Utility of the Multinational Association for Supportive Care in Cancer (MASCC) Risk Index Score as a Criterion for Nonadmission in Febrile Neutropenic Patients with Solid Tumors

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ABSTRACT

Objectives: This retrospective study was initiated in febrile neutropenic inpatients with solid tumors in 4 community hospitals, to discover how the Multinational Association for Supportive Care in Cancer (MASCC) risk index score (RIS) of 21 or greater correlated with complications occurring in 198 episodes: whether it could help determine which patients not to admit, the savings of not admitting patients without complications, and whether an algorithm could facilitate management of those not admitted.

Methods: Febrile neutropenic episodes in patients with solid tumors were identified electronically between October 1, 2008, and November 15, 2010. Electronic charts were reviewed manually for inclusion criteria and data extraction. Episodes were stratified by an MASCC RIS below 21 or 21 or greater. Complications were correlated with the index.

Results: Inclusion criteria were met in 198 episodes. Sensitivity, specificity, and positive and negative predictive values of the MASCC RIS vs complications were 94%, 29.6%, 57.7%, and 82.9%, respectively. In episodes with an RIS 21 or greater, 42.3% had complications, misclassifying to low risk 69 episodes with complications. "Unable to eat" correlated with complications in 84% of episodes. In 3 patients stratified to no complication, a complication developed 24 hours after admission.

Conclusions: An MASCC RIS of 21 or greater could not be used as a criterion for "no complication/do not admit." Inability to eat should be an admission criterion. Savings of approximately $1 million per 100 uncomplicated admissions could be realized if appropriate criteria for nonadmission could be devised. An algorithm to facilitate outpatient management is suggested.

INTRODUCTION

Treatment of malignancies is routine in community hospitals. Chemotherapy, one of the common forms of treatment, frequently results in neutropenic fever. Guidelines for the management of febrile neutropenia include antimicrobial therapy and, for patients with solid tumors, antecedent granulocyte colony-stimulating factor.[1,2] Before these guidelines, virtually all febrile neutropenic patients were hospitalized. However, the depth and duration of neutropenia in patients receiving chemotherapy for hematologic and lymphoproliferative neoplasms is more profound than that occurring following chemotherapy for patients with solid tumors; thus, complications following chemotherapy for solid tumors are less frequent. Some investigators postulated that patients not experiencing complications would not need hospitalization, and thus, they have striven to identify these noncomplicated cases prospectively and manage them on an outpatient basis, resulting in substantial savings.

To this end, a stratification tool, the Multinational Association for Supportive Care in Cancer (MASCC) risk index score (RIS) was developed to predict the risk of serious complications. These risk criteria are listed in the Sidebar: Klastersky Criteria.[3]

There are 2 important features to note. First, only 2 of the 10 Klastersky criteria are objective, which introduces a problem in the methods. There is no objective definition of these criteria: confusion or altered mental state, such as the Glasgow Coma Scale; congestive heart failure requiring treatment, such as pulmonary edema with a Pao_2 below 60 mmHg; bleeding severe enough to require transfusion, such as a hemoglobin level below 7 g/dL; arrhythmia or electrocardiographic changes requiring treatment, such as systolic blood pressure (BP) below 90 mmHg; or renal failure requiring treatment, such as a creatinine level above 4 mg/dL. Furthermore, the last criterion is completely subjective: "other complications judged serious and clinically significant by the investigator." Second, an exclusion to this criterion was included as a footnote: "Viral or fungal, microbiologically documented primary infection during the febrile episode, without any described complication and resolving under therapy, was considered a part of the infectious process and was not considered a serious complication."[3p3040]

Table 1 lists the components of the MASCC RIS.[3] (Note that only 4 of the 7 criteria are objective. Burden of illness, chronic obstructive pulmonary disease (COPD), and "no dehydration" are not objective criteria.) An MASCC RIS of 21 or above equals a low risk of complications; an MASCC RIS below 21 equals a high risk of complications.

Using an MASCC RIS of 21 or greater as low risk, only 6% of a validation group (n = 551) experienced serious complications compared with 39% who had a score below 21. Validation of this index

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Table 1. Components of the Multinational Association for Supportive Care in Cancer Index[a]

Clinical characteristic	Score[b]
Burden of illness (1 of the 3 options only):	
No or mild symptoms	5
Moderate symptoms	3
Severe symptoms	0
No hypotension (systolic BP > 90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or no prior fungal infection in patient with hematologic neoplasm	4
No dehydration (hydration with IV fluids not required)	3
Outpatient at onset of fever	3
Age < 60 years	2

[a] Burden of illness, no chronic obstructive pulmonary disease, and no dehydration are not objective criteria.
[b] Maximum score: 26 (5 + 5 + 4 + 4 + 3 + 3 + 2). Low risk for complication = score ≥ 21; high risk for complication = score < 21.
BP = blood pressure; IV = intravenous.

has been declared in publications from academic (university) medical centers. However, the definitions in all these studies (eg, burden of illness, COPD, or dehydration) were not consistently provided, and the mix of patients with solid vs hematologic and lymphoproliferative neoplasms was not the same, raising the question of whether the results are comparable.[4-8]

The current retrospective study of inpatients from 4 community hospitals was devised to answer the following questions.

1. How many times were the named items in the Klastersky criteria used as reasons for admission to the hospital by the general internists admitting patients? (As noted earlier, when a febrile neutropenic patient with an infection makes initial contact with a health care practitioner for that febrile episode, the Klastersky criteria do not consider that infection a complication, and, in addition, there are unnamed complications in the Klastersky criteria.)
2. Are there additional complications, not listed by name in the Klastersky criteria, that a physician might consider important in the nonadmission decision?
3. Would the course of patients stratified to the low-risk category (MASCC RIS ≥ 21) be without serious complications and, thus, be able to be managed as outpatients (ie, stratified to "Do not admit")?
4. If inpatients with an MASCC RIS of 21 or higher did experience complications, what were they and on what day of hospitalization did they occur?
5. If the patients with an MASCC RIS of 21 or above were not admitted and experienced complications, what management algorithm could be proposed to identify these complications early?
6. What savings would be realized if all the patients without serious complications were not admitted to the hospital?

