Title
Axillary, oral and rectal routes of temperature measurement during treatment of acute kawasaki disease

Permalink
https://escholarship.org/uc/item/3d4969xr

Journal
Pediatric Infectious Disease Journal, 35(1)

ISSN
0891-3668

Authors
Kanegaye, JT
Jones, JM
Burns, JC
et al.

Publication Date
2016-01-01

DOI
10.1097/INF.0000000000000923

Peer reviewed
Axillary, Oral and Rectal Routes of Temperature Measurement During Treatment of Acute Kawasaki Disease

John T. Kanegaye, MD,*† Jefferson M. Jones, MD, MPH,*† Jane C. Burns, MD,*† Sonia Jain, PhD,‡ Xiaoqing Sun, MS,§ Susan Jimenez-Fernandez, MD,* Erika Berry, BA,* Joan M. Pancheri, RN, BSN,† Preeti Jaggi, MD,§ Octavio Ramilo, MD,§ and Adriana H. Tremoulet, MD, MAS**†

Background: Important therapeutic decisions are made based on the presence or absence of fever in patients with Kawasaki disease (KD), yet no standard method or threshold exists for temperature measurement during the diagnosis and treatment of these patients. We sought to compare surface and internal (rectal or oral) routes of temperature measurement for the detection of fever as a marker of treatment resistance.

Methods: From a randomized, placebo-controlled trial of infliximab as an adjunct to primary intravenous immunoglobulin treatment for acute KD, we collected temperature measurement (within 5 minutes) axillary and internal temperature measurements and performed receiver-operating characteristic and Bland-Altman analyses. We also determined the ability of surface temperatures to detect treatment resistance defined by internal temperature measurements.

Results: Among 452 oral-axillary and 439 rectal-axillary pairs from 159 patients, mean axillary temperatures were 0.25 and 0.43°C lower than oral and rectal temperatures and had high receiver-operating characteristic areas under curves. However, axillary temperatures ≥38.0°C had limited sensitivity to detect fever defined by internal temperatures. Axillary thresholds of 37.5 and 37.2°C provided maximal sensitivity and specificity to detect oral and rectal temperatures ≥38.0°C, respectively.

Conclusions: Axillary temperatures are an insensitive metric for fevers defining treatment resistance. Clinical trials should adopt temperature measurement by the oral or rectal routes for adjudication of treatment resistance in KD.

Key Words: Kawasaki disease, fever measurement methods

(Pediatr Infect Dis J 2016;35:50–53)

Accepted for publication September 14, 2015.

From the *Department of Pediatrics, University of California San Diego School of Medicine, La Jolla, California; †Rady Children’s Hospital San Diego, San Diego, California; ‡Department of Family and Preventive Medicine, University of California San Diego School of Medicine, La Jolla, California; and §Department of Pediatrics, The Ohio State University and Nationwide Children’s Hospital, Columbus, Ohio. J.T.K. and J.M.J. contributed equally to the study. Supported in part by the Food and Drug Administration Orphan Drug Program (FD 003514; to J.C.B. and A.H.T.); National Heart, Lung, Blood Institute at the National Institutes of Health (RO1 HL69413; to J.C.B. and J.T.K.); and The Harold Amos Medical Faculty Development Program from the Robert Wood Johnson Foundation (to A.H.T.). The authors have no conflicts of interest to disclose.

Address for correspondence: John T. Kanegaye, MD, Division of Emergency Medicine, Rady Children’s Hospital San Diego, 3020 Children’s Way (MC 5075), San Diego, CA 92123. E-mail: jkanegaye@rchsd.org.

© 2015 Wolters Kluwer Health, Inc. All rights reserved. ISSN: 0891-3668/16/3501-0050 DOI: 10.1097/INF.0000000000000923

Fever is invariably present in children with acute Kawasaki disease (KD) and is the clinical sign that dictates many interventions, including retreatment after initial therapy with intravenous immunoglobulin (IVIG). Despite the importance of fever in KD, no detailed study of best practice for fever measurement has been performed in this patient population, and approaches vary widely across medical centers and between the United States and Japan, the country of highest incidence. Previous clinical studies of patients with KD have not specified a standard route of temperature measurement. The lack of uniformity in fever definition may contribute to differences in treatment failure rates among sites and studies. A phase III clinical trial of intensification of primary IVIG treatment of acute KD with infliximab provided an opportunity to analyze agreement within a large set of temperature readings concurrently measured by different routes and to inform best practices for temperature routes and thresholds in KD research and clinical practice. We postulated that axillary temperatures would differ significantly from oral and rectal temperatures and lack sensitivity for detecting fever in patients with KD.

