Evidence-based approach to treatment of febrile neutropenia in hematologic malignancies

Juan Gea-Banacloche[1]

[1]*Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Applying the principles of evidence-based medicine to febrile neutropenia (FN) results in a more limited set of practices than expected. Hundreds of studies over the last 4 decades have produced evidence to support the following: (1) risk stratification allows the identification of a subset of patients who may be safely managed as outpatients given the right health care environment; (2) antibacterial prophylaxis for high-risk patients who remain neutropenic for ≥ 7 days prevents infections and decreases mortality; (3) the empirical management of febrile neutropenia with a single antipseudomonal beta-lactam results in the same outcome and less toxicity than combination therapy using aminoglycosides; (4) vancomycin should not be used routinely empirically either as part of the initial regimen or for persistent fever, but rather should be added when a pathogen that requires its use is isolated; (5) empirical antifungal therapy should be added after 4 days of persistent fever in patients at high risk for invasive fungal infection (IFI); the details of the characterization as high risk and the choice of agent remain debatable; and (6) preemptive antifungal therapy in which the initiation of antifungals is postponed and triggered by the presence, in addition to fever, of other clinical findings, computed tomography (CT) results, and serological tests for fungal infection is an acceptable strategy in a subset of patients. Many practical management questions remain unaddressed.

Evidence-based medicine

Practicing evidenced-based medicine means "integrating individual clinical expertise with the best available external clinical evidence from systematic research."[1] This definition acknowledges that anyone's personal experience is limited but valuable, and then assumes that systematic research has produced evidence applicable to the particular case. The key point is the qualifier "best," meaning that the evidence has to be appraised, which is not easy. Some helpful online resources that focus on evidence-based medicine include http://www.cebm.net, http://plus.mcmaster.ca/EvidenceUpdates/Default.aspx, and http://acpjc.acponline.org/.

The "right" hierarchy of evidence is a matter of academic debate, although the principles are agreed upon: a properly conducted randomized controlled trial (RCT) is usually better evidence than an observational study, which is generally better than a case series, which beats a case report. A systematic review of all RCTs usually is preferable over a single trial. At the bottom of the ladder is "mechanism-based reasoning" (very frequently used during ward rounds when there is nothing better). An example of how different levels of evidence may support different conclusions regarding the use of vancomycin in neutropenic patients is presented in Table 1. This example uses the ranking proposed by the Oxford-based Centre for Evidence-based Medicine (CEBM).[2,3]

When confronted with a clinical decision, instead of personally sieving through the evidence, one may look up guidelines offered by professional societies or ask for the opinion of an expert. EBM's most important concept is that any recommendation must be supported by evidence and that the quality of the evidence must be made explicit.

Professional organizations have indeed embraced some form of assessment of the evidence in their published guidelines. Unfortunately, different organizations keep using different grading systems, creating a sometimes confusing amalgam of letters and numbers to rank the strength of a given recommendation and the quality of the evidence on which the recommendation is based (Table 2). This may make the interpretation of guidelines more cumbersome than in the past. For example, the very first Infectious Diseases Society of America (IDSA) guideline for the management of febrile neutropenia (FN) had a simple "star rating scheme similar to that used for theatrical productions,"[12] which was easier to follow than the current "A–D" and "I–III."[13]

This chapter provides a review and comments on a selection of the evidence-based guidelines for fever and neutropenia published recently. The terminology used by the guidelines issued by the European Society for Medical Oncology (ESMO),[14] the IDSA,[15] the National Comprehensive Cancer Network (NCCN)[16] and the American Society of Clinical Oncology (ASCO)[17] are presented on Table 2.

ASCO has also endorsed the pediatric guidelines proposed by the International Pediatric Fever and Neutropenia Guideline Panel for the Management of Fever and Neutropenia in Children with Cancer and/or Undergoing Hematopoietic Stem Cell Transplantation.[20] These are notable for being the first fever and neutropenia guidelines that explicitly use the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) approach to qualify the strength of the recommendation and the quality of the evidence. The GRADE framework (http://www.gradeworkinggroup.org/), recently adopted also by the IDSA, is an attempt to develop a universal system to formulate and grade evidence-based practice guidelines. It explicitly separates "strength of recommendation" from "quality of the evidence" and proposes unambiguous definitions. Recommendations can only be "strong" or "weak" (based on whether the desirable effects of the recommendation outweigh the undesirable effects)[21] and the quality of evidence can only have 4 levels: high, moderate, low, and very low (based on how likely it is

Table 1. Example of how recommendations vary depending on the levels of evidence: vancomycin in FN

Step (level) according to the CEBM[2,3]	Type of evidence	Finding	Recommendation based on level of evidence
Step 5 (Level 5)	Mechanism-based reasoning	More than half the cases of bacteremia during neutropenia are due to gram-positive infections[4]	Vancomycin should be added empirically either at the beginning or during persistent fever
Step 4 (Level 4)	Case-series, case-control studies, or historically controlled studies	Early initiation of vancomycin in patients with *S mitis* bacteremia resulted in improved outcome[5,6]	Start empirical vancomycin when *S mitis* is suspected
Step 3 (Level 3)	Nonrandomized controlled cohort/follow-up study	Neutropenic patients with gram-positive infections who did not receive vancomycin before identification of the pathogen did not have worse outcomes[7]	Vancomycin should not be started until a pathogen that requires it is found
Step 2 (Level 2)	Randomized trial or observational study with dramatic effect	Early vancomycin did not result in improved outcome[8]	Vancomycin should not be part of the initial regimen
		Vancomycin after 48-60 h of persistent fever did not result in improved outcome[9]	Vancomycin should not be added empirically after 48-72 h of fever
Step 1 (Level 1)	Systematic review of randomized trials	The use of glycopeptides can be safely deferred until the documentation of a resistant gram-positive infection[10,11]	Vancomycin should not be started until a pathogen that requires it is found