Klastersky criteria[1]

Systolic blood pressure (BP) < 90 mmHg or need for [vaso]pressor support to maintain BP

Arterial oxygen pressure (Pao_2) ≤ 60 mmHg while breathing room air or need for mechanical ventilation

Intensive care unit admission

Disseminated intravascular coagulation

Confusion or altered mental state

Congestive cardiac failure seen on chest x-ray and requiring treatment

Bleeding severe enough to require transfusion

Arrhythmia or ECG [electrocardiographic] changes requiring treatment

Renal failure requiring investigation and/or treatment with IV [intravenous] fluids, dialysis, or any other intervention

Other complications judged serious and clinically significant by the investigator

1. 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 Aug;18(16):3038-51.

METHODS

Patient Selection

Management of febrile neutropenic patients, at the time of this study and at the medical centers listed, was admission to the hospital, evaluation in the usual manner with appropriate laboratory tests and imaging studies, administration of granulocyte colony-stimulating factor (89%), and antimicrobial agents. All but 10 patients received acceptable antimicrobial regimens. Charts were retrospectively reviewed for the following inclusion criteria: adult inpatients with solid tumors who became neutropenic (absolute neutrophil count < 500/μL, except for 2 that were 600/uL) after chemotherapy, who were given an admission or discharge diagnosis of neutropenic fever, who had documented fever by self-report or on admission, and who received antimicrobial therapy for neutropenic fever. Patients younger than 18 years and those whose admissions lasted less than 24 hours were excluded. All inpatient electronic medical records of patients admitted to 4 Kaiser Permanente (KP) hospitals in California were searched for drug-induced neutropenia (International Classification of Diseases, Ninth Revision, code 288.0) and fever-presenting conditions classified elsewhere (code 780.61). The hospitals were San Diego Medical Center (admissions from October 1, 2008, to November 15, 2010); Irvine Medical Center and Anaheim Medical Center (Orange County; admissions from October 1, 2008, to April 30, 2010); and Woodland Hills Medical Center (admissions from October 1, 2008, to April 30, 2010). The charts of these patient episodes were sequentially and manually screened for inclusion criteria and reviewed in detail. If inclusion criteria were met, data were extracted.

Data included: age, sex, admission date, discharge date, death date, the type of solid tumor, whether it was metastatic beyond local nodes, admitting physician's reason for admission, length of stay (LOS), reason for extended hospital stay, intensive care unit care, comfort care, other diagnoses in the problem list which might be considered immunocompromising,

smoking status, diagnosis of COPD, occurrence of fever associated with neutropenia, days to temperature ≤ 37.5 and ≤ 38 C, an ANC < 500 cells/uL, return of ANC to greater than 500 cells/uL, duration of neutropenia, death, reception of filgrastim before and subsequently after admission, gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain, "unable to eat,"), serum biochemical tests (creatinine > 2 mg/dL, potassium < 3 mEq/L, sodium of < 130 mEq/L, phosphorus of < 2.7 mg/dL), density/intensity of chemotherapy, types of infections, positive bacterial cultures, microorganisms isolated, antimicrobial agents prescribed when outpatient and inpatient, results of pertinent imaging studies, MASCC RIS components, and medical complications listed in the Klastersky criteria.

All febrile neutropenic patient episodes meeting inclusion criteria were divided into 2 groups on the basis of complications: Group 1, no complication (equivalent to "do not admit"), or Group 2, complication (equivalent to "admit"). Group 1 (n = 100) had only fever and neutropenia, had none of the medical complications (Table 2) on admission or within 24 hours of admission, and were able to eat. Group 2 (n = 98) had 1 or more of the complications listed in Table 2 at admission or within 24 hours of admission. There were 3 patients in Group 1 in whom complications developed 24 hours after admission, which if they had been present on presentation would have classified each patient into Group 2 initially. Each patient episode was assigned to an MASCC RIS of 21 or greater or below 21, and these scores were correlated with the no complication and complication groups (Figure 1). The KP Southern California institutional review board approved the study.

Medical Centers

In 2012, beds and discharges per month were as follows: San Diego, 392 beds and 32,491 discharges; Orange County, 350 beds (2 hospitals), 28,564 discharges; and Woodland Hills, 262 beds and 13,741 discharges. All 4 hospitals fall into the tertiary care category, providing a full range of basic and sophisticated diagnostic and treatment services, including many specialized services.

Statistical Analysis

A sample size of 200 episodes was chosen as the basis for another study, not yet published, from which this analysis was done. Two episodes did not meet criteria, leaving 198 episodes. Standard methods of calculating sensitivity, specificity, positive predictive value, and negative predictive value were used. The Wilcoxon rank sum test was used to compare for those who were unable to eat and for those who were able to eat.

RESULTS

Patient characteristics are shown in Table 3.

Klastersky Criteria versus Complications

Table 2 lists the components of the Klastersky criteria; complications, which includes the reasons for admission and subsequent complications; the MASCC RIS; and LOS. There are 69 patients in Table 2 who had an MASCC RIS of 21 or above and had reasons for admission and/or complications. Only 20 patients of the 69 had complications named in the Klastersky criteria as a reason for admission. If the Klastersky criteria were to be applied, the other 49 reasons for admission would have to be assumed to fall into the last Klastersky category, "other complications judged serious or clinically significant by the investigator." Thirty-eight patients were unable to eat, 22 had identified infections, 21 could be considered to have mucositis, and 5 were found to have typhlitis.

Risk Index Score versus Complications

The sensitivity of the MASCC RIS was 94% (94 of 100 episodes) with a 95% confidence interval (CI) of 87.4% to 97.8%, and specificity was 29.6% (29/98; 95% CI = 20.8% to 39.7%). The positive predictive valve was 57.67% (94/163; 95% CI = 49.7% to 65.4%), and the negative predictive valve was 82.9% (29/35; 95% CI = 66.34% to 93.4%).

