

## Necrotizing soft-tissue infections

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*This letter concerns an article in a Cleveland Clinic Journal of Medicine supplement (Infections in Hospitalized Patients: Urgent Challenges, Evolving Management) distributed to only a portion of the Journal's regular readership, owing to the terms of the grant supporting the supplement. The supplement is available free to all online at [www.ccjm.org/toc/hospitalinfections.htm](http://www.ccjm.org/toc/hospitalinfections.htm).*

**TO THE EDITOR:** I read with great interest your excellent supplement, *Infections in Hospitalized Patients: Urgent Challenges, Evolving Management* (August 2007). I was particularly interested in the section on necrotizing fasciitis in the article by Merlino and Malangoni on complicated skin and soft-tissue infections.<sup>1</sup> The authors state that amputation may be necessary in up to one-third of patients with necrotizing soft-tissue infections involving the extremities, citing a retrospective patient series at a university center reported by McHenry et al in 1995.<sup>2</sup> However, McHenry et al reported an amputation rate of nearly 50% if the infection involved an extremity, in addition to an overall mortality rate of 29% in the series.<sup>2</sup>

Additionally, Drs. Merlino and Malangoni make no mention of the role of adjunctive hyperbaric oxygen therapy for necrotizing soft-tissue infections. This may represent a bias on their part, as the 1995 report by McHenry et al (of which Dr. Malangoni was a coauthor) states: "No patient in our series was treated with hyperbaric oxygen. To date, the efficacy of hyperbaric oxygen in treatment of [necrotizing soft-tissue infections] has not been established by controlled studies, and delays in debridement have been reported with its use."<sup>2</sup>

I believe it is important to include this potentially useful adjunctive therapy in discussions of necrotizing soft-tissue infections, in light of several recent papers that support the use of hyperbaric oxygen—in terms of lower mortality, lower rates of morbidity (amputation), earlier wound closure, and no delays to debridement—in these difficult cases.<sup>3-6</sup>

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**IN REPLY:** We thank Dr. Cianci for his thoughtful comments. Our review on the treatment of complicated soft-tissue infections<sup>1</sup> was not intended to be a dissertation on the management of necrotizing fasciitis. We agree that any comprehensive discussion of this entity should include a review of the role and possible benefits of hyperbaric oxygen.

The literature on the benefits of hyperbaric oxygen for necrotizing soft-tissue infections is inconsistent. The Undersea and Hyperbaric Medicine Society makes the following statement on its use for these infections: "The primary treatments for necrotizing soft tissue infection are surgical excision of infected tissue and administration of appropriate antibiotics. *In selected cases [emphasis added], addition of hyperbaric oxygen therapy may be both lifesaving and cost effective.*"<sup>7</sup>

Unfortunately, no prospective controlled trials have examined hyperbaric oxygen therapy for this indication. The concern about retrospective studies in this population is that sicker patients are likely to be excluded from treatment with hyperbaric oxygen because they cannot be sustained or attended to in a hyperbaric chamber. These exclusions would bias the treatment effect to favor hyperbaric oxygen when in fact there might be no benefit. In addition, the use of hyperbaric oxygen is associated with complications, including barotrauma, oxygen toxicity, and decompression illness, that may be detrimental to the many patients with necrotizing soft-tissue infections who are critically ill.

The literature on the risk of extremity amputation for these infections has been relatively consistent over time, and this risk is significantly influenced by delays in presentation and debridement.<sup>8</sup> Primary therapy remains fluid resuscitation, broad-spectrum antibiotics, and rapid and aggressive surgical debridement. Any delay in treatment—especially to transfer a patient with an active infection to another facility solely to institute hyperbaric oxygen therapy—is ill-advised and may result in loss of life.

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## CT screening for lung cancer

(JUNE 2007)

*The CCJM publishes editorials, such as the one from Dr. Yankelevitz in our June 2007 issue, to provide our readers with an alternative view of a topic reviewed in our journal. They do not undergo our usual peer review process; we expect an “opinion piece,” and count on the authors to present their perspective in a forthright, accurate manner. Drs. Bach and Yankelevitz obviously disagree about defining symptoms due to risk factors for lung cancer and those due to early lung cancer. A detailed discussion can be found in letters to JAMA 2007; 298:513–516.*

**TO THE EDITOR:** My colleagues and I recently published an evaluation of computed tomographic (CT) screening, in which we found that screening did not reduce lung cancer mortality rates.<sup>1</sup> In an editorial in the *Cleveland Clinic Journal of Medicine*,<sup>2</sup> Yankelevitz characterizes our study differently, and in doing so makes several inaccurate claims.

First, as we stated in our manuscript, all eligible subjects who were screened in our three cohorts and who could be followed through public death records (99% of enrolled subjects) were included in our analyses of lung cancer mortality rates. Yankelevitz thinks we should have excluded from our study several of the patients who died, because they could have harbored symptoms of lung cancer at study entry. As our study enrolled older patients with heavy smoking histories, nonspecific pulmonary symptoms were likely common, and so my colleagues and I disagree with Yankelevitz. We believe we assessed the cohort most relevant to our study question. Either way, it was inaccurate for

Yankelevitz to suggest that he was presenting new information about our study in his editorial. He was just stating his opinion.