Evidence may suggest different courses of action. Properly conducted randomized trials (when feasible) are the source of the most solid evidence, particularly when the effect is found to be in the same direction in several studies analyzed by systematic reviews or meta-analyses. The empirical use of vancomycin is debated to this day, but the evidence supporting it, even in the commonly suggested indications, is limited.

that future research will change the estimate of the effect or even the direction of the effect).[22] Once the basic concept is accepted, the classification is easy to follow and logical: an intervention that is potentially lifesaving may get a strong recommendation even when the evidence supporting it is of low quality (eg, empirical addition of antifungal therapy in children with persistent FN[20]) and, conversely, very-high-quality evidence may generate only a weak recommendation if the undesirable consequences have not been fully explored (eg, fluoroquinolone prophylaxis in afebrile patients who are expected to remain neutropenic for ≥ 7 days, supported by meta-analyses but rejected by the Australian guidelines[23]). Critical appraisal of the evidence is essential, but leaves room for subjectivity. Randomized trials begin as high-quality evidence and observational studies as low-quality evidence, but the former may be downgraded (eg, because of lack of blinding or variability in results) and the latter upgraded (eg, because of a very large magnitude of effect).

Evidence-based guidelines for FN

In the following sections, I will summarize recommendations regarding prophylaxis of fever during neutropenia, risk stratification, and the 4 distinct fever syndromes characterized by Bow in his review.[24] A uniform structure will be used: definition, background, recommendation from the guidelines, and highlights/limitations of the evidence.

Some limitations of the evidence generated in FN studies should be mentioned. First, fever is not a clinicopathological entity. Fever is used as a surrogate marker for infection, but in fact is a diagnostic test of unclear sensitivity and specificity. An undetermined fraction of patients with fever (who were included in the trial) do not have infection and another fraction of patients without fever (who were excluded from the trial) do in fact have an infection that could benefit from treatment with the antimicrobial agent. This means that the population of interest and the effect of the intervention may be diluted out due to misclassification. Second, for a wide array of daily clinical decisions in the management of neutropenic patients, there is only very low-quality evidence (or no evidence at all), usually in the form of case reports and case series, and the guidelines remain silent (Table 3).

There are hundreds of trials comparing antibiotics for the first episode of fever, but one of the most common scenarios, recrudescent fever (a second episode of fever after the first one resolved with antimicrobial treatment), has barely been addressed and it is not easy to envision a RCT that could do it properly. The Pediatric Fever and Neutropenia Guideline Panel has presented a list of "research gaps" in FN in their Guidelines.[20]

Prevention of fever during neutropenia using antimicrobial agents

Definition

Antimicrobial agents used in afebrile neutropenic patients with the aim of decreasing infections and death. Fever may be the primary end point of some of the studies, but it is worth noting that the use of anti-infective drugs must logically be aimed at preventing infection.

Background

The use of antimicrobials to prevent infections has always been controversial. As a general rule, prophylaxis tends to work (ie, the incidence of the infection of interest decreases). The controversy derives from the assessment of the unintended (and frequently unmeasured) consequences of prophylaxis and the analysis of the cost/benefit ratio of the intervention for the individual patient, the hospital, and the community.

Recommendations from the guidelines

Antibacterial prophylaxis. ESMO,[14] IDSA,[13] ASCO,[17] and NCCN[16] recommend antibacterial prophylaxis with a fluoroquinolone for patients who are going to be neutropenic for ≥ 7 days. The

Table 2. Evidence grading used on selected recent guidelines for fever and neutropenia

	ESMO[18]	IDSA[13]	Australian[19]	NCCN[16]	IPF NGP[20]
Strength of recommendation	A There is evidence of type I or consistent findings from multiple studies of types II, III, and IV.	A There is good evidence to support a recommendation for or against use.	A Body of evidence can be trusted to guide practice.	Complete version at http://www.nccn.org Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.	Pediatric, adheres to the GRADE system 1: Strong: the desirable effects of an intervention clearly outweigh the undesirable effects 2: Weak: the trade-offs are less certain—either because of low quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced
	B There is evidence of types II, III, and IV and findings are generally consistent.	B There is moderate evidence to support a recommendation for or against use.	B Body of evidence can be trusted to guide practice in most situations.	Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.	
	C There is evidence of types II, III, and IV, but findings are inconsistent.	C There is poor evidence to support a recommendation.	C Body of evidence provides some support for recommendation(s), but care should be taken in its application.		
	D There is little or no systematic empirical evidence.		D Body of evidence is weak and recommendation must be applied with caution.		
Quality of the evidence	I Evidence is obtained from meta-analysis of multiple, well-designed, controlled studies; randomized trials have with low false-positive and low false-negative errors (high power).	I There is evidence from >1 properly randomized, controlled trials.	I A systematic review of level II studies.	The NCCN guidelines combine the quality of the evidence with the strength of the recommendation	A (high): Further research is very unlikely to change the confidence in our estimate of effect.
	II Evidence is obtained from at least one well-designed experimental study; randomized trials have high false-positive and/or false-negative errors (low power).	II There is evidence from >1 well-designed clinical trials without randomization, from cohort or case-controlled analytic studies (preferably from >1 center), from multiple time series, or from dramatic results from uncontrolled experiments.	II RCT		B (moderate): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
	III Evidence is obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled, single-group, pre-post, cohort, time, or matched case-control series.	III There is evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.	III-1 Pseudorandomized controlled trial (ie, alternate allocation or some other method) III-2 Comparative study with concurrent controls: ● Nonrandomized, experimental trial ● Cohort study ● Case-control study ● Interrupted time series with a control group III-3 Comparative study without concurrent controls: ● Historical control study ● Two or more single arm study ● Interrupted time series without a parallel control group		C (low or very low): ● Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. ● Very low: Any estimate of effect is very uncertain
	IV Evidence is from well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies.				
	V Evidence is from case reports and clinical examples.		IV Case series with posttest or pretest/posttest outcomes		

IPF NGP indicates International Pediatric Fever and Neutropenia Guideline Panel.

