Nurse to Bed Ratio and Nutrition Support in Critically Ill Patients

By Carolina Keiko Yamamoto Honda, MD, MSc, Flávio Geraldo Rezende Freitas, MD, PhD, Patricia Stanich, RD, MSc, Bruno Franco Mazza, MD, MSc, Isac Castro, PhD, Ana Paula Metran Nascente, MD, Antonio Toneti Bafi, MD, Luciano Cesar Pontes Azevedo, MD, PhD, and Flávia Ribeiro Machado, MD, PhD

**Background** Inadequate nutrition support is common among critically ill patients, and identification of risk factors for such inadequacy might help in improving nutrition support.

**Objective** To determine how often daily calorie goals are met and the factors responsible for inadequate nutrition support.

**Methods** A single-center prospective cohort study. Each patient’s demographic and clinical characteristics, the need for ventilatory support, the use and dosage of medications, the number of nursing staff per bed, the time elapsed from admission to the intensive care unit until the effective start of enteral feeding, and the causes for nonadministration were recorded. Achievement of daily calorie goals was determined and correlated with risk factors.

**Results** A total of 262 daily evaluations were done in 40 patients. Daily calorie goal was achieved in only 46.2% of the evaluations (n = 121), with a mean of 74.8% of the prescribed volume of enteral nutrition infused daily. Risk factors for inadequate nutrition support were the use of midazolam (odds ratio, 1.58; 95% CI, 1.18-2.11) and fewer nursing professionals per bed (odds ratio, 2.56; 95% CI, 1.43-4.57).

**Conclusion** Achievement of daily calorie goals was inadequate, and the main factors associated with this failure were the use and dosage of midazolam and the number of nurses available. (American Journal of Critical Care. 2013;22:e71-e78)
Inadequate intake of calories and protein is a common problem in intensive care units (ICUs) and results from a combination of a hypercatabolic state and a reduction in the nutrient supply. The reduced nutrient supply may be due to an underestimation of the amount of calories and protein needed or to the difference between the number of calories prescribed and the number received. The percentage of prescribed calories that is actually received varies between 51% and 99%. The main factors responsible for the interruption of enteral nutrition are gastrointestinal intolerance (gastric reflux, vomiting, or diarrhea), procedures or examinations, problems with the feeding tube, and airway management. However, most previous studies involved evaluation of whether or not patients met their nutrition goals during the entire ICU stay rather than on a daily basis. Some factors that vary daily, such as doses of vasoactive and sedation drugs, have already been reported. However, the excessive workload for nursing staff has not been adequately studied, although this factor is thought to be important for quality improvement among critically ill patients.

Our hypothesis was that some factors that vary daily might compromise the overall delivery of nutrition support. Thus in this study, we aimed to determine the percentage of the time that the daily prescribed calorie goal was achieved and to identify the risk factors that are responsible for a calorie intake less than the prescribed level. To achieve this goal, we assessed caloric intake on a daily basis instead of classifying patients according to whether the caloric goal was met during their entire ICU stay.

Materials and Methods

This prospective cohort study was conducted from July to September 2007 in a 24-bed general ICU of a tertiary university hospital. The institution’s ethics committee approved the study and waived the need for informed consent because of the study’s observational nature. All study procedures were performed according to the ethical standards of the Helsinki Declaration of 1975.

All patients admitted during this period were evaluated and prospectively included, on a consecutive basis, if they met the following criteria: older than 18 years, predicted ICU stay longer than 48 hours, functioning gastrointestinal tract, and enteral nutrition indicated by the attending physician. Exclusion criteria were known intolerance to enteral nutrition because of malabsorption syndromes, such as short bowel syndrome or digestive fistula, pregnancy, or supplemental oral or parenteral nutrition.

Upon admission, demographic characteristics (age, sex, diagnostic category, and presence of comorbid conditions) and scores on the Acute Physiology and Chronic Health Evaluation II (APACHE II) at ICU admission and the Sequential Organ Failure Assessment (SOFA) on the day of inclusion were recorded. Additionally, we evaluated the following clinical characteristics on a daily basis: consciousness level; use and dose of norepinephrine, sedatives, and opioids; need for invasive or noninvasive mechanical ventilation; serum levels of lactate; and central venous oxygen saturation. We used the Ramsay sedation scale to access the level of consciousness in sedated patients and the Glasgow Coma Scale in the remaining patients. The ratio of nursing staff to beds was obtained by dividing the number of nurses or nurse technicians by the total number of patients on a given day. This calculation means that on a given day all patients would have the same ratio. In the study ICU, nursing staff is scheduled routinely as 0.6 professionals for each patient, although many external factors can compromise this ratio.

