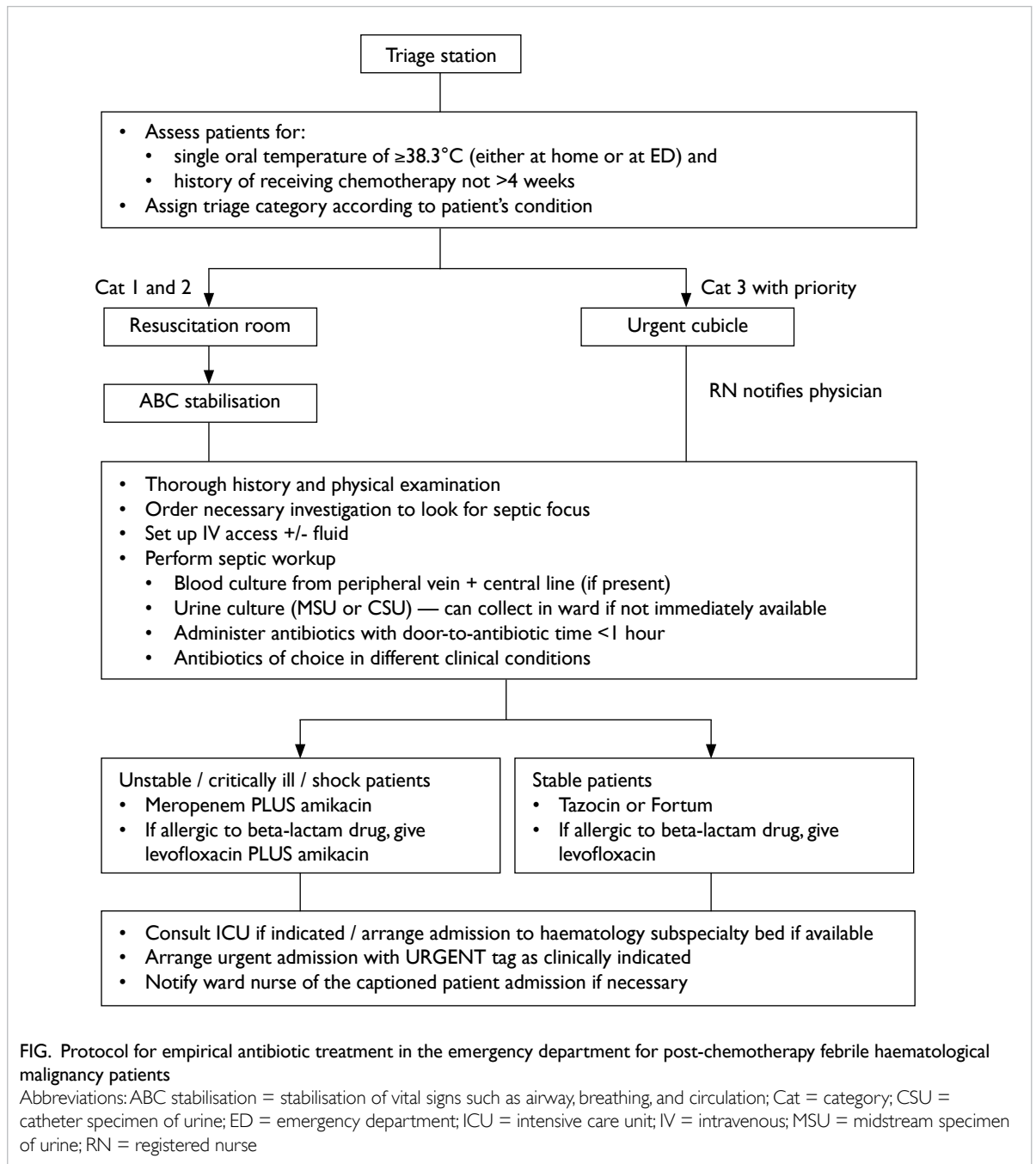
患者：從2011年6月至2012年7月期間，因接受化療後一個月內發燒而到急症室求診的血癌病人，並以2010年6月至2011年5月期間相類似的病例作一對照。

