The Influence of Mucositis on Oral Thermometry:
When Fever May Not Reflect Infection

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Background. The mouth is the most common site for measuring temperature. Oral mucositis may affect up to 40% of patients who receive chemotherapy. Thus far, mucositis has not been studied with regard to accurate thermometry.

Methods. One hundred consecutive patients (25 per group) were self-referred on the basis of perception of mucositis, temperature measurement at home, or malaise or were referred by a nurse on the basis of an assessment of a potential infectious process and/or mucositis. Oral and tympanic temperature were assessed simultaneously in patients with no fever and no mucositis (group A), those with mucositis (group B), those with fever and no mucositis (group C), and those with neutropenia but not fever or mucositis (group D).

Results. The 4 groups of patients had higher oral temperatures than tympanic temperatures (group A, 36.9°C vs. 36.8°C [δ = 0.12°C; P = .062]; group B, 38.0°C vs. 37.1°C [δ = 0.89°C; P < .001]; group C, 38.7°C vs. 38.4°C [δ = 0.27°C; P < .001]; and group D, 37.0°C vs. 36.7°C [δ = 0.27°C; P < .001]). Scheffe a-posteriori test revealed that only the δ temperature in group B differed significantly (95% confidence limits, −2.471, −1.584; P < .001). A linear regression model that examined the effect of other variables on the δ temperature found that only mucositis was a significant factor (95% confidence limits, 0.582, 0.820; P < .001).

Conclusions. Mucositis causes an increase in oral temperature but does not elevate systemic body temperature, thereby casting doubt on the diagnosis of infection. Conceivably, mucositis may provide an “inflammation bias” that could lead to the overuse of antibiotics and growth factors in 20%–40% of patients with cancer. When one considers issues of antimicrobial resistance and cost, this concern should be tested and clarified in a prospective study based on accurate temperature measurement.

The accepted normal body temperature, as assessed by oral thermometry, is 36.8°C ± 0.4°C [1, 2]. In clinical practice, “body temperature” is approximated by temperature readings obtained at various anatomic sites (rectal, oral, tympanic, axillary, and arterial). None of the noninvasive thermometric measurements is universally accepted as optimal for monitoring body temperature. Because of the rectum’s isolation from the external environment, rectal temperature is considered by many to provide the most accurate approximation of body temperature. However, obtention of rectal temperature is inconvenient and carries a risk of bacteremia [3]. In theory, tympanic membrane is the ideal site for measuring core temperature, because the tympanum is perfused by a tributary of the artery that supplies the body’s thermoregulatory center [4]. The mouth is still the most commonly assessed site, because it is accessible and has a long tradition of use in clinical practice [5]. However, erroneous oral temperature measurements can be caused by a number of factors, including mastication (significant increase in oral temperature), swallowing (temporary decrease in oral temperature), and consumption of ice water (temporary decrease in oral temperature) [6]. Nevertheless, to the best of our knowledge, inflammation of the oral mucosa (i.e., mucositis carrying the classic definition of rubor, calor, dolor, and functio lesae) has not been studied with regard to accurate thermometry.

Several scales have been used to grade the severity of oral mucositis on the basis of mucosal appearance, severity of pain, and functional impairment of the patient [7]. The National Cancer Institute’s Common
Toxicity Criteria for Adverse Events [8] defines 5 grades of oral mucositis, with grade 0 denoting no toxic effect seen on oral mucosa and grade 5 denoting death due to a toxic effect of mucositis. In patients with cancer, oral mucositis is common [9, 10], affecting up to 40% of patients who are undergoing chemotherapy; severe mucositis (i.e., grades 3 and 4) occurs in 5%–15% of such patients. The pathogenesis of chemotherapy-induced mucositis is only partially understood; it is related to chemotherapeutic agents and to host factors [11].

Mucositis is a critical risk factor for bacteremia and sepsis, because it causes the breakdown of an anatomic barrier that separates microorganisms from the systemic circulation. Notably, 20%–40% of patients with treatment-related neutropenia experience mucositis [12].

Because fever is the key—and sometimes only—manifestation of serious infection, accuracy in temperature measurement and in the threshold for defining fever are crucial in the decision-making process, especially for immunocompromised patients [13]. In neutropenic patients, there is no predictive pattern of fever that can be used to exclude a noninfectious etiology [14].