A dietitian and a senior ICU physician not related to the study planned the daily nutritional strategy. The total calorie goal was 20 to 25 kcal/kg in the acute phase of injury and 25 to 30 kcal/kg during the chronic phase.
the recovery phase, which was defined by the presence of hemodynamic and respiratory stability. The patient’s weight was estimated by measuring the circumference of the wrist. As a routine, our hospital provides enteral nutrition thought gastric delivery of bolus feedings with 6 to 8 daily servings, progressing to the calorie goal on day 4.

The reasons for discontinuation of enteral nutrition were clearly defined in the unit protocol. The reasons were recorded daily and classified into 1 of the following categories: problems with the enteral nutrition tube, gastrointestinal intolerance to the diet (reflux, vomiting, or diarrhea), fasting due to medical procedures, extubation, gastrointestinal bleeding, and severe hemodynamic instability. The unit protocol defined gastric reflux as 1 episode of a residual volume greater than 200 mL withdrawn from the gastric tube. Reflux was routinely checked every 3 hours before the next bolus administration of enteral nutrition. Diarrhea was defined as more than 3 liquid bowel movements in 24 hours.

One of the authors (C.K.Y.H.) prospectively collected all data directly from the charts and at bedside daily. The number of nurses was assessed in each round also by C.K.Y.H., who was not in charge of the patients and could not influence patients’ care or the amount of diet received. We determined the time elapsed in the following steps: ICU admission, prescription of enteral nutrition, enteral tube insertion, abdominal radiography to check tube location, and the start of enteral nutrition. Patients were observed until one of the following: achievement of the previously defined total calorie goal, introduction of parenteral or oral nutrition, discharge from the ICU, or death.

**Statistical Analysis**

Sample size was calculated on the basis of the previous findings of the influence of fentanyl in nutrition adequacy. We assumed that fentanyl would be used in only 30% of the days in the group with adequate daily caloric intake, compared with 50% of the days in the group with inadequate daily caloric intake, with a power of 80% and an α of 0.05. We estimated that a sample size of 103 daily observations in each group would be necessary.

Categorical variables were presented as percentages and continuous variables either as mean and standard deviation (SD) or as median and interquartile range (IQR), as appropriate. The Mann-Whitney or Student t test and the χ² test were used to compare continuous quantitative and categorical variables, as appropriate.

We evaluated the daily calorie intake as a percentage of the prescribed calorie intake, considering only the patients able to receive enteral nutrition. We excluded all patients in whom enteral nutrition was prescribed but withheld by a doctor’s order or not initiated because the enteral route was not yet available, as these external factors would have introduced bias in the analysis. Enteral nutrition was considered adequate if the patient received at least 65% of the recommended calories (group 1 ≥65% and group 2 <65%). Considering the intermittent administration of the enteral nutrition, this percentage corresponded to not receiving the prescribed volume at least twice in a day.

We compared patients with (group 1) and patients without (group 2) adequate daily caloric intake. The multivariate stepwise forward logistic regression model included all variables with a P value lower than .20 in the univariate analysis. A second model was generated excluding the variables related to patients’ characteristics that did not change daily, such as demographic data and severity scores on admission, as they would have led to bias. We used the Hosmer-Lemeshow test to calibrate our final model. We categorized the number of nurses per bed, considering the best cutoff point in the receiver operating characteristic curve. To minimize missing data, we did a weighted analysis to associate the use with the dosage used of norepinephrine, midazolam, fentanyl, and tramadol. In this weighted analysis, a 0 value was given to patients who did not receive the medication and a value of 1 was assigned to the patients who received the medication. The dose was transformed into a value between 0 and 1, with 1 corresponding to the dose of the 90th percentile of the sample. Each value was then represented according to its proportion relative to this 90th percentile value. We analyzed the level of consciousness as a single variable considering scores on both the Ramsay sedation scale and the Glasgow Coma Scale according to their respective 90th percentile.