主要結果測量：急症科醫生的達標率、於針對性治療方案實行前後由到達急症室至注射抗生素的時間的分別和該治療方案對急症室和醫院服務的影響。

結果：共69名病人參與本研究。當中50名為實驗病例，19名為對照病例。急性骨髓性白血病是最常見的血癌病症。88%的病人出現敗血病的徵狀。在實驗病例當中，由到達急症室至注射抗生素的平均時間為47分鐘；而對照組則為300分鐘。有86%的實驗病人可於低於目標時間的60分鐘內注射抗生素。實驗組的病人於急症室的逗留時間（76分鐘比105分鐘）與住院日數（11天比15天）都比對照組為短。

結論：針對性的治療方案能有效縮短敗血症患者注射抗生素的時間以符合國際標準。達標率亦令人滿意。這研究證明了透過各職系如護士、藥劑師和急症科醫生的通力合作，即使在極繁重的工作環境，治療方案也能有效實踐。

recruited in the protocol. There were two patients who fulfilled the inclusion criteria but were excluded from the study since they refused any investigation or treatment in ED despite explanation. The charts were reviewed by two emergency physicians and two senior nurses. Any discrepancy was resolved by discussion among investigators. The protocol was implemented on a 24-hour basis. According to the protocol, fever was defined by a single measurement of oral temperature of $>38.3^{\circ}\text{C}$ either at the triage station or self-reported at home. Neutropenia was defined as absolute neutrophil count (ANC) of $<1 \times 10^9/\text{L}$. Sepsis was defined by Bone criteria¹¹ (ie >2 out of 4 of the following: leukocyte count <4 or $>12 \times 10^9/\text{L}$, respiratory rate $>20/\text{min}$, oral temperature $>38^{\circ}\text{C}$ or $<35^{\circ}\text{C}$, pulse >90 beats/min). Door-to-antibiotic time was charted in the medical record. Lengths of stay in the A&E and hospital were retrieved from the Clinical Data Analysis and Reporting System. The primary outcome was mean DTA time. Secondary outcomes included compliance of the ED physician with the protocol, mean ED length of stay, mean hospital length of stay, and the adverse outcome rate. Adverse outcomes included occurrence of a serious medical complication or death during index admission; these criteria are commonly cited in oncology literature.¹² Adverse outcome was charted from patients' medical record during the index admission.



Chi squared tests were performed when comparing categorical parameters between the protocol and referent groups. Student's *t* tests were performed for parametric variables. All statistical analyses were performed using the Statistical Package for the Social Sciences (Windows version 17; SPSS Inc, Chicago [IL], US). A *P* value of less than 0.05 was regarded as statistically significant.

The study was conducted in the A&E of QEH, Hong Kong, a tertiary referral centre for haematological malignancy patients. The A&E of QEH is an urban ED with a daily attendance of 500 and is one of the busiest EDs in Hong Kong. This study was approved by the chief of service of the

department.

Results

A total of 69 patients were recruited; 19 patients were referents while 50 belonged to the protocol group. Baseline demographic data are shown in Table 1. Overall, 49% of the patients were male. Their mean age was 56 years (range, 20–81 years). Leukaemia was the most commonly encountered haematological malignancy, accounting for 51% of cases (*n*=35/69). Among these, acute myeloid leukaemia was the most prevalent subtype. Lymphoma was the second most common haematological malignancy, making up