Table 3. Examples of clinical scenarios in FN for which evidence-based recommendations are not available

1	A 62-year-old man with hairy cell leukemia and prolonged neutropenia was admitted for evaluation. Only prophylaxis was oral fluconazole. The day after admission, he developed his first fever. Blood cultures obtained and ceftazidime started. The blood cultures grew susceptible *E coli*.	Should this patient antibiotic treatment be "downgraded" to ceftriaxone or ciprofloxacin?
2	A patient with AML in first remission was admitted for allogeneic stem cell transplantation and started on prophylactic levofloxacin. Known carrier of VRE. First fever on day +6. Hemodynamically stable and asymptomatic.	Should VRE coverage be included as part of the initial antibiotic regimen?
3	A patient with relapsed AML and a history of invasive aspergillosis was admitted for reinduction. ANC < 100. Prophylaxis with levofloxacin and caspofungin. A CT-PET showed a new pulmonary nodule. Afebrile.	What is the best diagnostic and therapeutic strategy for this patient?
4	18-year-old man with refractory ALL was transferred for a phase 1 clinical trial. He had been on cefepime and metronidazole for typhlitis in another hospital. Fluconazole prophylaxis. Forty-eight hours after admission, he developed a new fever and worsening abdominal pain.	What change (if any) should be made to his antibacterial coverage? What change (if any) should be made to his antifungal coverage?
5	A 28-year-old woman with AML had been in the hospital for several weeks undergoing myeloablative stem cell transplantation. She experienced VRE bacteremia and urinary tract infection with an ESBL-producing *Klebsiella pneumoniae*. She was on meropenem, daptomycin, and caspofungin. Afebrile for the last week, she seemed to be engrafting. She developed a new fever and the CT showed new patchy multifocal pulmonary infiltrates.	Should another antifungal be substituted or added? Should the antibacterial coverage be modified?

All patients were seen by the author at the NIH Clinical Center. Patient 1 was downgraded to ceftriaxone; patient 2 was treated with piperacillin-tazobactam and defervesced uneventfully; patient 3 was started on voriconazole, but the bronchoalveolar lavage showed *Cunninghamella* and he was successfully treated for mucormycosis with liposomal amphotericin B and surgical resection; patient 4 had *Enterococcus faecalis* bacteremia; patient 5 had CMV pneumonitis.
AML indicates acute myelogenous leukemia; VRE, vancomycin-resistant enterococcus; ANC, absolute neutrophil count; and ALL, acute lymphocytic leukemia.

Australian guidelines recommend avoiding antibacterial prophylaxis in general and consider it only for stem cell transplantation patients and palliative patients with BM failure.[23]

Antifungal prophylaxis. Antifungal prophylaxis recommendations are particularly complex in all guidelines because they require an assessment of the risk of *Candida* versus mold (mainly *Aspergillus*) infection. For outpatients, ASCO recommends antifungal prophylaxis with a triazole in outpatients who are expected to be neutropenic for ≥ 7 days.[17] The IDSA recommends fluconazole prophylaxis for patients at risk for *Candida* and advises considering posaconazole for selected patients undergoing intensive chemotherapy for acute leukemia or myelodysplastic syndrome[13] based on a single RCT that showed improvement in overall survival in this group.[25] The NCCN divides patients in low, intermediate, and high risk of fungal infections and provides detailed examples of each category with the recommendation to "consider" a variety of antifungal prophylaxis agents with different degrees of consensus.[16] The Australian guidelines provide very specific pathogen-specific recommendations.[26]

Highlights and limitations of the evidence

Antibacterial prophylaxis. Several meta-analyses support a beneficial effect in fever, documented infections, and overall mortality by administering fluoroquinolone prophylaxis to patients who are neutropenic for ≥ 7 days.[27-30] The low quality of many of the studies included in the meta-analyses, the lack of an effect on mortality in any single trial (including the latest and more influential[31]), and the paucity of long-term data on bacterial resistance and patient colonization with resistant pathogens are the arguments for the Australian guidelines to not recommend its routine use.[23]

Antifungal prophylaxis. There is convincing evidence that fluconazole reduces the rates of invasive candidiasis[32] and death[33] in patients at high risk of fungal infection. There is also evidence that antifungal agents with activity against *Aspergillus* are more effective than fluconazole in reducing the rates of invasive aspergillosis both during neutropenia[34,35,36] and in other high-risk settings[37,38] However, there is only one RCT (not blinded) showing that a mold-active drug (posaconazole) improved survival compared with fluconazole or itraconazole.[25] The conflict between the biological effect (less aspergillosis) and the clinical outcome effect (improved survival in only one trial) makes it difficult to formulate unambiguous guidelines.

Risk stratification

Definition

Patients who develop neutropenia during chemotherapy for cancer can be categorized as at high risk or low risk of a poor outcome based on a variety of factors.

Background

The mortality of an episode of fever and neutropenia varies widely.[39] The risk of complications and poor outcomes has practical implications for management (choice of antibiotics, inpatient vs outpatient setting).