As in most clinical situations, the body temperature in patients with cancer is usually measured orally, regardless of the presence of local inflammation, such as mucositis. Can “calor” (locally elevated temperature) affect body temperature and the decision to treat “fever” in patients with chemotherapy-induced neutropenia? We embarked on a study to measure the body temperature with 2 different methods (tympanic and oral) to determine the effect of mucositis on oral temperature measurements.

PATIENTS AND METHODS

This study was performed in the Day Care Unit of Davidoff Center, Rabin Medical Center (Petach Tikva, Israel). Body temperature was assessed by 2 methods simultaneously: tympanic temperature with a digital thermometer (Brown Thermo Scan IRT 4520) and oral temperature with a glass mercury thermometer. Both oral and tympanic thermometers were calibrated in a water bath with a temperature of 38°C. There was no discrepancy in the temperature reading for both thermometers. Oral temperature was recorded after 2 min. Tympanic temperature was recorded in accordance with manufacturer guidelines in a similar position in the ear (automatic sound) for each patient.

We included consecutive patients who were either self-referred on the basis of a perception of mucositis, fever, or malaise or who were referred by a nurse because of a suspicion of infection or mucositis. The control group consisted of patients with cancer who did not have any symptoms, neutropenia, and/or fever that were evaluated for reasons other than fever, neutropenia, or mucositis (e.g., administrative reasons or prescription writing). To increase the study’s power, we continued the study until 25 patients were included in each group.

Group A was the control group; group B consisted of patients with mucositis, with or without fever; group C consisted of patients with fever but without mucositis; and group D consisted of patients with neutropenia who had neither mucositis nor fever. The data from all patients were included in the analysis. All patients were assessed for mucositis by nursing staff, and the findings were verified by one of the investigators (N.B.C.). N.B.C. performed all of the thermometry assessments.

Mucositis was defined on the basis of the National Cancer Institute’s Common Toxicity Criteria for Adverse Events toxicity scale [8], as follows: grade 0, no findings; grade 1, erythema of the mucosa; grade 2, patchy ulceration; grade 3, confluent ulceration; grade 4, tissue necrosis; and grade 5, death due to mucositis.

The sample size of 25 patients for each of the groups B, C, and D was based on preliminary data, to get a power of >99% for the δ temperature (i.e., the oral temperature minus the tympanic temperature) for mucositis. In the first step, the patients’ characteristics were examined and compared between the 4 groups (A–D). The numerical measurements were expressed as means ± SDs and were compared using 1-way analysis of variance (ANOVA), whereas the categorical measurements were expressed as percentages and were compared using the χ² test. Because the oral, tympanic, and δ temperatures were found to be normally distributed, we then used Student’s t test to compare the mean oral and tympanic temperatures in each group and 1-way ANOVA to compare the mean values among the 4 groups and among the different grades of mucositis (no mucositis, mucositis with a grade of 1 or 2, and mucositis with a grade >2). For all ANOVA models, the a-posteriori Scheffe test was performed to detect specific differences between groups. Later, a multivariate regression model was used to examine the effect of several explanatory variables on the δ temperature.

All the analyses were performed using SPSS software, version 14.0.1 (SPSS); Splus, version 6.1 for Windows Professional Edition Release 1 (Lucent Technologies); and nQuery Advisor, version 2.0 (Statistical Solutions). The study was approved by the hospital’s Research Ethics Committee.

RESULTS

Table 1 shows the patients’ clinical characteristics. The comparisons of the mean oral temperature versus the mean tympanic temperature in each of the 4 groups are presented in Table 2. The difference between the oral and tympanic temperature measurements defines the variable “δ temperature” in line 3 (Table 2). The 4 groups of patients had higher oral than tympanic temperature measurements. In group A (the control group), the mean oral and tympanic temperatures were 36.89°C and 36.76°C, respectively (δ ± SD, 0.12°C ± 0.31°C; P = .062); in group B (patients with mucositis), the measurements
were 38.0°C and 37.1°C, respectively (δ ± SD, 0.89°C ± 0.24°C; P < .001); in group C (febrile patients without mucositis and neutropenia), the measurements were 38.66°C and 38.39°C, respectively (δ ± SD, 0.27°C ± 0.20°C; P < .001); and in group D (neutropenic patients without fever or mucositis), the measurements were 37.0°C and 36.73°C, respectively (δ ± SD, 0.27°C ± 0.09°C; P < .001). In 3 of these groups of patients (groups B, C, and D), the differences were statistically significant (P < .001), and in the fourth (group A), there was a trend toward a difference between the oral temperature measurement (36.9°C) and the tympanic temperature measurement (36.8°C; P = .062).