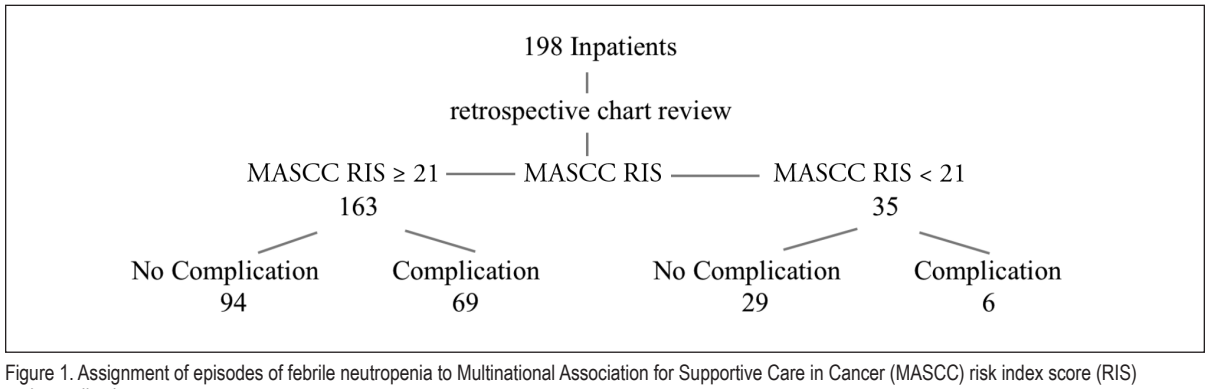

Figure 1. Assignment of episodes of febrile neutropenia to Multinational Association for Supportive Care in Cancer (MASCC) risk index score (RIS) and complications.[a]

[a] Three complications occurred after admission to the hospital in patients stratified to "no complication" and would have occurred on an outpatient basis if the patients had not been admitted.

Table 2. Klastersky criteria and complications in 69 patients with an MASCC RIS ≥ 21

Patient episode number	Klastersky criteria (named)	Klastersky criteria (Presumed to be in "Other complications judged serious and clinically significant by the investigator")	Reason for admission	Complication after admission	MASCC RIS	Length of stay, days
1	None	None	Cellulitis	None	21	3
2	SBP < 90 mmHg/need for vasopressors	Nausea, vomiting	SBP < 98 mmHg in a 90 year old	None	21	5
3	None	Unable to eat	Unable to eat, mucositis	None	21	5
4	None	Unable to eat, K 2.9 mEq/L	Unable to eat, K 2.9 mEq/L	Day 3: K 3 mEq/L	21	5
5	None	Unable to eat, nausea, diarrhea, abdominal pain	Unable to eat, nausea, diarrhea, abdominal pain	None	21	5
6	None	Unable to eat, nausea, vomiting, abdominal pain	Unable to eat, nausea, vomiting, abdominal pain	None	21	5
7	SBP < 90 mmHg/need for vasopressors	Diarrhea	Diarrhea/SBP < 90 mmHg	None	21	6
8	Arrhythmia, ECG changes	Unable to eat, nausea, vomiting	Unable to eat, nausea, vomiting, atrial flutter	None	21	6
9	None	Unable to eat, difficulty swallowing	Unable to eat, difficulty swallowing	None	21	6
10	None	Nausea, vomiting	Nausea, vomiting, bacteremia	None	21	7
11	None	Nausea, abdominal pain, K < 3 mEq/L	Nausea, abdominal pain, Typhlitis, K < 3 mEq/L	None	21	7
12	None	Unable to eat, diarrhea	Unable to eat, diarrhea	Stomatitis	21	7
13	None	Nausea, vomiting,	Nausea, Vomiting, positive blood culture	None	21	7
14	SBP < 90 mmHg/need for vasopressors, arrhythmia, ECG changes	Nausea, vomiting	Nausea, vomiting,	Low SBP within first 24 hours, SVT 3 days	21	8
15	SBP < 90 mmHg/need for vasopressors, bleeding requiring transfusion	Penile bleeding	Penile bleeding	Day 3: Na 124 mEq/L, Day 4: SBP < 90 mmHg, Day 7: fluid overload	21	9
16	Confusion, altered mental state	Unable to eat	Unable to eat, confusion, brain metastases	None	21	9
17	None	Unable to eat, nausea, diarrhea	Unable to eat, nausea, diarrhea, *C diff*	Day 2: K 2.6 mEq/L, Day 5: atrial fibrillation	21	11
18	None	Unable to eat, nausea, abdominal pain	Unable to eat, nausea, abdominal pain, mucositis	Day 5: K 2.3 mEq/L, required TPN, fever	21	13
19	None	Unable to eat, nausea, vomiting, diarrhea, lower GI bleeding, K 2.8 mEq/L, Mg 0.8 mEq/L	Unable to eat, nausea, vomiting, diarrhea, lower GI bleeding, K 2.8 mEq/L, Mg 0.8 mEq/L	None	21	15
20	SBP < 90 mmHg/need for vasopressors, ICU admission	Unable to eat, diarrhea, K 2.2 mEq/L	Unable to eat, diarrhea, mucositis, K 2.2 mEq/L	Day 4: hypotension, ICU, pneumonia, *C diff*, MI	21	18
21	None	Unable to eat, nausea, vomiting, diarrhea	Unable to eat, nausea, vomiting, diarrhea, *C diff*	None	21	19
22	Renal failure	Nausea, vomiting, abdominal pain	Nausea, vomiting, abdominal pain, ARF, bilateral hydronephrosis	Day 10: K 2.9 mEq/L, Day 14: colostomy	21	20
23	Confusion, altered mental state	Unable to eat	Unable to eat, cellulitis, mucositis	Day 4: confusion, carcinomatous meningitis	21	29
24	None	Unable to eat, abdominal pain, inpatient chemotherapy required,	Unable to eat, abdominal pain, SBO	Inpatient chemotherapy required, neutropenia, fever, bacteremia	21	31
25	None	Nausea, diarrhea, abdominal pain	Nausea, diarrhea, abdominal pain, typhlitis	None	22	4
26	None	None	Pleural effusion	None	22	6
27	None	K 2.2 mEq/L, Hb 6.6 g/dL	Bacteremia, K 2.2 mEq/L, decubitus débridement	Day 2: Hb 6.6 g/dL	22	6
28	None	Nausea, K 2.6 mEq/L	Nausea, K 2.6 mEq/L	None	22	6
29	SBP < 90 mmHg/need for vasopressors, confusion, altered mental state, or seizure	Nausea, vomiting, diarrhea, abdominal pain, K 2 mEq/L,	Nausea, vomiting, diarrhea, abdominal pain, altered mental state	Day 2: K 2 mEq/L, Day 3 SBP < 90 mmHg	22	8
30	SBP < 90 mmHg/need for vasopressors, Pao_2 < 60 mmHg/need for ventilation	Impending hip fracture	Impending hip fracture	Day 3: hypotension, Day 5: hypoxia, ARDS	22	8
31	None	Unable to eat, difficulty swallowing, Day 4: K 5.6 mEq/L, Day 9: K 6.1 mEq/L	Unable to eat, difficulty swallowing, mucositis	Day 4: K 5.6 mEq/L, Day 9: K 6.1 mEq/L	22	10
32	Pao_2 < 60 mmHg/need for ventilation,	Nausea, diarrhea	Nausea, diarrhea, dehydration, Cr 2.7 mg/dL	Day 3: hypoxia: Day 4: Cr 5.3 mg/dL, Day 6: colitis, hemodialysis	22	11
33	None	Na 126 mEq/L	Pneumonia, Na 126 mEq/L	None	23	3
34	None	Nausea, diarrhea, abdominal pain, Na 118	Nausea, diarrhea, abdominal pain, hypotension, Na 118 mEq/L	None	23	3