Recommendations from the guidelines

The adult guidelines from Australia,[40] ESMO,[14] and ASCO[17] recommend the use of the Multinational Association for Supportive Care in Cancer (MASCC) index[41] to identify patients at low risk of complications who could be treated as outpatients. The NCCN guidelines offer a more detailed discussion of risk of infection (beyond neutropenia), but they also support the use of the MASCC index.[16] The pediatric guidelines also support the concept of risk stratification and emphasize the importance of using strategies that have been validated locally.[20]

Highlights and limitations of the evidence

The most commonly endorsed stratification strategy is the MASCC index, which was designed as a tool to identify adult patients at low risk of complications.[41] To obtain a MASCC score, points are allocated and added up. Points are given for burden of illness (no or mild symptoms = 5 points, severe symptoms = 3 points), absence of hypotension (5 points), absence of chronic obstructive pulmonary disease (4 points), solid tumor OR no previous fungal infection (4 points), absence of dehydration (3 points), outpatient status (3 points) and age < 60 years (2 points). The points are added up, and patients with a score of ≥ 21 points (of 26 possible) are considered "low risk" and can be considered for oral therapy. The index has been validated in multiple settings and performs well, although it may function better in solid tumors than in hematologic malignancies.[39] Although most guidelines recommend its use, some point out potential limitations and provide specific clinical criteria to supplement the MASCC score and improve its discriminating power. The IDSA guidelines make a distinction between "expert" clinical criteria derived from clinical trials and the MASCC index: patients with neutropenia expected to last ≥ 7 days, those who are clinically unstable or with significant comorbidities, and those with some underlying cancers or high-intensity chemotherapy are all "high risk" and the recommendation is hospitalization and IV antibiotics.[13] Similarly, the ASCO guidelines present a list of conditions that makes the outpatients high risk independently of their MASCC score.[17] Needless to say, even if the conditions proposed by the guideline developers seem to be perfectly sound, until they are validated prospectively, they must be considered expert opinion.

Fever and neutropenia syndromes[24]

First episode of fever

Definition. Fever is a single oral temperature $\geq 38.3°C$ or sustained temperature $\geq 38°C$ for 1 hour.[13] Slightly different definitions may have been used in different trials over the years. Neutropenia is defined as an absolute neutrophil count of < 500 cells/mm^3 or that is expected to decrease to < 500 cells/mm^3 during the next 48 hours.[13]

Background. Most, if not all, episodes of fever during neutropenia are supposed to be infectious in origin. Infection, however, is documented only in a minority of cases. The percentages are roughly as follows: fever of unknown origin 50%-60%; microbiologically documented infection (frequently bacteremia) 10%-20%; clinically documented infection (eg, typhlitis or cellulitis without any pathogen being isolated) 20%-30%.[13] Much higher rates of bacteremia were documented before the current practice of early initiation of empirical antibiotics.[42]

Recommendations from the guidelines. For high-risk patients, all of the guidelines recommend starting monotherapy with a beta-lactam with activity against *Pseudomonas aeruginosa* (piperacillin-tazobactam, imipenem, meropenem, cefepime, ceftazidime) and add the important caveat that some form of combination therapy should be chosen in patients who are clinically unstable and when there is suspicion (or high risk) of infection caused by resistant gram-negative (a second gram-negative agent should be added) or gram-positive bacteria (vancomycn or linezolid should be added). All the guidelines recommend not including vancomycin routinely in the initial regimen and not adding it empirically for persistent fever. The details regarding when to actually use vancomycin are more variable. The IDSA strongly recommends adding vancomycin in cases of hemodynamic instability, pneumonia, clinically evident catheter-related infection, skin and soft tissue infections, severe mucositis when fluoroquinolone prophylaxis has been used and ceftazidime is used empirically, and known colonization with methicillin-resistant *Staphylococcus aureus*, although the quality of the evidence is low.[13]

For patients who are considered "low risk" and eligible for outpatient management, the regimen of choice is the combination of fluoroquinolone and amoxicillin-clavulanic acid (or clindamycin for penicillin-allergic patients) as long as no fluoroquinolone prophylaxis was used, the patient tolerates oral medication, and the rate of resistance to fluoroquinolones is less than 20%.[17] It is likely that moxifloxacin monotherapy will be supported in future editions of the guidelines.[43] When a fluoroquinolone cannot be used, a broad-spectrum beta-lactam active against *Pseudomonas* and suitable for outpatient use should be used.

Highlights and limitations of the evidence. The first episode of fever during neutropenia has been studied extensively and recommendations for initial management get the strongest recommendation with the highest quality evidence in all the guidelines (Table 4).

Two systematic reviews and a meta-analysis support the recommendation of the intravenous antipseudomonal beta-lactam used as monotherapy.[46,47] The use of combination therapy (typically beta-lactam plus aminoglycoside) has shown to be associated with higher toxicity and no superior outcome. Interestingly, however, an Australian survey in 2009 showed that almost half the doctors would choose a combination regimen when presented with a low-risk inpatient with fever and neutropenia,[48] suggesting that physicians may be more concerned with the possibility of failure of the antibiotic regimen than with toxicity. Regarding the choice of beta-lactam, no single agent is clearly superior, although piperacillin-tazobactam compares favorably in terms of equivalent efficacy and less toxicity (as long as the frequency of resistant bacteria is low).[10,49] Concerns regarding increased overall mortality with cefepime have been largely dismissed by the IDSA[13] and ASCO[17] after a reanalysis of the cefepime data by the FDA, although the authors of the original meta-analysis remain unconvinced.[49]