MATERIALS AND METHODS

Study Population
Subjects were patients with KD enrolled and treated in a randomized, placebo-controlled phase III trial of infliximab as an adjunct to IVIG treatment. The patients were 4 weeks to 17 years old, had fever for 3–10 days (illness day 1: first day of fever ≥38.0°C) at the time of study enrollment and met the American Heart Association definition of KD. The institutional review boards of the University of California San Diego and Nationwide Children’s Hospital reviewed and approved this study, and all parents provided signed, informed consent.

Study Design and Definitions
Nurses measured temperatures using digital thermometers (model Adtemp II 413, American Diagnostic Corp, Hauppauge, NY) every 6 hours by both surface (axillary) and internal (rectal or oral, based on the nurse’s assessment of age and developmental level) routes before scheduled aspirin doses. Each patient had 2 thermometers, each designated for a specific route. Additional temperatures were measured if clinically indicated. During infusions of IVIG and study medication, nurses obtained hourly measurements by the axillary route only. After discharge, the legal guardian used the same model of thermometer to record temperatures by a single route once daily between 4:00 and 6:00 pm for 3 days. We defined treatment resistance as fever occurring between 36 hours and 7 days after completion of the IVIG infusion without another likely source and used a threshold of ≥38.0°C by any route.

We included temperature pairs if a surface and an internal temperature (eg, oral-axillary or rectal-axillary) were recorded within 5 minutes of each other. If >2 temperature measurements occurred within 5 minutes, only the first 2 qualifying temperatures were included. Among patients with treatment resistance, we determined whether axillary temperatures were sufficient to identify the need for retreatment at any time during the inpatient observation period.

Statistical Analysis
We conducted descriptive analyses and generated a scatterplot of surface-internal temperature pairs, calculating Pearson correlation coefficient for the paired measurements. We analyzed
the agreement between the internal and surface temperatures with Bland-Altman plots to which we added linear regression lines showing the relationship of temperature differences against mean temperature. We conducted a receiver-operating characteristic (ROC) analysis, calculating areas under the curve (AUCs) as a measure of the ability of surface temperatures to detect fever defined by internal temperatures. Sensitivities and specificities were calculated for surface temperatures of ≥37.5 and ≥38.0°C with 95% confidence intervals (CIs) computed using the bootstrap approach. We also identified the surface temperature threshold corresponding to the highest sum of sensitivity and specificity. P values <0.05 were considered statistically significant. Statistical analyses were performed in R-project (http://cran.r-project.org), version 3.0.2.

RESULTS
Of 196 patients enrolled, 195 completed the study and provided 6869 total temperature measurements. After excluding temperatures taken during medication infusion (35%) and temperatures not paired within 5 minutes, 1782 temperature measurements (25.9%) from 159 patients qualified for analysis, yielding 452 oral-axillary pairs (median patient age: 4.5 years; range: 1.9–13.6 years) and 439 rectal-axillary pairs (median patient age: 2.0 years; range: 0.2–6.5 years). Strong correlations existed between surface and internal temperatures: for all pairs, 0.852 (P < 0.001); for oral-axillary pairs, 0.859 (P < 0.001); for rectal-axillary pairs, 0.854 (P < 0.001; Fig. 1). The mean oral temperature was higher than the mean surface temperature by 0.25°C (95% CI: −0.78 to 1.28°C); the mean rectal temperature was higher than the mean surface temperature by 0.43°C (95% CI: −0.66 to 1.53°C), but the differences were not statistically significant (Fig. 2). The axillary-oral temperature difference tended to disappear at higher mean temperatures, but axillary-rectal differences remained constant.

ROC analysis revealed high AUCs for the axillary route of detection of fever defined by internal temperature ≥38.0°C: 0.983 (95% CI: 0.970–0.997) against oral measurements; 0.967 (95% CI: 0.949–0.985) against rectal measurements and 0.972 (95% CI: 0.959–0.984) against any internal method. However, the axillary temperature threshold of 38.0°C had limited sensitivity for detection of fever defined by internal temperatures (Table 1). An axillary temperature threshold of 37.5°C had highest sensitivity and specificity (0.94 for both) for the detection of fever defined by oral temperatures ≥38.0°C, and axillary threshold of 37.2°C was optimal to detect rectal temperatures ≥38.0°C (Table 1).