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Patient episode number	Klastersky criteria (named)	Klastersky criteria (Presumed to be in "Other complications judged serious and clinically significant by the investigator")	Reason for admission	Complication after admission	MASCC RIS	Length of stay, days
35	None	Unable to eat, nausea, vomiting, diarrhea, difficulty swallowing, Hb 6.6 g/dL	Unable to eat, nausea, vomiting, diarrhea, difficulty swallowing	Day 2: Hb 6.6 g/dL	23	6
36	None	None	Pneumonia	None	23	7
37	None	Unable to eat, nausea, vomiting, diarrhea	Unable to eat, nausea, vomiting, diarrhea, abdominal pain, mucositis, colitis	None	23	8
38	None	Unable to eat, nausea, vomiting, abdominal pain, intestinal perforation	Unable to eat, nausea, vomiting, abdominal pain, intestinal perforation	None	23	8
39	None	Unable to eat, nausea, vomiting, abdominal pain, SBO	Unable to eat, nausea, vomiting, abdominal pain SBO	None	23	10
40	None	Unable to eat	Unable to eat, mucositis	None	24	3
41	None		Cellulitis	None	24	5
42	None	Unable to eat, nausea	Unable to eat, nausea, difficulty swallowing, mucositis	None	24	5
43	None	Unable to eat	Unable to eat, mucositis	None	24	5
44	None	Nausea, vomiting, diarrhea, abdominal pain	Nausea, vomiting, diarrhea, abdominal pain, typhlitis	None	24	6
45	None	None	Abscess	None	24	6
46	SBP < 90 mmHg/need for vasopressors	None	Perirectal abscess	Day 1: hypotension	24	6
47	None	Unable to eat, nausea, vomiting	Unable to eat, nausea, vomiting, mucositis	None	24	6
48	SBP < 90 mmHg/need for vasopressors	Unable to eat	Unable to eat	Day 3: hypotension	24	7
49	Pa_{O_2} < 60 mmHg/need for ventilation, arrhythmia, ECG changes	None	Syncope, K 2.1 mEq/L	Day 2: SVT, hypoxia	24	8
50	None	Nausea, vomiting, abdominal pain	Nausea, vomiting, abdominal pain, colitis	None	24	8
51	None	Unable to eat, diarrhea, K 2.5 mEq/L	Unable to eat, diarrhea, difficulty swallowing, mucositis, K 2.5 mEq/L	None	24	8
52	None	Unable to eat, nausea, vomiting, diarrhea, K 2.7 mEq/L	Unable to eat, nausea, vomiting, diarrhea, difficulty swallowing, K 2.7 mEq/L	None	24	8
53	None	None	Bacteremia	ARF	24	12
54	None	None, chest pain	Chest pain	None	24	13
55	None	Unable to eat, nausea, vomiting, intractable hiccups	Unable to eat, nausea, vomiting, esophagitis	Day 1: intractable hiccups	24	20
56	None	Unable to eat, nausea, vomiting	Unable to eat, nausea, vomiting	None	26	3
57	None	None	Cellulitis	None	26	4
58	None	Nausea, vomiting, diarrhea, abdominal pain	Nausea, vomiting, diarrhea, abdominal pain, typhlitis	None	26	4
59	None	Nausea, vomiting, abdominal pain	Nausea, vomiting, abdominal pain, typhlitis	None	26	5
60	None	Unable to eat, abdominal pain	Unable to eat, abdominal pain, typhlitis	None	26	5
61	None	Unable to eat, nausea, vomiting	Unable to eat, nausea, vomiting	Day 1: perianal herpes simplex virus	26	5
62	None	Nausea, diarrhea, K 2.6 mEq/L	Nausea, diarrhea, K 2.6 mEq/L	Enterovaginal fistula	26	6
63	None	Unable to eat, vomiting, abdominal pain	Unable to eat, vomiting, abdominal pain, mucositis	None	26	7
64	None	Unable to eat, nausea, vomiting, diarrhea, abdominal pain, hypokalemia	Unable to eat, nausea, vomiting, diarrhea, abdominal pain, enteritis	Low K	26	7
65	None	Unable to eat, nausea, vomiting, rectal pain	Unable to eat, nausea, vomiting, rectal pain	None	26	9
66	None	Hb < 6 g/dL, unable to eat, abdominal pain, K 2.9 mEq/L	Unable to eat, abdominal pain, Hb 5.4 g/dL, K 2.9 mEq/L	None	26	9
67	None	Unable to eat, nausea, difficulty swallowing	Unable to eat, nausea, mucositis, difficulty swallowing	None	26	10
68	None	Unable to eat, nausea	Unable to eat, nausea, mucositis	Day 2: fever, Day 6: ARF	26	11
69	None	Unable to eat, nausea, vomiting, diarrhea, abdominal pain	Unable to eat, nausea, vomiting, diarrhea, abdominal pain, esophagitis, colitis	Day 6: ARF	26	13

ARDS = acute respiratory distress syndrome; ARF = acute renal failure; *C diff* = *Clostridium difficile*; Cr = creatinine; ECG = electrocardiogram; GI = gastrointestinal tract; Hb = hemoglobin; ICU = intensive care unit admission; K = potassium; MASCC = Multinational Association for Supportive Care in Cancer; Mg = magnesium; MI = myocardial infarction; Na = sodium; Pa_{O_2} = partial pressure of oxygen; RIS = risk index score; SBO = small-bowel obstruction; SBP = systolic blood pressure; SVT = supraventricular tachycardia; TPN = total parenteral nutrition.