With use of the 1-way ANOVA method, it was found that there was a statistically significant difference between the mean δ temperatures in the 4 groups (P < .001). By using the Schef- a-posteriori test, we found that the δ temperature measurement in groups A, B, C, and D resembled each other and differed significantly (95% confidence limits, −2.471, −1.584; P < .001) from the oral versus tympanic measurement in the group of patients with mucositis (group B).

We also compared the grade [7] of mucositis among all the studied patients. The mean δ temperatures for no mucositis, grade 1 or 2 mucositis, and grade 3 mucositis were 0.2200, 0.9048, and 0.8500, respectively (P < .001). The degree of mucositis (i.e., the severity of mucositis) did not influence the δ temperature measurement.

Table 3 contains the results of the regression model used to examine the effect of the explanatory variables on the δ temperature. In this analysis, the presence of mucositis was the only significant factor to increase the δ temperature, with a coefficient of 0.701°C (95% confidence limits, 0.512°C, 0.820°C; P < .001). In practical terms, this finding indicates that the presence of mucositis increases oral temperature more than the tympanic temperature. Numerically, mucositis increases the mean δ temperature by 0.701°C (i.e., the regression coefficient) in favor of the oral measurement. All other factors were found to be nonsignificant with regard to the increase in the δ temperature.

**DISCUSSION**

In this report, we found that oral inflammation (i.e., mucositis) results in an increase in oral temperature but not in body temperature. Oral measurements of 38.2°C (100.7°F) due to mucositis occur with normal body temperature, thereby casting doubt on the diagnosis of infection. The severity of mucositis did not alter this finding, because most of the reported patients had mucositis with a mild to moderate grade. It could be that,
with severe mucositis, the $\delta$ temperature may be larger. As part of the inflammation process, mild-to-moderate mucositis may cause similar “calor” to that of more-severe mucositis.

Accurate definition of fever is essential for medical practice, because fever may be the only sign of infection. In patients with cancer, febrile neutropenia is a medical emergency [15, 16] that requires prompt therapy. The American Society of Clinical Oncology and the Infectious Disease Society provide a precise definition of fever [17]: an elevation of body temperature greater than normal (i.e., 37.0°C [98.6°F]). In practice, a single oral temperature of >38.3°C (>101°F) or 2 readings of >38.0°C (>100.4°F) are considered to be significant. On the other hand, the medical literature has not distinguished temperature measurement with and without local inflammation, although the consequences of this may be substantial [18]. Revised American Society of Clinical Oncology guidelines from 2006 lowered the threshold (from 40%) for prophylactic treatment, recommending administration of growth factors for any patient who has a ≥20% risk of developing neutropenic fever or specific chemotherapy schedules and for elderly patients with chronic debilitating diseases.

It is worrisome, however, that in the studies that led to these guidelines, 20%–40% of the patients also had mucositis. Indeed, up to 60% of the patients who received anthracycline-based chemotherapy for breast cancer and the 20%–35% of patients who received 5-fluorouracil–based chemotherapy for colon cancer are expected to develop mucositis as one of the most common adverse effects of these regimens. Conceivably, it is possible that the recommendations for prophylactic growth factor support were, in part, based on oral temperature measurements that did not reflect body temperature, but instead an increased local oral temperature caused by mucositis. More broadly speaking, the implication is that “infection” may be overdiagnosed in patients with cancer because of oral inflammation.