TABLE 1. Baseline characteristics of study patients*

	Referent (n=19)	Protocol (n=50)	P value
Age (years)	53 (20-79)	58 (28-81)	0.13
Male	12 (63%)	22 (44%)	0.16
Co-morbidities			
Diabetes mellitus	1 (5%)	8 (16%)	
Hypertension	3 (16%)	11 (22%)	
Chronic obstructive pulmonary disease	0	1 (2%)	
Congestive heart failure	0	2 (4%)	
Ischaemic heart disease	0	1 (2%)	
Cerebrovascular disease	0	1 (2%)	
Hepatitis B	5 (26%)	2 (4%)	
Total No. of patients with co-morbidities	9 (47%)	26 (52%)	0.18
Characteristics of haematological malignancy			0.75
Leukaemia	11 (58%)	24 (48%)	
Lymphoma	7 (37%)	22 (44%)	
Multiple myeloma	0	3 (6%)	
Miscellaneous	1 (5%)	1 (2%)	
Last chemotherapy dose to ED visit (days)	12 (0-19)	12 (0-36)	0.98
ANC <1 x 10 ⁹ /L†	13 (68%)	31 (62%)	0.62
Sepsis criteria‡	16 (84%)	45 (90%)	0.68

Abbreviations: ANC=absolute neutrophil count; ED = emergency department

* Data are shown as mean (range) or No. (%)

† Based on blood result at index ED visit

‡ According to Bone criteria¹¹

42% (n=29/69) of the cases. The mean duration of the last chemotherapy dose to ED visit was 12 days in both groups of patients. At least one co-morbidity was present in 47% of patients in the referent group and in 52% of patients in the protocol group (P=0.18).

During the index ED visit, the mean door-to-consultation time was 15 and 12 minutes in referent group and protocol group, respectively (P=0.40). Overall, 88% (n=16/19 in referent and n=45/50 in protocol group) of the patients fulfilled the sepsis criteria; 64% (n=44/69) had ANC of <1 x 10⁹/L, although the result was not known at the time of consultation. All protocol group patients received antibiotics after blood cultures were taken during their ED stay compared to none in the control group. Tazobactam-piperacillin (Tazocin; Pfizer, Taiwan) was the most commonly prescribed antibiotic in ED. The mean DTA time in the protocol group was 47 minutes compared to 300 minutes in referent group (P<0.05). Overall, 86% (n=43/50) of protocol group patients could achieve the target DTA time of less than 1 hour (P<0.05). The shortest time required for antibiotic administration in the referent group was 70 minutes. The mean length of stay in ED was 105 minutes in the referent group versus 76 minutes in the protocol group (P=0.46). The major outcomes are shown in Table 2.

The duration of fever, which was defined as oral temperature of >38°C for 24 hours, was 4 days in the referent group and 3 days in the protocol group (P=0.09). One patient from the referent group suffered from septic shock and required intensive care unit (ICU) admission; no patient from this group died. Six patients in the protocol group had adverse outcomes; three had septic shock requiring inotropic support, one of them required ICU admission, while three patients died during index admission. Adverse event rate was 5% in the referent group versus 14% in the protocol group (P=0.45). Overall, 25% (n=17/69) of patients had bacteraemia. *Escherichia coli* was recovered in five samples of which two were extended-spectrum beta-lactamase (ESBL)-producing bacteria. *Streptococcus mitis* was the second most common pathogen and was found in four samples. Overall, 43% (n=30/69) of the patients had microbiologically documented infection. The mean length of hospital stay was 15 days in the referent group compared with 11 days in the protocol group (P=0.15).

Discussion

Chemotherapy-induced sepsis is a medical emergency that requires urgent assessment and treatment with antibiotics. Our study shows that

TABLE 2. Comparison of outcomes of patients with post-chemotherapy fever between the protocol and referent groups*