Table 3. Characteristics of 198 patient episodes of solid tumors,[a]

Characteristic	No. of patients (%)	MASCC RIS score < 21 (n = 35), no. (%)	MASCC RIS score ≥ 21 (n = 163), no. (%)
Age, years			
Median	61	67.5	59
Range	18-86	35-81	18-86
Sex			
Male	57 (29)	17	40
Female	141 (71)	18	123
Neoplasms			
Breast	93 (47.0)	7 (20.0)	86 (52.8)
Gastrointestinal	39 (19.7)	6 (17.1)	33 (20.3)
Lung	18 (9.1)	7 (20.0)	11 (6.8)
Sarcoma	12 (6.1)	5 (14.3)	7 (4.3)
Head and neck	9 (4.5)	2 (5.7)	7 (4.3)
Ovary	8 (4.0)	3 (8.6)	5 (3.1)
Prostate	7 (3.5)	2 (5.7)	5 (3.1)
Bladder	4 (2.0)	2 (5.7)	2 (1.2)
Testis	2 (1.0)	0 (0)	2 (1.2)
PNET	2 (1.0)	1 (2.9)	1 (0.6)
Unknown	2 (1.0)	0 (0)	2 (1.2)
Melanoma	1 (0.5)	0 (0)	1 (0.6)
Uterus	1 (0.5)	0 (0)	1 (0.6)
Total neoplasms	198 (100)	35 (100)	163 (100)
Comorbidities			
Diabetes mellitus	16 (8.1)	4 (11.4)	15 (9.2)
CKD stage ≥ 3	18 (9.1)	6 (17.1)	12 (7.4)
Cirrhosis	2 (1.0)	1 (2.9)	1 (0.6)
Rheumatoid arthritis	2 (1.0)	1 (2.9)	1 (0.6)
Systemic lupus	0 (0)	0 (0)	0 (0)
CREST	0 (0)	0 (0)	1 (0.6)
Polymyalgia rheumatica	2 (1.0)	0 (0)	2 (1.2)
Transplant	1 (0.5)	0 (0)	1 (0.6)
Anti-TNF	1 (0.5)	0 (0)	1 (0.6)
Hepatitis B	1 (0.5)	0 (0)	1 (0.6)
Hepatitis C	5 (2.5)	0 (0)	5 (3.1)
HIV infection	1 (0.5)	0 (0)	1 (0.6)
Hypogammaglobulinemia	2 (1.0)	0 (0)	2 (1.2)
Hemochromatosis	2 (1.0)	1 (2.9)	1 (0.6)
Ulcerative colitis	1 (0.5)	0 (0)	1 (0.6)
Other			
Unable to eat	54 (27.3)	16 (45.7)	38 (23.3)
GCSF, inpatient after admission	177 (89.4)	31 (88.6)	146 (89.6)
GCSF, outpatient before admission	33 (16.7)	6 (17.1)	27 (16.6)
Chemotherapy density and intensity meeting GCSF criteria	51 (25.8)	5 (14.3)	46 (28.2)
Documented infection	38 (19.2)	12 (34.3)	26 (16)
Antimicrobials before admission	18 (9.1)	4 (11.4)	14 (8.6)
Adequate antimicrobial regimen on admission	187 (94.4)	34 (97.1)	153 (93.9)

[a] Some percentages may not total to 100 because of rounding.

CKD = chronic kidney disease; CREST = calcinosis, Raynaud syndrome, esophageal dysmotility, sclerodactyly, and telangiectasia; GCSF = granulocyte colony-stimulating factor; HIV = human immunodeficiency virus; MASCC = Multinational Association for Supportive Care in Cancer; PNET = primitive neuroectodermal tumor; RIS = risk index score; TNF = tumor necrosis factor.

There were 163 inpatient episodes with an MASCC RIS of 21 or higher. Sixty-nine of these had complications and/or reasons for admission on presentation. Thirty-eight of the 69 were unable to eat; 32 of the 38 had reasons for admission and/or complications. The other 31 of the 69 patients, those who were able to eat, required admission for various other reasons. See Table 2 for the reasons for admission and subsequent complications of the 32 episodes.

There were 35 episodes with an MASCC RIS below 21 (high risk for complication). Six of these patient episodes were misclassified by the MASCC RIS because no complication occurred that required hospitalization. The mean LOS for these 6 patients was 4.7 days (5, 3, 5, 5, 4, and 6 days, the last with a urinary tract infection that could have been treated orally with ciprofloxacin) compared with a mean LOS of 4.6 days for Group 1 and 7.6 days for Group 2.

Inability to Eat

Inability to eat was considered a serious complication and reason for admission; thus, it placed a patient episode in Group 2: complication. There were 54 episodes of 198 in which patients were unable to eat, 38 of whom had an MASCC RIS of 21 or above and 16 of whom had a score below 21. These 38 patient episodes were a subset of the 69 discordant patient episodes with an MASCC RIS of 21 or greater and a complication (Table 2). Inability to eat was associated with other serious complications in 32 of 38 episodes (84%). The 38 patients who were unable to eat had a mean LOS of 9.66 days compared with the mean LOS of the 31 patients who could eat, 7.0 days ($p = 0.08$ by Wilcoxon rank sum test). The mean MASCC RIS of those unable to eat and those able to eat was 23.1 and 22.8, respectively.

Correlation of Index with Other Outcomes

There was no useful correlation between the MASCC RIS and either the days to a body temperature at or below 37.5°C or the LOS (data not shown). Table 4 shows a correlation with deaths and the potential cost savings of preventing hospital admission (Table 5).

DISCUSSION

If patients with identified infections; intractable vomiting and diarrhea, either of the latter caused by mucositis or another complication; and inability to eat are included in the patients to whom the MASCC RIS is applied, the sensitivity of an MASCC RIS of 21 or greater to identify patients as a criterion for nonadmission was high (94%), but the positive predictive value was only 57.7% and the specificity only 29.6%. The range of the specificity of the MASCC RIS in some published studies (Table 6) varied from 40% to 95% (mean = 67.5%) in prospective studies and from 52% to 63.7% (mean = 60.9%) in retrospective studies. The variance of the specificity in these studies and the present study has not been explained, and a detailed analysis is beyond the scope of this article; however, a more detailed analysis is available in the guideline from the American Society of Clinical Oncology (ASCO).[9] In most of these publications, it is not clear if patients, presenting with identifiable infections; intractable vomiting and diarrhea, either of the latter caused by mucositis or another complication; and the inability to eat and swallow medications were excluded before the calculation of the MASCC RIS because these clinical features were considered aspects of the febrile neutropenic syndrome and not complications. Thus, study design is a possible factor accounting for the variance. Another factor might be that the median age of the patients in the studies listed in the references was about 51 years compared with 61 years in the present study. In the MASCC RIS, 2 points are awarded for age younger than 60 years, indicating that those patients aged 60 years or older are at increased risk of complications. As noted earlier, in 69 of 163 inpatient episodes with an MASCC RIS of 21 or more, admission was necessary because of complications present on admission or which occurred during hospitalization (Table 2). The patients with these 69 misclassified inpatient episodes would not have been admitted if an MASCC RIS of 21 or greater was used as the criterion for nonadmission. If these patients were not admitted, the complications that occurred during hospitalization would have occurred outside the hospital, resulting in either reevaluation in a health care setting or death.