Second, as we stated in our manuscript, we compared the observed (“O”) and expected (“E”) number of deaths from lung cancer using the equation  $(O - E)^2/E$ , which produces a chi-squared statistic with 1 degree of freedom. So, our primary result of 38.8 expected deaths vs 38 observed resulted in the equation  $(38 - 38.8)^2/38.8$ , a chi-squared statistic of 0.02, and a two-sided *P* value of .90. Yankelevitz declares that removing from our analysis five patients who died would create the appearance of a statistically significant reduction in the number of lung cancer deaths. Yet removing five deaths changes the calculation to  $(33 - 38.8)^2/38.8$ , which has a chi-squared statistic of 0.87 and a *P* value of .35. So here too Yankelevitz was inaccurate when he suggested that our findings were sensitive to small changes in the number of observed events. One only achieves a *P* value less than .05 after removing 12, not 5, of the 38 deceased patients from the analysis.

Lastly, Yankelevitz asserts that patients who have any symptoms suggestive of lung cancer are actually ineligible for enrollment in a screening program. Yet in Yankelevitz's own multicenter International Early Lung Cancer Action Program (I-ELCAP) study of CT screening, which he claims in his editorial showed that screening is beneficial, there was no exclusion of subjects for symptoms of lung cancer. Instead, the protocol specified a common regimen of screening but allowed each participating institution to specify its criteria for enrollment.<sup>3</sup> The Danish Lung Cancer Screening trial, begun in 2004, has no exclusion for patients based on symptoms (<http://clinicaltrials.gov>), and neither does the Dutch-Belgian randomized lung cancer screening trial (the “NELSON” trial).<sup>4</sup> The National Lung Screening Trial in the United States (the Lung Screening Study) excludes subjects who had recent profound weight loss (> 15 pounds) or hemoptysis, but not other symptoms that could be due to lung cancer.<sup>5</sup> So, here again, it was inaccurate for Yankelevitz to assert as scientific dogma a set of standards for eligibility that neither he, nor his colleagues in I-ELCAP, nor the large consortia of scientists evaluating screening in the United States and Europe apply.

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**IN REPLY:** There really should be no confusion about what screening for a cancer is about. On the National Cancer Institute Web site's "Dictionary of Cancer Terms,"<sup>1</sup> screening is defined as "checking for disease when there are *no symptoms* [emphasis added]," and the National Cancer Institute expert advisory panel, the Physician Data Query, gives the following definition: "Screening is a means of detecting disease early in *asymptomatic* people [emphasis added]."<sup>2</sup> The American Cancer Society defines screening as "the search for disease, such as cancer, in people *without symptoms* [emphasis added]."<sup>3</sup> The recently published American College of Chest Physicians guidelines on screening for lung cancer, of which Bach is the lead author, states that the objective was to "review the evidence for and against screening for lung cancer with low-dose CT and offer recommendations regarding its usefulness for *asymptomatic* patients [emphasis added]."<sup>4</sup>

In my editorial, I referred to an article by Bach et al<sup>5</sup> that stated that the subjects of their study were "individuals with a smoking history and no prior history or symptoms suggestive of lung cancer." In his letter he changes the description of the cohort to one that includes participants who had "nonspecific symptoms," rejects the notion that being asymptomatic is a requirement for screening, and implies that the International Early Lung Cancer Action Program (I-ELCAP) has no such criteria for ensuring absence of symptoms.

That is incorrect. The I-ELCAP protocol clearly states in its section on indications for screening that, "symptomatic persons are ineligible for enrollment."<sup>6</sup> When Bach notes that each participating institution specified its criteria for enrollment, this is without context. The protocol makes it obvious that the indications we are referring to are age and smoking history, not the absence of symptoms of lung cancer.<sup>6</sup> Regarding the National Lung Screening Trial, the only large study in the United States outside of the I-ELCAP, on its

Web site under "eligibility" it states, "no present symptoms suggestive of current lung cancer, *including*: unexplained weight loss of over 15 pounds within the past 12 months or unexplained hemoptysis [emphasis added],"<sup>7</sup> with the implication that other symptoms are also considered.

The reason I noted that only 5 deaths needed to be excluded from the analysis of Bach et al to result in a statistically significant reduction in mortality by CT screening for lung cancer in contrast to the 12 deaths said to be required by Bach is as follows. In Bach et al,<sup>5</sup> it is reported that the mathematical model employed actually predicts 48.3 deaths, not 38.8, and the data show 39 observed deaths, not 38. But Bach et al lower the number of deaths the model predicts by arbitrarily excluding those predicted in year 1 of CT screening, while in an earlier publication that describes the validation of the model,<sup>8</sup> Bach includes deaths in year 1. After such a major change it seems to me that Bach's claim that a validated model was employed is unjustified. Part of the rationale given for the exclusion of year 1 was that even though "CT screening would have appeared to reduce lung cancer mortality by 20% [with inclusion of year 1 deaths] . . . this reduction would not have been statistically significant."<sup>5</sup> However, the exclusion of 5 participants with symptoms of lung cancer on entry and who died of their lung cancer causes the number of observed deaths to be only 34, and results in a significant difference between the observed and expected deaths. Thus, with the exclusion of 5 participants, not 12, Bach et al would show a benefit associated with CT screening.

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