Multivariate analyses were expressed with their respective odds ratio and 95% confidence intervals. Results were considered significant if the P value was .05 or less. Statistical analysis was done by using SPSS 17.0 package for Windows and GraphPad Prism for Windows version 5.0.

**Results**

We included 40 patients comprising 262 daily evaluations. The demographic and clinical characteristics of the total population are presented in

---

**Weight was estimated by measuring the circumference of the patient’s wrist.**

---

Downloaded from http://ajcc.aacnjournals.org/ by AACN on November 3, 2017
Table 1. The time elapsed between all steps, from ICU admission to the effective start of enteral nutrition, is shown in the Figure.

We found that a mean of 74.8% of the prescribed calories was infused daily. Adequate enteral nutrition, defined as receiving 65% of the daily calories, was achieved in 189 of the daily evaluations (group 1); on 73 occasions, the 65% target was not achieved (group 2). The reasons for non-administration were problems with the enteral nutrition tube (34.2%), reflux (27.4%), examinations and procedures (19.2%), unidentified causes (9.6%), vomiting (8.2%), extubation (6.8%), gastrointestinal bleeding (5.5%), and hemodynamic instability (4.1%). No interruptions in feedings were caused by diarrhea.

The univariate analysis of risk factors for non-compliance with daily goals showed no differences between the groups with respect to lactate levels; the use or dose of norepinephrine, fentanyl, and tramadol; the need for invasive or noninvasive mechanical ventilation; and score on the Glasgow Coma Scale. Midazolam was more frequently used in group 2 (52.1%) than in group 1 (34.9%) with a $P$ of .02. Ramsay sedation scale analysis showed deeper levels of sedation in group 2 than in group 1 ($P = .007$). Group 2 was assisted by fewer nursing professionals ($P = .006$). After categorizing the number of nursing staff per bed, the area under the curve to predict inadequacy was 0.61 (SD, 0.04; 95% CI, 0.53-0.68), $P = .007$, and the best cutoff point in the receiver operating characteristic curve was 0.51. The percentage of the days with a nursing staff/bed ratio less than 0.51 was significantly higher in group 2 (65.8% vs 44.4%, $P = .002$). A detailed comparative analysis of group 1 and group 2 is shown in Table 2. Multivariate analysis based on weighted variables indicated the following 2 risks factors: use of midazolam (odds ratio, 1.58; 95% CI, 1.18-2.11; $P = .002$) and the number of nursing professionals per bed (odds ratio, 2.56; 95% CI, 1.43-4.57; $P = .002$).

Discussion

Our results show that most ICU patients in this study did not achieve the prescribed daily calorie goal. Those patients received midazolam more often and were assisted by fewer nursing professionals.

This study also confirms previously published data regarding the delay in starting enteral nutrition. In a similar study, authors reported a median time of 18 (12-24) hours from ICU admission to the effective start of enteral nutrition.
tube placement. Another potential cause, although not assessed in this study, is the delay before the first delivery of a feeding after the nutrition sector has been informed by the nurses of the availability of the enteral tube. If bolus feeding or night interruption is used, the impact of this delay would be even greater. Optimization of patients’ extrinsic factors can contribute to improvement in nutritional support.