A significant limitation of the evidence is that randomized trials of antibiotics in neutropenic patients have been performed since the 1980s. Some of the data are more than 20 years old and their applicability in the current microbiological milieu has been questioned. The global epidemiology (eg, increasing frequency of gram-positive isolates) has changed, and the local epidemiology at some centers: (eg, high prevalence of multiresistant pathogens) may make the evidence on which the guidelines are based irrelevant. For example, the newest version of the IDSA guidelines have taken ceftazidime out of the list of "preferred" single agents based on current susceptibility patterns.[13] Similar concerns are raised by the NCCN.[45] As the guideline-endorsed practice of fluoroquinolone prophylaxis becomes more common, it is possible that the relative efficacy of monotherapy versus combination therapy will again be questioned. There have also been changes in the population of neutropenic patients and their infectious diseases risks. Stem cell transplantation, immunomodulators, and biological agents may all increase the immune compromise. It is reasonable to wonder whether the information acquired in the course of leukemia trials in the 1990s is the best source of evidence to decide on the management of the prolonged neutropenia experienced by the recipient of a cord blood transplantation.[51]

Table 4. Evidence-based recommendations for FN syndromes

Fever and neutropenia syndrome	Treatment recommendation from guidelines	Grading according to guidelines				
		ESMO[14]	IDSA[13]	Australian[44]	NCCN[45]*	IPNP[20]†
First fever in patients at high risk of complications	Monotherapy with intravenous anti-*Pseudomonas* beta-lactam	I, A	A-I	A	1 2B for ceftazidime	1A
	Avoid routine use of vancomycin	NA	A-I	A	2A	1A
	In special circumstances diverse combinations are recommended	NA	B-III or C-III	D	2A	1B
Persistent fever in patients at high risk for invasive fungal infections	Add empirical antifungal coverage	II, A	A-I	NA	2A	1C†
	Preemptive approach (withhold antifungals if no investigations negative)	NA	B-II	NA	NA	NA†
Recurrent fever	Not addressed by the guidelines separately from persistent fever					
	Expert opinion recommends changing the antibacterial and antifungal regimen and looking for superinfection, including viral					
Engraftment fever	Not addressed by the guidelines					
	Expert opinion recommends: look for preexistent focus, rule out superinfection, consider engraftment syndrome					

The ASCO Guidelines[17] are not included because they refer specifically to outpatient management and do not offer grading of the recommendations. The Australian guidelines do not specify grading of recommendation for the empirical addition of antifungal agents during FN, but they have published detailed pathogen-specific antifungal management advice.[26]

IPN indicates International Pediatric Fever and Neutropenia Guideline Panel for the Management of Fever and Neutropenia in Children with Cancer and/or Undergoing Hematopoietic Stem Cell Transplantation; and NA, not addressed. For definitions of the fever and neutropenia syndromes, see text.

*The NCCN guidelines address only prophylaxis; the recommendations in this table are from the online version accessed May 3, 2013 at www.nccn.org.

†The pediatric panel different grading of these recommendations reflects the lack of pediatric-specific data.

Persistent fever

Definition. An episode of fever during neutropenia that does not resolve after 5 days of broad-spectrum antibacterial agents.

Background. IFI was identified as a common cause of this syndrome in the 1970s.[52] Two randomized trials established the benefit of adding amphotericin B (one after 7, the other after 4 days of persistent fever) compared with continuing the antibacterial regimen in terms of preventing fungal infection, although they did not have power to demonstrate a survival advantage.[53,54] These 2 studies took place before systemic antifungal prophylaxis with fluconazole was used and approximately half the fungal infections documented were caused by *Candida*. However, the initiation of antifungal therapy after 4-7 days of fever became standard of care, and most RCTs have focused on the choice of drug (liposomal amphotericin B,[55] voriconazole,[56] caspofungin[57,58]). To reduce the perceived unnecessary use of empirical antifungal therapy, with its attendant toxicity and cost, an alternative approach to empirical antifungal therapy has been proposed and called preemptive antifungal therapy.[59] The goal is to use the currently available diagnostic modalities (CT, serum galactomannan, and/or b-D-glucan) to postpone starting antifungal therapy until IFI is more likely. By design, this approach means that patients receiving "preemptive" antifungals are more likely to actually have an IFI than patients receiving "empirical" therapy by the time the antifungal agent is started.[60]

Recommendations from the guidelines. All guidelines recommend thinking about fungal infection as a cause of persistent fever and advise some kind of diagnostic workup (including chest ± sinus CT) directed at identifying or ruling out fungal infection in patients who are at high risk for it (notice that the high risk for fungal infection is NOT the same as the "high risk" identified by a MASCC score < 21). The IDSA considers patients with neutropenia expected to last ≥ 7 days "high risk" and advises to "consider empirical antifungal therapy" for them after 4-7 days of fever.[13] The IDSA also endorses the use of the "preemptive" antifungal therapy strategy for selected patients.[13] The guidelines generally agree that, if it is decided to initiate empirical antifungal therapy for persistent fever, caspofungin or liposomal amphotericin B are the drugs of choice. They differ somewhat in their assessment of the quality of the evidence.

Highlights and limitations of the evidence. The true frequency of IFI as a cause of persistent fever varies with the clinical setting, but it seems likely that most patients with persistent fever do not have fungal infection. In the 2 original studies (performed before fluconazole prophylaxis was available), the documented fungal infections in the groups randomized to NOT receiving amphotericin were 6 of 16 patients.[53] and 6 of 64 patients.[54] Subsequent trials have found even lower rates ($< 10\%$), but this may be an underestimation given that all the patients received antifungal therapy after 96 hours.[55-58] Therefore, the superiority of any agent is going to be based on relatively few true cases. Because it is unknown how frequent breakthrough fungal infection truly is in neutropenic patients who are receiving systemic antifungal prophylaxis, it is impossible to be certain whether the empirical substitution or addition of another antifungal agent (and which one) is the best possible strategy. Regarding the preemptive approach, the few studies published so far seem promising.[60,61]

Recurrent or recrudescent fever

Definition. Recurrent fever refers to a new episode of fever that takes place after the initial episode has resolved with antimicrobial therapy when the patient remains neutropenic ("recrudescent neutropenic fever syndrome"[24]).