	Referent (n=19)	Protocol (n=50)	P value
Blood culture in ED	3 (16%)	50 (100%)	<0.05
Door-to-consultation time (mins)	15 (6-54)	12 (3-109)	0.40
Door-to-antibiotic time (mins)	300 (70-904)	47 (23-156)	<0.05
Door-to-antibiotic time <1 hour	0	43 (86%)	<0.05
ED LOS (mins)	105 (16-771)	76 (25-291)	0.46
Duration of fever (days)	4 (1-11)	3 (1-10)	0.09
Hospital LOS (days)	15 (4-43)	11 (1-52)	0.15
Mortality	0	3 (6%)	<0.05
No. of adverse outcomes	1 (5%)	7 (14%)	0.45

Abbreviations: ED = emergency department; LOS = length of stay

* Data are shown as mean (range) or No. (%)

88% of post-chemotherapy febrile patients fulfilled the sepsis criteria. Overall, 25% of patients had bacteraemia, a rate similar to that reported in the literature.⁴ Hence, prompt identification and early administration of broad-spectrum empirical antibiotics is the cornerstone of management. In a retrospective study of 2731 patients with septic shock (only 7% of whom were neutropenic), each hour delay in initiating effective antimicrobials decreased survival by around 8%.¹³ Another cohort study showed that the in-hospital mortality among adult patients with severe sepsis or septic shock decreased from 33% to 20% when time from triage to appropriate antimicrobial therapy was ≤ 1 hour compared with >1 hour.¹⁴ Our protocol suggested Tazocin as the first-line antibiotic, in accordance with the 2010 Infectious Diseases Society of America guideline.⁴ However, the rising trend of ESBL *E. coli* infection may raise concern of antibiotic resistance. A larger-scale cohort study should be carried out to update the local microbiology prevalence and amend the empirical antibiotic recommendations accordingly.

Implementation of the protocol in our department could significantly reduce the mean DTA time from 300 minutes to 47 minutes ($P<0.05$). Furthermore, 86% of patients could achieve the target DTA time of <1 hour. The result was satisfactory when compared with similar studies conducted in Europe and North America where reported median DTA ranged from 154 minutes to 3.9 hours.¹⁵⁻¹⁷ Audits from the UK report that only 18% to 26% of patients receive initial antibiotic within the target DTA of 1 hour.⁸ According to the authors, the most common reasons for failure to comply with this time frame included failure to administer the initial dose of the empirical antibacterial regimen until the patient has been transferred from ED to the inpatient ward, prolonged time between arrival and clinical assessment, lack of awareness of the natural history of neutropenic fever syndrome and

its evolution to severe sepsis and shock, failure of the ED to stock appropriate antibacterial medications, and non-availability of neutropenic fever protocols in the ED for quick reference.⁸ The last two points were further supported by studies. A chart review of 201 febrile neutropenic patients in Canada showed that the electronic clinical practice guideline could decrease the DTA time by 1 hour (3.9 hours vs 4.9 hours).¹⁶ Another retrospective observational study of timeliness of antibiotic administration in severely septic patients presenting to a US community ED showed that storing key antibiotics could decrease the mean DTA time by 70 minutes (167 minutes vs 97 minutes).¹⁸ The percentage of severely septic patients receiving antibiotics within 3 hours of arrival to the ED increased from 65% pre-intervention to 93% post-intervention.¹⁸ Before the implementation of this protocol, multiple briefing sessions were held with nurses and physicians to increase awareness about prompt treatment of post-chemotherapy fever. Antibiotics were stocked in the ED and were readily available. The protocol could be easily downloaded from the department website. Regular collaboration existed between the nursing manager and the pharmacist to replenish the antibiotic stock. Thus, successful implementation of the protocol involved a joint effort by different parties.

There was a trend towards reducing the duration of fever and length of hospital stay in the intervention group. Although this does not imply causation, especially in view of the small sample size, the correlation makes one ponder whether a delay in antibiotic delivery indeed increases the length of hospital stay. Similar correlation was demonstrated in a UK review.¹⁵ However, we could not demonstrate an impact on mortality and adverse outcome. The reason may partly be related to the small sample size, heterogeneous nature of haematological malignancies, and overall low incidence of mortality (4%) in our study as compared to 49.8% in-hospital mortality rate reported in an 11-year review.¹⁹ Our

result shows that the length of ED stay was similar between control and intervention groups, thus, demonstrating that this protocol did not add further burden to the overcrowding ED.