Table 2
Risk factors for not achieving the daily calorie goal in a multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1a (n = 189)</th>
<th>Group 2b (n = 73)</th>
<th>Pc</th>
<th>Odds ratio (95% CI)d</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFA score, median (25th percentile-75th percentile)</td>
<td>6.0 (4.0-8.0)</td>
<td>6.0 (4.0-9.5)</td>
<td>.54</td>
<td>NA</td>
</tr>
<tr>
<td>Lactate levelb&lt;br&gt;Value, median (25th percentile-75th percentile), mg/dL</td>
<td>16 (15.1)</td>
<td>7 (14.9)</td>
<td>.50</td>
<td>NA</td>
</tr>
<tr>
<td>Central venous oxygen saturation &lt;70%,f&lt;br&gt;No. (%) of patients</td>
<td>78 (74.3)</td>
<td>40 (81.6)</td>
<td>.21</td>
<td>NA</td>
</tr>
<tr>
<td>Norepinephrine&lt;br&gt;Use, No. (%) of patients</td>
<td>62 (32.8)</td>
<td>25 (34.2)</td>
<td>.47</td>
<td>NA</td>
</tr>
<tr>
<td>Dose, median (25th percentile-75th percentile), µg/kg per minute</td>
<td>0.13 (0.07-0.20)</td>
<td>0.14 (0.06-0.18)</td>
<td>.74</td>
<td>NA</td>
</tr>
<tr>
<td>Weighted data, median (25th percentile-75th percentile)</td>
<td>0 (0.0-0.12)</td>
<td>0 (0.0-0.12)</td>
<td>.89</td>
<td>NA</td>
</tr>
<tr>
<td>Midazolam&lt;br&gt;Use, No. (%) of patients</td>
<td>66 (34.9)</td>
<td>38 (52.1)</td>
<td>.02</td>
<td>NA</td>
</tr>
<tr>
<td>Dose, median (25th percentile-75th percentile), µg/d</td>
<td>119.0 (61.0-192.0)</td>
<td>142.5 (72.0-610.0)</td>
<td>.15</td>
<td>NA</td>
</tr>
<tr>
<td>Weighted data, median (25th percentile-75th percentile)</td>
<td>0 (0.0-1.4)</td>
<td>1.07 (0.0-1.6)</td>
<td>&lt;.001</td>
<td>1.51 (1.13-2.03)</td>
</tr>
<tr>
<td>Fentanyl&lt;br&gt;Use, No. (%) of patients</td>
<td>105 (55.6)</td>
<td>39 (53.4)</td>
<td>.38</td>
<td>NA</td>
</tr>
<tr>
<td>Dose, median (25th percentile-75th percentile), µg/d</td>
<td>72 (52-120)</td>
<td>72 (66-120)</td>
<td>.34</td>
<td>NA</td>
</tr>
<tr>
<td>Weighted data, median (25th percentile-75th percentile)</td>
<td>1.12 (0.0-1.6)</td>
<td>1.11 (0.0-1.4)</td>
<td>.90</td>
<td>NA</td>
</tr>
<tr>
<td>Tramadol&lt;br&gt;Use, No. (%) of patients</td>
<td>35 (18.5)</td>
<td>9 (12.3)</td>
<td>.15</td>
<td>NA</td>
</tr>
<tr>
<td>Dose, median (25th percentile-75th percentile), mg/d</td>
<td>200 (150-300)</td>
<td>150 (150-200)</td>
<td>.31</td>
<td>NA</td>
</tr>
<tr>
<td>Weighted data, median (25th percentile-75th percentile)</td>
<td>0 (0.0-0.0)</td>
<td>0 (0.0-0.0)</td>
<td>.19</td>
<td>NA</td>
</tr>
<tr>
<td>Consciousness level evaluation, median&lt;br&gt;(25th percentile-75th percentile)</td>
<td>5 (4-6)</td>
<td>6 (6-6)</td>
<td>.003</td>
<td>NA</td>
</tr>
<tr>
<td>Ramsay Scale</td>
<td>10 (7-11)</td>
<td>11 (11-14)</td>
<td>.90</td>
<td>NA</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>0.8 (0.6-1.0)</td>
<td>1.0 (0.8-1.0)</td>
<td>.03</td>
<td>NA</td>
</tr>
<tr>
<td>Mechanical ventilation, No. (%) of patients</td>
<td>163 (86.2)</td>
<td>60 (82.2)</td>
<td>.26</td>
<td>NA</td>
</tr>
<tr>
<td>Invasive</td>
<td>4 (2.1)</td>
<td>2 (2.7)</td>
<td>.37</td>
<td>NA</td>
</tr>
<tr>
<td>Noninvasive</td>
<td>60 (82.2)</td>
<td>60 (82.2)</td>
<td>.37</td>
<td>NA</td>
</tr>
<tr>
<td>Nursing staff/bed ratio, median (25th percentile-75th percentile)</td>
<td>0.54 (0.47-0.66)</td>
<td>0.49 (0.46-0.54)</td>
<td>.006</td>
<td>2.56 (1.43-4.57)</td>
</tr>
<tr>
<td>Abbreviations: NA, variable not examined in the multivariate analysis; NS, nonsignificant values in multivariate analysis; SOFA, Sequential Organ Failure Assessment.</td>
<td>45 Patients who received at least 65% of prescribed calories.</td>
<td>46 Patients who received less than 65% of prescribed calories.</td>
<td>47 Univariate analysis: Mann Whitney or χ² test.</td>
<td>48 Multivariate analysis by stepwise forward logic regression, adjusted by the baseline SOFA score. Hosmer-Lemeshow test = 0.71. In multivariate analysis, only weighted data were used.</td>
</tr>
</tbody>
</table>
A discrepancy also was noted between the prescribed and infused volumes, with only 74.8% of the prescribed volume being received daily. This result, far from ideal, is similar to results published previously, where the mean daily percentage intake varied from 51% to 99%.6,12,14 In those studies, the main causes of feeding interruption were gastrointestinal intolerance (gastric reflux, vomiting, or diarrhea), interruption for medical procedures, problems with the feeding tube, and airway management (extubation).4,11,13-27 Our study showed similar results.