There were also 3 inpatient episodes with an MASCC RIS of 21 or above (Group 1), in which a complication occurred 24 hours after admission, a complication that would have been

Table 4. Patient deaths

MASCC RIS	Circumstances and causes leading to death	Death related to initial infection	Comfort care	Neoplasm	Death after discharge, within 28 days of admission[a]	Duration of neutropenia/ length of stay, days	Days to temperature ≤ 38°C/days to temperature ≤ 37.5°C
13	Bacteremia, *Staphylococcus aureus*	Yes	Yes	Sarcoma	No	7 / 7	6 / 6
19	Readmitted with intestinal perforation, died same day	No	No	Advanced lung cancer	No	3 / 8	8 / 8
19	Unable to eat, became obtunded on TPN	No	Yes	Advanced ovarian cancer	No	2 / 18	1 / 2
19	Pneumonia	Yes	Yes	Lung cancer	No	1 / 4	1 / 1
21	*Clostridium difficile,* low BP, ICU, HAP, AMI	No	Yes	Advanced esophageal cancer	No	9 / 18	3 / 3
21	SBO, died 31 days after admission	No	Yes	Colon cancer	No	6 / 31	1 / 1
21	Encephalopathy	No	Yes	Advanced breast cancer	No	1 / 29	7 / 9
22	Multiple intraabdominal, extraintestinal air-fluid levels	No	No	Advanced endometrial cancer	Yes	5 / 6	2 / 4
22	ARDS, progressive hypoxemia, hypotension	Yes	Planned for next day	Advanced prostate cancer	No	2 / 8	8 / 8
22	Diarrhea, colitis, ARF, hypotension	Yes	Yes	Advanced lung cancer	No	4 / 8	4 / 4
23	Sepsis, then acute hypotension	Yes	Yes	Advanced breast cancer	No	2 / 3	1 / 3
23	Admitted with SBO and discharged; readmitted following week with intestinal perforation, intraabdominal abscess (declined abcess drainage)	No	No	Ovarian cancer	Yes	3 / 4	3 / 3
24	Fluid overload, failed to respond to diuresis	No	Yes	Metastatic; primary cancer not known	No	6 / 9	6 / 9
24	Readmitted obtunded, ARF, hypotensive	No	No	Breast cancer	Yes	3 / 14	3 / 8
24	New SVT, hypoxemia	No	Yes	Gastric cancer	No	8 / 8	4 / 7

[a] "No" = died in hospital.

AMI = acute myocardial infarction; ARDS = acute respiratory distress syndrome; ARF = acute renal failure; BP = blood pressure; HAP = hospital-acquired pneumonia; ICU = intensive care unit admission; MASCC = Multinational Association for Supportive Care in Cancer; RIS = risk index score; SBO = small-bowel obstruction; SVT = supraventricular tachycardia; TPN = total parenteral nutrition.

Table 5. Savings of preventing hospital admission	
Savings	**No complication**
Approximate cost of 1 day of hospitalization (2012 US dollars)	$2124
Number of patient episodes	100
Number of patient episode days x number of patient episodes	455
Estimated cost of hospitalization (2012 US dollars)	$966,420

best managed in the hospital. If the patients had not been admitted, or had been admitted and discharged after 24 hours of observation, they would have experienced these complications as outpatients. Those complications were hypokalemia (serum potassium concentration of 2.9 mEq/L) on Day 2, hypophosphatemia (phosphorus level of 2.2 mg/dL) on Day 3, and recurrent fever on Day 4. An additional 52-year-old woman, not identified as feeling or appearing sick or being dehydrated, had a temperature of 38.7°C, a BP of 81/54 mmHg, and a pulse of 130/min (3 criteria for systemic inflammatory response syndrome[10]) in urgent care. She was referred to the Emergency Department, where she was hydrated and placed on an intravenous antimicrobial regimen. She was intermittently hypotensive until the BP finally stabilized 25 hours and 37 minutes later. Her MASCC RIS was 21 at the time of admission, but the RIS would have been different depending on when, in the course of this patient episode, it was calculated.

If the MASCC index were to be used to determine "do not admit," it would have to be employed after determining whether a person was or was not able to eat or swallow …

Because many complications, such as hypokalemia, hypophosphatemia, and recurrent fever, cannot be predicted with an MASCC RIS of 21 or higher, use of a protocol, algorithm, or guideline seems appropriate to help clinicians decide on the proper management. One is the ASCO guideline from 2012,[9] and another is the National Comprehensive Cancer Network (NCCN) guideline.[11] The recommended initial observation period in the ASCO guideline is 4 hours, and in the NCCN guideline it is 2 to 12 hours. The hypotensive patient described could have been considered stable at 2 to 4 hours and possibly discharged to home. However, the physician, simply using clinical judgment, decided this patient needed admission. This decision was consistent with the ASCO guideline, which clearly states that a patient with criteria for systemic inflammatory response syndrome should be admitted. Therefore, following the ASCO guideline would have ensured admission for this last patient, but using an MASCC RIS of 21 or higher would not. The limitataion of the MASCC RIS is evident by consulting Table 4 of the ASCO guideline (available at: http://jco.ascopubs.org/content/31/6/794/T4.expansion.html).[9] The table lists 41 exclusions (42 if the footnote regarding systemic inflammatory response syndrome is included) to using an MASCC RIS of 21 or greater as a criterion for treating a febrile neutropenic patient as an outpatient.[9] Furthermore, neither the NCCN guideline for the management of nonadmitted patients nor the ASCO guideline specify frequency of laboratory testing for these potential outpatients. Rubenstein et al[12] suggested obtaining a complete blood cell count every other day and biochemical panels on Day 7 or the last day of observation. If the biochemical panels for the patients with hypokalemia and hypophosphatemia had been drawn on Day 7, a delay in detection would have occurred. The protocol for patients discharged from the hospital on a regimen of oral antimicrobial therapy in the article by Klastersky et al[13] included temperature recorded every 6 hours, laboratory tests every other day for 5 days, and phone contact with the patient every other day. The ASCO guideline recommends daily telephone contact and "frequent evaluation for at least 3 days in clinic or at home."