Background. Recurrent or recrudescent fever is a relatively common occurrence in clinical practice that has not been adequately studied, presumably due to the logistical difficulties associated with designing a RCT for a very heterogeneous patient population. The one systematic investigation of this syndrome analyzed data on 836 neutropenic patients who had had a first fever that responded to antimicrobials and then had remained afebrile for 4 days.[62] A total of 129 (15%, confidence interval 13%-18%) of the 836 patients developed a second episode of fever or infection. There were 40 bacterial/fungal microbiologically documented infections (15 of

them fungal), 11 viral infections, 39 clinically documented infections, and 39 cases of fever of unknown origin. Other small series support the notion that both bacterial and fungal infections are common causes of this syndrome.[63] The relative likelihood of one versus the other probably varies with the clinical scenario.

Recommendations from the guidelines. The various guidelines do not address this clinical circumstance separately from persistent fever. They usually include recommendations for "persistent or recurrent fever" (ie, diagnostic workup for IFI and addition/modification of the antifungal regimen), but these 2 may be clinically and etiologically different situations. Expert advice includes modifying antibacterial and antifungal therapy to cover potential "holes" in the coverage.[24]

Highlights and limitations of the evidence. There is no good-quality evidence regarding the management of recrudescent fever.

Engraftment fever (myeloid reconstitution syndrome)

Definition. Bow defined this syndrome as "new onset or worsening of clinically or radiologically appreciable foci, consistent with an inflammatory and/or infectious process, in temporal relationship to neutrophil recovery after aplasia."[24]

Background. The 3 likely causes of this situation are superinfection, immune reconstitution syndrome, and engraftment syndrome. Apparent worsening of pulmonary aspergillosis has been described at the time of neutrophil recovery,[64] so it has been postulated that this situation represents a variation of the "immune reconstitution syndrome" well characterized in AIDS patients after starting effective antiviral therapy. However, fever at this time may also represent superinfection (like the recurrent/recrudescent fever) or, particularly in the setting of stem cell transplantation, a manifestation of engraftment syndrome, a cluster of signs and symptoms including fever, rash, and pulmonary infiltrates originally described after autologous stem cell transplantation but also seen with variable frequency after allogeneic transplantation.[65]

Recommendations from the guidelines. This syndrome is not addressed by any of the guidelines.

Limitations and highlights of the evidence. There is no good evidence regarding the diagnosis or management of engraftment syndrome, which is usually treated with corticosteroids when severe. Diagnostic criteria have been proposed, but not externally validated. A basic point is that engraftment syndrome is a diagnosis of exclusion.

Summary and conclusion

Clinical research on FN over the last 4 decades has generated an impressive body of evidence that allows strong recommendations for the 2 more stereotypical clinical situations: initial fever and persistent fever. However, as the course of the neutropenic episode extends over time and the complexity of the patient increases, there is an increase in uncertainty and obtaining generalizable evidence becomes more difficult. For example, many patients with persistent fever may already be receiving antifungal agents with activity against *Aspergillus*. What is the best therapeutic strategy in this situation? Similar unanswered questions include the best management of fever in patients who are receiving levofloxacin prophylaxis, the approach to recrudescent (as opposed to persistent) fever, the long-term consequences of the utilization of particular antimicrobial strategies, and the management of patients known to be colonized with resistant pathogens. Finally, the variety of recommendations published by different professional organizations may be confusing. Too many guidelines addressing the issues slightly differently require the reader to become familiar with different grading systems. This issue has been noticed before and the solution is not obvious,[66] but the lack of homogeneity in how practice guidelines are formulated has the potential to generate confusion at best and disregard at worst. It seems desirable to develop a common language that will help the individual physician interpret the guidelines appropriately and for this the GRADE system could be a strategy worth considering.

Disclosures

Conflict-of-interest disclosure: The author declares no competing financial interests. Off-label drug use: Ceftazidime, meropenem, piperacillin-tazobactam, and voriconazole are not FDA approved for fever and neutropenia. Their use in fever and neutropenia is discussed.

Correspondence

Juan Gea-Banacloche, MD, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Building 10, Hatfield CRC, Room 3-3130, Bethesda, MD 20892-1203; Phone: 301-435-2326; Fax: 301-480-4354; e-mail: banacloj@mail.nih.gov.

References

1. Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996;312(7023):71-72.
2. Group OLOEW. The Oxford 2011 levels of evidence. Oxford centre for evidence-based medicine. http://www.cebm.net/mod_product/design/files/CEBM-Levels-of-Evidence-2.1.pdf. Accessed August 26, 2013.
3. Howick J, Chalmers I, Glasziou P, Greenhalgh T, Heneghan C, et al. The 2011 Oxford CEBM levels of evidence: Introductory document. http://www.cebm.net/index.aspx?o=5653. Accessed August 26, 2013.
4. Zinner SH. Changing epidemiology of infections in patients with neutropenia and cancer: emphasis on gram-positive and resistant bacteria. *Clin Infect Dis*. 1999;29(3):490-494.
5. Han XY, Kamana M, Rolston KV. Viridans streptococci isolated by culture from blood of cancer patients: clinical and microbiologic analysis of 50 cases. *J Clin Microbiol*. 2006;44(1):160-165.
6. Elting LS, Rubenstein EB, Rolston KV, Bodey GP. Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. *Clin Infect Dis*. 1997;25(2):247-259.
7. Rubin M, Hathorn JW, Marshall D, Gress J, Steinberg SM, Pizzo PA. Gram-positive infections and the use of vancomycin in 550 episodes of fever and neutropenia. *Ann Intern Med*. 1988;108(1):30-35.
8. Karp JE, Dick JD, Angelopulos C, Charache P, Green L, et al. Empiric use of vancomycin during prolonged treatment-induced granulocytopenia. Randomized, double-blind, placebo-controlled clinical trial in patients with acute leukemia. *Am J Med*. 1986;81(2):237-242.
9. Cometta A, Kern WV, De Bock R, Paesmans M, Vandenbergh M, et al. Vancomycin versus placebo for treating persistent fever in patients with neutropenic cancer receiving piperacillin-tazobactam monotherapy. *Clin Infect Dis*. 2003;37(3):382-389.