This study has two limitations that need to be discussed. First, the study used a retrospective chart review design and there were inherent challenges with missing information and poor documentation. Second, prior to implementation of the protocol, the febrile haematological malignant patients were often instructed to either attend the day ward or A&E; this partly explains the relatively small case number in the control group. In addition, we relied on the diagnosis coding for case identification in the control group; some cases might have been missed as a result of error in coding. Even if they attended ED, the lack of awareness and reluctance of physicians to prescribe antibiotics led to a significant delay in administration of the first dose of antibiotic. Although the number of control cases was small, mean DTA time of 300 minutes echoed the same in a similar study performed overseas.¹⁶ Efforts were made to use accepted chart review methods to assess outcomes that were automatically recorded in the electronic ED information systems, and to examine the nurse records of antibiotic administration.

Conclusion

Implementation of a treatment protocol in post-chemotherapy febrile haematological malignancy patients can significantly shorten the mean DTA time to <1 hour, which is now the standard of care worldwide. The key to effective implementation lies in orchestration of efforts between administrators, physicians, nurses, and pharmacists. We can prove that the protocol is feasible even in a busy urban ED.

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Declaration

No conflicts of interests were declared by authors.

References

- Klastersky J. Management of fever in neutropenic patients with different risks of complications. *Clin Infect Dis* 2004;39 Suppl 1:S32-7.
- Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 Update of recommendations for the use of white cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006;24:3187-205.
- Herbst C, Naumann F, Kruse EB, et al. Prophylactic antibiotics or G-CSF for the prevention of infections and improvement of survival in cancer patients undergoing chemotherapy. *Cochrane Database Syst Rev* 2009;(1):CD007107.
- Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2011;52:e56-93.
- Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580-637.
- Bate J, Gibson F, Johnson E, et al. Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients (NICE Clinical Guideline CG151). *Arch Dis Child Educ Pract Ed* 2013;98:73-5.
- Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2013;31:794-810.
- Clarke RT, Warnick J, Stretton K, Littlewood TJ. Improving the immediate management of neutropenic sepsis in the UK: lessons from a national audit. *Br J Haematol* 2011;153:773-9.
- André S, Taboulet P, Elie C, et al. Febrile neutropenia in French emergency departments: results of a prospective multicentre survey. *Crit Care* 2010;14:R68.
- Hui EP, Leung LK, Poon TC, et al. Prediction of outcome in cancer patients with febrile neutropenia: a prospective validation of the Multinational Association for Supportive Care in Cancer risk index in a Chinese population and comparison with the Talcott model and artificial neural network. *Support Care Cancer* 2011;19:1625-35.
- Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;101:1644-55.
- Klastersky J, Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer Risk Index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000;18:3038-51.
- Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;34:1589-96.
- Gaieski DE, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med* 2010;38:1045-53.
- Sammot SJ, Mazhar D. Management of febrile neutropenia in an acute oncology service. *QJM* 2012;105:327-36.
- Lim C, Bawden J, Wing A, et al. Febrile neutropenia in EDs: the role of an electronic clinical practice guideline. *Am J Emerg Med* 2012;30:5-11, 11.e1-5.
- Nirenberg A, Mulhearn L, Lin S, Larson E. Emergency department waiting times for patients with cancer with febrile neutropenia: a pilot study. *Oncol Nurs Forum* 2004;31:711-5.
- Hitti EA, Lewin JJ 3rd, Lopez J, et al. Improving door-to-antibiotic time in severely septic emergency department patients. *J Emerg Med* 2012;42:462-9.
- Légrand M, Max A, Peigne V, et al. Survival in neutropenic patients with severe sepsis or septic shock. *Crit Care Med* 2012;40:43-9.