Data in the present study support the ASCO guideline for management of these patients. Although the ASCO guideline recognizes the lack of data supporting multiple aspects of outpatient management, modifications to the guideline, following discharge to an outpatient setting, could include recording the patient's vital signs approximately every 6 to 8 hours, establishing phone contact with the patient or caregiver within 8 to 12 hours following discharge, and serum biochemical tests (electrolytes, creatinine, calcium, phosphorus, and magnesium) daily or every other day for 3 times, or until results are normal.

Importance of Inability to Eat

This study chose inability to eat, as an admission criterion, vs inability to swallow oral medications because "unable to eat" was recorded in the progress notes. In my view, neither is adequate or objective because outpatients need both adequate nutrition and appropriate medications. Some patients who are unable to eat can swallow oral medications, and some patients who are unable (or unwilling) to swallow oral medications are able and willing to swallow nutritional liquid drinks. Inability to swallow oral medications is considered by the ASCO guideline to be an exclusion for outpatient management. It is not named as one of the complications in the Klastersky criteria. In the study by Klastersky et al,[13] which identified patients who were stable and ready for discharge from the hospital after 24 hours of observation, the equivalent of "unable to eat"—"able to swallow"—was employed after stratification by the MASCC index and was not incorporated into the MASCC index. Those unable to swallow were excluded from early discharge despite an MASCC RIS of 21 or higher. If the MASCC RIS were to be used to determine "do not admit," it would have to be employed after determining whether a person was or was not able to eat or swallow, or the criterion "unable to eat/unable to swallow oral medications" would have to be incorporated into the MASCC RIS.

As noted earlier, inability to eat was associated with other serious complications, and all physicians admitting patients in this study considered it a criterion for admission. However, because

there are 42 exclusions in the ASCO guideline[9] for managing a patient as an outpatient, as mentioned earlier, there is questionable utility to modifying the MASCC RIS to include "unable to eat/unable to swallow oral medications." That inability to eat is important has been highlighted in a study by Escalante et al,[14] who noted that 80% of patients with Grade 3 or higher mucositis required admission. The NCCN guideline also includes Grades 3 to 4 mucositis as a criterion for high risk. Until patients who are unable to eat or to swallow oral medications, yet who have no other complications, can be managed as outpatients, they will require admission.

Limitations of Klastersky Criteria and Index

The Klastersky criteria are inadequate as nonadmission criteria for these reasons: 1) only 2 of the 10 complications are objective; 2) the majority, 49 of the 69, of the complications experienced by the patients in this study with an MASCC RIS of 21 or higher were not among the named complications; and 3) inability to eat and inability to swallow are not named.

The MASCC RIS of 21 or above is inadequate for the nonadmission decision for these reasons: 1) only 4 of the 7 components of the MASCC RIS are objective; 2) it misclassified to low risk 42.3% of patient episodes with complications; 3) it has to be checked against 42 other exclusions based on the ASCO guideline[9]; and 4) "unable to eat/unable to swallow" are not incorporated.

Alternative to Index

The alternative to the MASCC RIS is clinical judgment or a more reliable index. Although the MASCC RIS has been incorporated into both Infectious Diseases Society of America[1] and ASCO guidelines,[9] I believe a fair question is: Is this index really superior to clinical judgment? Furthermore, I believe it would be beneficial to conduct a study in which a physician assigns an MASCC RIS at the point of entry to health care and again at the point when an admitting physician, blinded to the MASCC RIS, evaluates the patient regarding admission. The admitting physician would decide, on the basis of clinical acumen and the ASCO guideline, whether the patient should be admitted. The patient would be observed in the hospital for 24 hours. Complications would be correlated with the MASCC RIS and the clinical decision.

Savings

The cost of intensive outpatient management would probably be less than the cost of inpatient management

Table 6. Sensitivity and specificity of the MASCC RIS in various studies

Source, year	Type of study	Solid tumor, lymphoma, %	MASCC RIS	No serious medical complication	Serious medical complication	Total	Sensitivity, %	Specificity, %	Deaths, %
Uys,[8] 2004	Prospective	70	≥ 21	57	1	58	95		0
			< 21	3	19	22		95	36.4
Total				60	20	80			
Baskaran,[5] 2008	Retrospective	34.5	≥ 21	68	14	82	93		7
			< 21	5	29	34		67	29
Total				73	43	116			
Innes,[6] 2008	Prospective	100	≥ 21	87	3	90	91.6		
			< 21	8	2	10		40	
Total				95	5	100			
André,[18] 2010	Prospective	56		Not SS/SSh	SS/SSh				
			≥ 21	70	22	92	70		NA
			< 20	38	67	105		75	NA
Total				108	89	197			
Ahn,[19] 2011	Retrospective	71.5	≥ 21	308	35	343	95		1.5
			< 21	15	38	53		52	18.9
Total				323	73	396			
Paesmans,[20] 2011	Retrospective	57	≥ 21	1349	139	1488	77		1
			< 21	410	244	654		63.7	14.2
Total				1759	383	2142			
Hui,[4] 2011	Prospective	79.7	≥ 21	137	23	160	81		1.9
			< 21	32	35	67		60	9
Total				169	58	227			
Bitar, 2013[a]	Retrospective	100		Don't admit	Admit				
			≥ 21	94	69	163	94		4.9
			< 21	6	29	35		29.6	11.4
Total				100	98	198			

[a] Results of the current study.

MASCC = Multinational Association for Supportive Care in Cancer; NA = not available; RIS = risk index score; SS/SSh = severe sepsis or septic shock.

(approximately $10,000 per uncomplicated admission[12]). In 1993, Rubenstein and colleagues[12] estimated the medication cost of outpatient management as $2302 for oral therapy and $7336 for intravenous therapy, but the total cost of managing the patients was not provided. Elting et al[15] calculated the costs of outpatient vs inpatient management in 2008 and found the total cost of inpatient management to be about twice that of outpatients.