10. Paul M, Borok S, Fraser A, Vidal L, Leibovici L. Empirical antibiotics against Gram-positive infections for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother*. 2005;55(4):436-444.
11. Vardakas KZ, Samonis G, Chrysanthopoulou SA, Bliziotis IA, Falagas ME. Role of glycopeptides as part of initial empirical treatment of febrile neutropenic patients: a meta-analysis of randomised controlled trials. *Lancet Infect Dis*. 2005;5(7):431-439.
12. Hughes WT, Armstrong D, Bodey GP, Feld R, Mandell GL, et al. From the Infectious Diseases Society of America. Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. J Infect Dis. 1990;161(3):381-396.
13. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, 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(4):e56-e93.
14. de Naurois J, Novitzky-Basso I, Gill MJ, Marti FM, Cullen MH, et al. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2010;21(suppl 5):v252-v256.
15. 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(4):e56-e93.
16. Baden LR, Bensinger W, Angarone M, Casper C, Dubberke ER, et al. Prevention and treatment of cancer-related infections. *J Natl Compr Canc Netw*. 2012;10(11):1412-1445.
17. Flowers CR, Seidenfeld J, Bow EJ, Karten C, Gleason C, 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(6):794-810.
18. Marti FM, Cullen MH, Roila F; ESMO Guidelines Working Group. Management of febrile neutropenia: ESMO clinical recommendations. *Ann Oncol*. 2009;20(suppl 4):166-169.
19. Lingaratnam S, Slavin MA, Koczwara B, Seymour JF, Szer J, et al. Introduction to the Australian consensus guidelines for the management of neutropenic fever in adult cancer patients, 2010/2011. Australian Consensus Guidelines 2011 Steering Committee. *Intern Med J*. 2011;41(1b):75-81.
20. Lehrnbecher T, Phillips R, Alexander S, et al; International Pediatric Fever and Neutropenia Guideline Panel. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. *J Clin Oncol*. 2012;30(35):4427-4438.
21. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, et al. Going from evidence to recommendations. *BMJ*. 2008; 336(7652):1049-1051.
22. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is "quality of evidence" and why is it important to clinicians? *BMJ*. 2008;336(7651):995-998.
23. Slavin MA, Lingaratnam S, Mileshkin L, Booth DL, Cain MJ, et al. Use of antibacterial prophylaxis for patients with neutropenia. Australian Consensus Guidelines 2011 Steering Committee. *Intern Med J*. 2011;41(1b):102-109.
24. Bow EJ. Neutropenic fever syndromes in patients undergoing cytotoxic therapy for acute leukemia and myelodysplastic syndromes. *Semin Hematol*. 2009;46(3):259-268.
25. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007(4);356:348-359.
26. Slavin A, Heath H, Thursky A, et al. Antifungal prophylaxis in adult stem cell transplantation and haematological malignancy. *Int Med J*. 2008;38(6b):468-476.
27. van de Wetering MD, de Witte MA, Kremer LC, Offringa M, Scholten RJ, Caron HN. Efficacy of oral prophylactic antibiotics in neutropenic afebrile oncology patients: a systematic review of randomised controlled trials. *Eur J Cancer*. 2005; 41(10):1372-1382.
28. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. *Ann Intern Med*. 2005;142(12 Pt 1):979-995.
29. Gafter-Gvili A, Fraser A, Paul M, Vidal L, Lawrie TA, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane Database Syst Rev*. 2012;1:CD004386.
30. Robenshtok E, Gafter-Gvili A, Goldberg E, Weinberger M, Yeshurun M, et al. Antifungal prophylaxis in cancer patients after chemotherapy or hematopoietic stem-cell transplantation: systematic review and meta-analysis. *J Clin Oncol*. 2007;25(34): 5471-5489.
31. Bucaneve G, Micozzi A, Menichetti F, Martino P, Dionisi MS, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *N Engl J Med*. 2005;353(10):977-987.
32. Goodman JL, Winston DJ, Greenfield RA, Chandrasekar PH, Fox B, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med*. 1992;326(13):845-851.
33. Slavin MA, Osborne B, Adams R, Levenstein MJ, Schoch HG, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation–a prospective, randomized, double-blind study. *J Infect Dis*. 1995;171(6):1545-1552.
34. van Burik JA, Ratanatharathorn V, Stepan DE, Miller CB, Lipton JH, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis*. 2004;39(10):1407-1416.
35. Winston DJ, Maziarz RT, Chandrasekar PH, Lazarus HM, Goldman M, et al. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. A multicenter, randomized trial. *Ann Intern Med*. 2003;138(9):705-713.
36. Marr KA, Crippa F, Leisenring W, Hoyle M, Boeckh M, et al. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. *Blood.* 2004;103(4):1527-1533.
37. Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med*. 2007;356(4):335-347.
38. Wingard JR, Carter SL, Walsh TJ, Kurtzberg J, Small TN, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood.* 2010;116(24):5111-5118.
39. Klastersky J, Paesmans M. The Multinational Association for Supportive Care in Cancer (MASCC) risk index score: 10 years of use for identifying low-risk febrile neutropenic cancer patients. *Support Care Cancer*. 2013;21(5):1487-1495.