Few studies12,16,22,28 evaluated the risk factors, intrinsic to the patient or not, that may predispose patients to interruption of enteral nutrition. Thus, we sought to determine these risk factors, which required a definition of adequacy of daily calorie intake. The 65% target was chosen both because this target is reported to be the usual intake in critically ill patients1,2,11-14 and because this target would make it easier to identify truly relevant risk factors. A higher target would result in fewer patients with adequate enteral nutrition, which might compromise the identification of those factors. Considering our intermittent administration, daily feeding would have been classified as inappropriate if a single dose of the enteral nutrition were missed.

Previous studies1,7,17 have identified sedation as a risk factor for gastrointestinal intolerance. In this study, we show that the use of midazolam was independently associated with the failure to reach the calorie goal. Severity of illness can lead to deeper sedation needs. Thus, severity and not the drug itself might be associated with inadequacy in enteral nutrition; however, we were not able to find any significant association with other severity markers in our multivariate analysis.

An independent association between nursing staff per bed and nutritional adequacy was clearly demonstrated. A reduction in nursing staff can lead to excessive workload, which is a potential cause of inadequacy in patients’ care. The correct assessment of gastric reflux, optimization of scheduling of procedures, and timely restarting of nutrition support afterwards are examples of nursing duties that might be compromised.

Our findings might have been influenced by the use of intermittent nutrition, as this type of feeding requires nursing assistance every 3 hours and missing doses has a greater effect on the daily adequacy than stopping an infusion of a continuous feeding. Nursing overload might also result in oversedation, and our patients did have high Ramsay scores. However, this finding is only an extrapolation of our data, as we did not assess whether oversedation was really present or if the patients needed the doses they were receiving. We think that this finding is a major contribution of our study, as this association between nursing staff and inadequacy has not been reported before. Previously published articles only correlate inadequate nutritional intake with nursing staff training and protocol implementation. Those studies showed that training and further integration on a multidisciplinary team for nutritional therapy lead to better performance.1,26,32,33 As this is an external risk factor that is reversible, our results might be useful for health care administrators in charge of the number of nursing staff.

Published reports4,17,27 suggest that the use of vasoactive drugs is associated with inadequate calorie intake, by being a marker of disease severity or by inducing gastrointestinal tissue hypoperfusion. However, in our study, neither the use of vasoactive drugs nor the lactate level was related to inadequacy. We must point out that, according to the institution’s nutrition protocol, patients receiving high doses of vasoactive drugs or with elevated lactate levels might be considered for interruption of enteral nutrition and therefore would not have been included in our analysis. Our protocol does not state that hemodynamic instability is an indication to withhold enteral nutrition but does allow physicians to interrupt feedings if they think the patient’s condition is too unstable until the severe hypoperfusion improves. As a consequence, in only 4.1% of the cases was enteral nutrition not administered because of hemodynamic instability, suggesting that the hemodynamic status is not a major issue in our ICU.

Although withholding enteral nutrition is a routine practice in many ICUs, it is not clear, based on the current weak evidence, that that action is sufficient. Thus, severe hyperlactatemia and high doses of vasopressors may not really be associated with failure in delivering enteral nutrition as suggested by our results. So, the lack of correlation only suggests that in those patients receiving enteral nutrition, which excludes the most severely and acutely ill patients, the use and dose of norepinephrine and the lactate levels were not correlated with inadequacy of caloric intake.