Study Limitations

There are some limitations to this study. First, as noted earlier, the MASCC RIS lists only 4 actual objective criteria. The burden of illness category is purely subjective, dependent on the recorder (Table 1). The burden of illness was assigned following a detailed review of the chart by the physician author and not by the admitting physician. The physician reviewing the charts for this study did review the publication by Pompei and associates,[16] which originally proposed the burden of illness designation. Although a retrospective chart review has some element of subjectivity, it is no less objective than the criteria used to evaluate charts in the original publication by Klastersky et al.[3]

Second, this study accepted designations such as COPD, dehydration, and other terms such as *vomiting, diarrhea, unable to eat,* and so on, without requiring an objective definition. (The ASCO guideline, Table 2, [available at: http://jco.ascopubs.org/content/31/6/794/T2.expansion.html] attempts to address this problem, but does not resolve it.[9])

Third, this was a retrospective review of the charts by a single physician. However, his experience included more than 37 years as a physician and 23 years as an infectious disease physician.

Fourth, the definition of febrile neutropenia was based on the admitting physician's acceptance of the self-report of fever or the documentation of fever in the clinic or Emergency Department and not a documented temperature of above 38.3°C on one occasion or above 38°C on 2 or more occasions during a 12-hour period.[17]

Fifth, this was a study of only febrile neutropenic patients with solid tumors, so the sensitivity and specificity of the MASCC RIS in this study should be compared only with similar studies of febrile neutropenic patients with solid tumors. (Table 6 shows data extracted from 7 studies with the percentage of patients with solid tumors or lymphoma and the sensitivity and specificity of the MASCC RIS for each.[4-6,8,18-20])

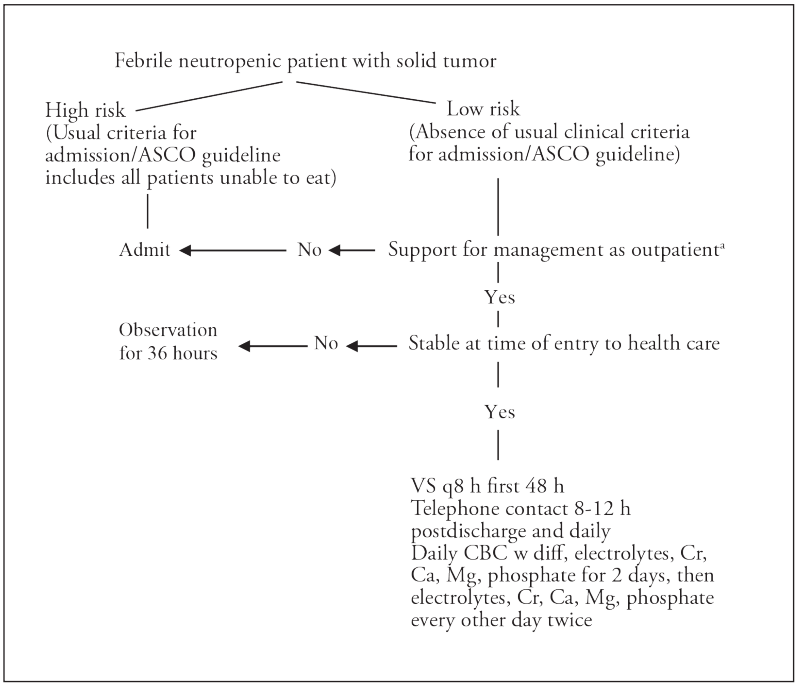

Figure 2. Proposed outpatient management algorithm.[b]

[a] Modified from the American Society of Clinical Oncology (ASCO) guideline, to include the following:
Patient agrees to outpatient treatment while neutropenic, including potential frequent visits to clinic/hospital.
Residence ≤ 1 hour or ≤ 30 miles (48 km) from clinic or hospital, even in inclement weather.
Patient's primary care physician and infectious disease physician, or oncologist agrees to outpatient management.
Attendant or attendants who agree to outpatient treatment and are competent at observation and communication, and at home 24 hours a day until neutropenia and other clinical problems resolve.
Telephone and transportation available 24 hours a day.
Either an oncology or infectious disease nurse practitioner or physician's assistant or a clinically trained home infusion pharmacist or clinically trained oncology nurse or infectious disease nurse able to communicate with patient daily.

[b] High risk indicates usual clinical criteria for admission (criteria on which a general internist bases a decision to admit or to not admit) using the 2013 clinical practice guideline from the ASCO, which includes all patients unable to eat. Low risk indicates absence of usual admission criteria/ASCO guideline.

Ca = calcium; CBC = complete blood count; Cr = creatinine; h = hours; Mg = magnesium; VS = vital signs.

CONCLUSIONS

This study answered the 6 questions presented in the Introduction. First, of 69 misclassified patients with complications and an MASCC RIS of 21 or greater, only 20 had serious complications named in the Klastersky criteria, meaning that the other 49 patients had complications not named and which had to be assumed to be included in the last component, "other complications judged serious and clinically significant by the investigator."

Second, there were additional complications, not named in the Klastersky criteria, which were important in the nonadmission decision, such as inability to eat (Table 2).

Third, the MASCC RIS of 21 or greater could not be used to make the nonadmission decision for a febrile neutropenic patient with a solid tumor because, in this study, a score of 21 or higher misclassified 42.3% of patients with complications to low risk.

Fourth, 3 patients with an MASCC RIS of 21 or greater experienced complications 24 hours after admission; the

complication and the day of occurrence were noted. Because 2 of the 3 complications that occurred were biochemical and the additional one was recurrent fever, the index is unlikely to be able to predict their occurrence.

Fifth, therefore, an algorithm or protocol for the management of outpatients is advisable. An algorithm has been constructed from the implications of the data in this study and the ASCO guideline (Figure 2).

Sixth, substantial savings could be realized if uncomplicated patients could be managed as outpatients (approximately $1 million per 100 uncomplicated admissions in 2012 dollars).

The possibility of creating an MASCC-like RIS from truly objective data, which could be used to predict complications and the safety of not admitting a febrile neutropenic patient, requires further investigation. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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State of Mind

A cancer is not only a physical disease, it is a state of mind.

— Michael Baden, MD, b 1934, physician and forensic pathologist