40. Worth LJ, Lingaratnam S, Taylor A, Hayward AM, Morrissey S, et al. Use of risk stratification to guide ambulatory management of neutropenic fever. Australian Consensus Guidelines 2011 Steering Committee. *Intern Med J*. 2011;41(1b):82-89.
41. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, 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;18:3038-3051.
42. Schimpff S, Satterlee W, Young VM, Serpick A. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. *N Engl J Med*. 1971;284(19): 1061-1065.
43. Kern WV, Marchetti O, Drgona L, Akan H, Aoun M, et al. Oral antibiotics for fever in low-risk neutropenic patients with cancer: a double-blind, randomized, multicenter trial comparing single daily moxifloxacin with twice daily ciprofloxacin plus amoxicillin/clavulanic acid combination therapy–EORTC infectious diseases group trial XV. *J Clin Oncol*. 2013;31(9): 1149-1156.
44. Tam CS, O'Reilly M, Andresen D, Lingaratnam S, Kelly A, et al. Use of empiric antimicrobial therapy in neutropenic fever. Australian Consensus Guidelines 2011 Steering Committee. *Intern Med J*. 2011;41(1b):90-101.
45. National Comprehensive Cancer Network (NCCN). Prevention and Treatment of Cancer-Related Infections V 1.2013. http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf. Accessed May 5, 2013.
46. Furno P, Bucaneve G, Del Favero A. Monotherapy or aminoglycoside-containing combinations for empirical antibiotic treatment of febrile neutropenic patients: a meta-analysis. *Lancet Infect Dis*. 2002;2(4):231-242.
47. Paul M, Soares-Weiser K, Leibovici L. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. *BMJ*. 2003;326(7399):1111.
48. Lingaratnam S, Slavin MA, Mileshkin L, Solomon B, Burbury K, et al. An Australian survey of clinical practices in management of neutropenic fever in adult cancer patients 2009. *Intern Med J*. 2011;41(1b):110-120.
49. Paul M, Yahav D, Bivas A, Fraser A, Leibovici L, Paul M. Anti-pseudomonal beta-lactams for the initial, empirical, treatment of febrile neutropenia: comparison of beta-lactams. *Cochrane Database Syst Rev*. 2010;11:CD005197.
50. Drug safety information for healthcare professionals >information for healthcare professionals: Cefepime (marketed as maxipime); available from http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm167254.htm. Accessed April 28, 2013.
51. Pulsipher MA. Pediatric-Specific Guidelines for Fever and Neutropenia: A Catalyst for Improving Care and Focusing Research. *J Clin Oncol*. 2012;30(35):4292-4293.
52. Stein RS, Kayser J, Flexner JM. Clinical value of empirical amphotericin B in patients with acute myelogenous leukemia. *Cancer*. 1982;50(11):2247-2251.
53. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. *Am J Med*. 1982;72(1): 101-111.
54. Empiric antifungal therapy in febrile granulocytopenic patients. EORTC International Antimicrobial Therapy Cooperative Group. *Am J Med*. 1989;86(6 Pt 1):668-672.
55. Walsh TJ, Finberg RW, Arndt C, Hiemenz J, Schwartz C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *N Engl J Med*. 1999;340(10):764-771.
56. Walsh TJ, Teppler H, Donowitz GR, Maertens JA, Baden LR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med*. 2004;351(14):1391-1402.
57. Maertens JA, Madero L, Reilly AF, Lehrnbecher T, Groll AH, et al. A randomized, double-blind, multicenter study of caspofungin versus liposomal amphotericin B for empiric antifungal therapy in pediatric patients with persistent fever and neutropenia. *Pediatr Infect Dis J*. 2010;29(5):415-420.
58. Walsh TJ, Pappas P, Winston DJ, Lazarus HM, Petersen F, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med*. 2002;346(4):225-234.
59. Segal BH, Almyroudis NG, Battiwalla M, Herbrecht R, Perfect JR, et al. Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. *Clin Infect Dis*. 2007;44(3):402-409.
60. Cordonnier C, Pautas C, Maury S, Vekhoff A, Farhat H, et al. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. *Clin Infect Dis*. 2009;48(8):1042-1051.
61. Tan BH, Low JG, Chlebicka NL, Kurup A, Cheah FK, et al. Galactomannan-guided preemptive vs. empirical antifungals in the persistently febrile neutropenic patient: a prospective randomized study. Int *J Infect Dis*. 2011;15(5):e350-e356.
62. Akova M, Paesmans M, Calandra T, Viscoli C. A European Organization for Research and Treatment of Cancer–International Antimicrobial Therapy Group study of secondary infections in febrile, neutropenic patients with cancer. *Clin Infect Dis*. 2005;40(2):239-245.
63. Cornelissen JJ, Rozenberg-Arska M, Dekker AW. Discontinuation of intravenous antibiotic therapy during persistent neutropenia in patients receiving prophylaxis with oral ciprofloxacin. *Clin Infect Dis*. 1995;21(5):1300-1302.
64. Miceli MH, Maertens J, Buvé K, Grazziutti M, Woods G, et al. Immune reconstitution inflammatory syndrome in cancer patients with pulmonary aspergillosis recovering from neutropenia: Proof of principle, description, and clinical and research implications. *Cancer*. 2007;110(1):112-120.
65. Spitzer TR. Engraftment syndrome following hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2001;27(9): 893-898.
66. Pentheroudakis G, Stahel R, Hansen H, Pavlidis N. Heterogeneity in cancer guidelines: should we eradicate or tolerate? *Ann Oncol*. 2008;19(12):2067-2078.