The inclusion criteria in studies of neutropenic fever are oral temperature >38.3°C or 2 consecutive orally measured temperatures >38.0°C. However, none of these studies stratified patients on the basis of whether they had mucositis. This common adverse effect perhaps provided an “inflammation bias” that could lead to the overdiagnosis of infection and the unnecessary administration of antibiotics and growth factors in up to 20%–40% of patients with cancer. If one considers the enormous implications of antimicrobial resistance and the associated cost, one would see that these concerns deserve to be tested in a prospective study that includes mucositis as a variable that may result in an increase in temperature measurements.

Rubenstein et al. [19] reported on the clinical practice guidelines for the prevention and treatment of cancer therapy–induced oral and gastrointestinal mucositis, and they described the incidence of and the preventive and therapeutic measures of this major chemotherapy/radiotherapy–induced adverse effect. On the basis of this report, there are few treatments [20] to prevent oral mucositis. Thus, patients will continue to experience this debilitating toxicity.

Tympanic thermometry remains the best means to approximately measure body temperature. Inaccuracy in tympanic

### Table 2. Oral and tympanic temperature measurements.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature, mean °C ± SD</td>
<td>36.89 ± 0.35</td>
<td>38.00 ± 0.43</td>
<td>38.66 ± 0.31</td>
<td>37.00 ± 0.25</td>
</tr>
<tr>
<td>Oral</td>
<td>36.76 ± 0.39</td>
<td>37.10 ± 0.46</td>
<td>38.39 ± 0.39</td>
<td>36.73 ± 0.28</td>
</tr>
<tr>
<td>Tympanic</td>
<td>0.12 ± 0.31</td>
<td>0.89 ± 0.24</td>
<td>0.27 ± 0.18</td>
<td>0.27 ± 0.09</td>
</tr>
<tr>
<td>$\delta$ Temperature*</td>
<td>0.0067, 0.25</td>
<td>0.79, 0.99</td>
<td>0.19, 0.34</td>
<td>0.22, 0.30</td>
</tr>
<tr>
<td>95% confidence limits</td>
<td>.062</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**NOTE.** Group A, control group (i.e., subjects without mucositis, fever, or neutropenia); group B, patients with mucositis; group C, febrile patients with neither neutropenia nor mucositis; group D, neutropenic patients with neither fever nor mucositis.

* Oral temperature minus tympanic temperature.

* Determined using the 2-sided parametric test.

### Table 3. Linear regression analysis for $\delta$ temperature as the predicted (outcome) variable.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Regression coefficient B (95% confidence limits)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>0.701 (0.582, 0.820)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0.071 (−0.052, 0.193)</td>
<td>.256</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>−0.11 (−0.196, 0.175)</td>
<td>.907</td>
</tr>
<tr>
<td>Sex</td>
<td>−0.19 (−0.166, 0.128)</td>
<td>.799</td>
</tr>
<tr>
<td>Malignancy site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>−0.015 (−0.511, 0.481)</td>
<td>.953</td>
</tr>
<tr>
<td>Colon</td>
<td>0.027 (−0.461, 0.516)</td>
<td>.911</td>
</tr>
<tr>
<td>Lung</td>
<td>0.058 (−0.439, 0.555)</td>
<td>.817</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.027 (−0.488, 0.543)</td>
<td>.917</td>
</tr>
<tr>
<td>Other</td>
<td>0.063 (−0.447, 0.573)</td>
<td>.806</td>
</tr>
</tbody>
</table>

**NOTE.** All other factors were found to have a nonsignificant effect on the $\delta$ temperature.
Mucositis May Spuriously Increase Oral Temperature


thermometry can be related to position, noncompliance with the manufacture’s guidelines, and reduced blood flow. In our study, a single investigator performed all tympanic and oral thermometry measurements to reduce operator inconsistency.

Our findings could have implications for nonmalignant diseases for which local inflammation elevates the local temperature, including otitis media, inflammatory bowel disease, follicular tonsillitis, and gingival infection. Furthermore, in malignant diseases treated with local radiotherapy (e.g., rectal, head, and neck malignancies and prostate cancer), the potential for a discrepancy between local and “true” body temperatures should be kept in mind.

We propose that the definition of fever should be broadened to include the stipulation that the site of measurement should have no evidence of local inflammation. In the presence of mucositis, oral temperature measurements should be disregarded. Tympanic thermometry should become standard for these patients. This practice could eliminate another source of overuse of antibiotics and growth factors.

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References