Our results suggest that an optimized nutrition strategy should be based both on improvement of patients’ extrinsic factors and on minimization of intrinsic factors. Improvement in intrinsic factors is difficult to achieve. However, external factors can
be changed. One example is shortening the steps preceding enteral nutrition, for example, recognizing the need for enteral nutrition sooner and performing abdominal radiography earlier. Sedation is progressively less used in ICUs, and further reductions would contribute to increase the adequacy of enteral nutrition. Overnight feeding can be used to compensate for interruptions because of examinations or procedures, as proposed by Petros and Engelmann. Optimization of the number of nursing staff is also a key factor, although the number of professionals per se does not ensure improvement in the quality of care; any increases in staff must be accompanied by training and integration with the multidisciplinary staff.

This study has several strengths. First, we studied, on a consecutive basis, a highly critically ill population, as can be observed by the illness severity scores. Thus, the results can be easily generalized to patients in critical condition. Another important aspect was the careful monitoring of the elapsed time before the beginning of nutritional support, which allowed us to identify reversible extrinsic causes for inadequate caloric intake. Third, the large number of daily evaluations for each patient allowed us to analyze the potential risk factors. By this method, patients could be in either group 1 or group 2 on different days, which allows us to evaluate some risk factors present on a daily basis. Another design, analyzing patients who reach or do not reach the goal after a period of time, would not allow factors such as the use and dose of medications, daily SOFA score, or number of nurses to be evaluated correctly. The correlation between adequate calorie intake and nursing staff was examined in an unprecedented way in this study, showing that the heavy workload placed on the nursing staff can interfere with patients’ nutrition.

This study also has some limitations. It was a single-center study with a small number of patients, 52.5% of whom were surgical patients. Thus, the applicability of the results may be limited in nonsurgical ICUs. We also did not analyze our results with respect to the type of surgery. Although the inclusion was consecutive, we did not capture the reasons why the other patients admitted to the unit were not included. Another point to be considered is the inability to include in the multivariate analysis factors such as the dose of sedatives and other drugs, as these data were present only in patients who were treated with these medications. Excluding patients not using these drugs would result in a large amount of lost data and consequently inconsistency. The weighted analysis, grouping the use and dose used in the same variable as explained in the methods section, may have minimized this limitation. We did not assess nurses’ compliance with the nutrition protocol, thus it is not possible to determine whether patients who could have received enteral nutrition were not receiving it just because of lack of compliance and not because of their own illness severity. We should also point out that this study did not aim to evaluate the impact of early enteral nutrition or early full caloric intake. These controversial issues were recently addressed by several studies that could not demonstrate any clear benefit in early enteral nutrition,15,34-37 enhanced enteral nutrition,38-40 or supplemental parenteral nutrition.41-47 Cluster randomized studies could not demonstrate that a protocolized nutritional care can change outcome either.41-47 Our main contribution was the evaluation of potential and avoidable risk factors related to our inability to reach the selected goals and not to discuss if these goals are relevant for patients’ outcomes.

In conclusion, in this study, the time elapsed between the indication for enteral nutrition and its effective start was too long. Most patients did not achieve the prescribed daily calorie goal, and this failure was most often associated with the use of midazolam and assistance by a reduced nursing staff.

Financial Disclosures
None reported.

REFERENCES


To purchase electronic or print reprints, contact American Association of Critical-Care Nurses, 101 Columbus, Aliso Viejo, CA 92656, Phone, (800) 889-1712 or (949) 362-2050 (ext 532); fax, (949) 362-2049; e-mail, reprints@aacn.org.
Nurse to Bed Ratio and Nutrition Support in Critically Ill Patients
Carolina Keiko Yamamoto Honda, Flávio Geraldo Rezende Freitas, Patricia Stanich, Bruno Franco Mazza, Isac Castro, Ana Paula Metran Nascente, Antonio Toneti Bafi, Luciano Cesar Pontes Azevedo and Flávia Ribeiro Machado

Am J Crit Care 2013;22 e71-e78 10.4037/ajcc2013610
©2013 American Association of Critical-Care Nurses
Published online http://ajcc.aacnjournals.org/

Personal use only. For copyright permission information:
http://ajcc.aacnjournals.org/cgi/external_ref?link_type=PERMISSIONDIRECT

Subscription Information
http://ajcc.aacnjournals.org/subscriptions/

Information for authors
http://ajcc.aacnjournals.org/misc/ifora.xhtml

Submit a manuscript
http://www.editorialmanager.com/ajcc

Email alerts
http://ajcc.aacnjournals.org/subscriptions/etoc.xhtml