In this clinical trial, 22 subjects had a rectal or oral temperature ≥38.0°C at least 36 hours after completion of their initial IVIG infusion and received a second treatment with IVIG as rescue therapy (17 during the initial admission and 5 during a readmission). If we had used axillary temperatures alone, 2 of the 17 subjects...
retreated during their initial admission may not have received additional therapy. This omission would have changed the conclusions of our clinical trial regarding the intensification of initial therapy with infliximab to prevent IVIG resistance. An axillary temperature threshold of 37.5°C would have detected the fever that prompted retreatment in only 1 of the patients, but a threshold of 37.2°C would not have improved detection.

**DISCUSSION**

In this first large-scale study of paired temperatures obtained during the same phase of illness and treatment from a cohort of patients with acute KD, surface temperatures were, on average, lower than oral and rectal temperatures. However, the temperature differences were highly variable and lacked statistical significance. Despite high ROC AUCs, axillary temperatures ≥38.0°C had limited sensitivity to detect fever defined by concurrent oral and rectal temperatures. The axillary temperature threshold of ≥37.5°C, commonly used by Japanese investigators, was more sensitive but still misclassified as afebrile in 6% and 20% of fevers defined by oral and rectal temperatures, respectively.

The diagnosis and treatment of KD rely on accurately identifying fever. IVIG resistance, with its increased risk for coronary aneurysms and need for additional treatment, is defined by the persistence or recurrence of fever. However, the 2004 American Heart Association statement, the Centers for Disease Control case definition and the American Academy of Pediatrics Committee on Infectious Diseases Red Book provide no definitions for fever in KD. Published temperature criteria for the adjudication of fever and treatment resistance as ≥38.0°C inadequately detects fevers identified by oral or rectal temperatures. The variation in surface–internal temperature differences in our study may affect fever detection. Although nurses were not blinded to the results of temperature pairs or to clinical condition, they were not aware of the study objective and were blinded to the treatment allocation. Therefore, the knowledge of initial temperature should not have influenced the second measurement. Because our subjects were under treatment for an illness characterized by changes in body temperature, an unknown number of paired temperature measurements may have been obtained during rapid temperature changes. Thus, surface–internal temperature differences may reflect true changes in body temperature and differences in route of measurement, particularly if the separation in measurements was greater than the documented 5 minutes. Other temperature route warrant study in KD, because data from other acutely ill pediatric populations suggest that the tympanic route is superior to the axillary route in detecting rectal temperature elevation. Finally, because the first detected temperature ≥38.0°C led to prompt IVIG retreatment, our data cannot determine whether a single temperature elevation by any route predicts sustained fever or whether fever undetected by a single axillary measurement is readily detected during the ensuing hours or days.

Axillary temperature measurement at thresholds of 37.5 or 38.0°C inadequately detects fevers identified by oral or rectal routes during the treatment of acute KD. If axillary temperature measurement must be used because of hospital protocol, a threshold of 37.2°C may be a better predictor of fever for patients with KD. Because of the importance of fever in the diagnosis and management of acute KD, temperatures should preferably be measured by the rectal or oral route with a standardized threshold to define fever for clinical care and research.

### TABLE 1. Performance of Axillary Temperature Measurement in Detecting Fever Defined by Concurrent Oral or Rectal Temperature Measurement in Hospitalized Children With Acute Kawasaki Disease

<table>
<thead>
<tr>
<th>Ability of axillary temperature ≥37.5°C to detect concurrent:</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral temperature ≥38.0°C</td>
<td>0.94 (0.88–0.98)</td>
<td>0.94 (0.92–0.97)</td>
</tr>
<tr>
<td>Rectal temperature ≥38.0°C</td>
<td>0.80 (0.71–0.89)</td>
<td>0.96 (0.94–0.98)</td>
</tr>
<tr>
<td>Ability of axillary temperature ≥38.0°C to detect concurrent:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral temperature ≥38.0°C</td>
<td>0.73 (0.63–0.84)</td>
<td>0.99 (0.98–1.0)</td>
</tr>
<tr>
<td>Rectal temperature ≥38.0°C</td>
<td>0.59 (0.47–0.70)</td>
<td>0.99 (0.99–1.0)</td>
</tr>
<tr>
<td>Ability of optimal axillary temperature ≥37.2°C to detect fever defined by rectal temperatures ≥38.0°C*†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral temperature ≥38.0°C</td>
<td>0.85 (0.80–0.90)</td>
<td>0.94 (0.91–0.96)</td>
</tr>
</tbody>
</table>

*With rounding, the values of sensitivity and specificity for the optimal axillary temperature threshold (37.45°C) to detect oral temperature ≥38.0°C are the same as for the axillary temperature threshold of 37.5°C.
†Optimal axillary temperature to detect rectal temperature ≥38.0°C rounded from 37.25°C.

© 2015 Wolters Kluwer Health, Inc. All rights reserved.
REFERENCES


