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PHARMACOLOGY

Performance of Bayesian Area Under the Concentration-Time Curve-Based Pharmacokinetic Dosing Based on a One-Compartment Model and Trough-Only Monitoring for Vancomycin

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ABSTRACT A novel Bayesian method was developed to interpret serum vancomycin concentrations (SVCs) following the administration of one or more vancomycin doses with potential varying doses and intervals based on superposition principles. The method was evaluated using retrospective data from 442 subjects from three hospitals. The patients were required to receive vancomycin for more than 3 days, have stable renal function (fluctuation in serum creatinine of ≤0.3 mg/dL), and have at least 2 trough concentrations reported. Pharmacokinetic parameters were predicted using the first SVC, and the fitted parameters were then used to predict subsequent SVCs. Using only covariate-adjusted population prior estimates, the first two SVC prediction errors were 47.3 to 54.7% for the scaled mean absolute error (sMAE) and 62.1 to 67.8% for the scaled root mean squared error (sRMSE). "Scaled" refers to the division of the MAE or RMSE by the mean value. The Bayesian method had minimal errors for the first SVC (by design), and for the second SVC, the sMAE was 8.95%, and the sRMSE was 36.5%. The predictive performance of the Bayesian method did degrade with subsequent SVCs, which we attributed to time-dependent pharmacokinetics. The 24-h area under the concentration-time curve (AUC) was determined from simulated concentrations before and after the first SVC was reported. Prior to the first SVC, 170 (38.4%) patients had a 24-h AUC of <400 mg · h/L, 186 (42.1%) had a 24-h AUC within the target range, and 86 (19.5%) had a 24-h AUC of >600 mg · h/L. After the first SVC was reported, 322 (72.9%) had a 24-h AUC within the target range, 68 (15.4%) had low values, and 52 (11.8%) had high values based on the model simulation. Target attainments were 38% before the first SVC and 73% after the first SVC. The hospitals had no policies or procedures in place for targeting 24-h AUCs, although the trough target was typically 13 to 17 mg/L. Our data provide evidence of time-dependent pharmacokinetics, which will require regular therapeutic drug monitoring regardless of the method used to interpret SVCs.

KEYWORDS AUC, Bayesian, dosing, pharmacokinetics, therapeutic drug monitoring, vancomycin

Updated 2020 guidelines for vancomycin dosing call for dose regimens targeting a 24-h area under the concentration-time curve (AUC) of 400 to 600 mg · h/L, which appears to minimize the risk of nephrotoxicity (1). The guidelines further recommend obtaining two postdose trough concentrations with the use of either one-compartment model equations or Bayesian modeling for interpretation. The use of one serum concentration (trough) has been commonplace for the past 2 decades, and there are economic

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consequences of increasing the number of serum vancomycin concentrations (SVCs) (2). With a one-compartment model, the only approach to determine pharmacokinetic parameters using one SVC is to fix one of two parameters and solve the other or to use Bayesian estimation (3). An evaluation of a two-compartment Bayesian module implemented in Adapt 5 (4) demonstrated that trough variation is reflected mostly by variation in 1 of the 4 parameters (volume of distribution for the central compartment (V_c) or clearance) depending on model parameterization. (see supplemental appendix B) (D. Nix, unpublished data). The Adapt 5 Bayesian module also includes measurement error in the concentration as part of the Bayesian objective function; however, the difference between measured and predicted concentrations is usually small. Consequently, we believe that a two-compartment model is too complex for the available information and that simplification to a one-compartment model is appropriate; however, there are still two parameters and measurement error that need to be handled. There are an infinite number of model curves based on two parameters that can pass through a single concentration, and this is complicated by the inclusion of measurement error. While analytical error is always present, there is no information about the direction or magnitude with only one concentration. For most laboratory measurements in medicine, we assume that the reported values are true, and in the absence of any information to the contrary, we should do the same with an SVC.

A one-compartment Bayesian method was used to estimate pharmacokinetic parameters (k_e) and volume of distribution (V_d) in the setting of a single concentration (usually trough), which was considered a true value. This simplification allows the estimation of
AQ: B parameters using various platforms without iterative algorithms. The performance of this method was evaluated using a retrospective record review of 442 patients who had at least two vancomycin serum concentrations collected during different dosing intervals. Pharmacokinetic parameters were estimated based on the first serum concentration, and the performance of the model in predicting future concentrations was evaluated. Given dose regimen changes, this served as a means to test the performance of the new
AQ: C method. The simple modified Bayesian method provides a cost-effective approach to
AQ: D monitoring vancomycin therapy. Interoccasion variability refers to differences in within-subject parameter values at different times (occasions). One study modeled interoccasion variability with vancomycin and reported a decrease in clearance (CL) of 20.5% and
AQ: E a decrease in V of 22.0% after 72 h (5). We attempt to shed some light on interoccasion
AQ: F variability and its importance for the therapeutic drug monitoring (TDM) of vancomycin.

RESULTS

A total of 442 subjects were included in the analysis. The initial target was 450 subjects; however, 8 subjects were later excluded due to unstable renal function, missing or erroneous time data, or a body mass index (BMI) of >35. The mean age ± standard deviation (SD) was 55.4 ± 15.8 years, the mean height was 172 ± 11.0 cm, the mean weight was 77 ± 17 kg, and the mean BMI was 25.9 ± 4.80 kg/m^2. Sixty-eight percent of the subjects were male. The median baseline serum creatinine (sCR) concentration (range) was 0.70 (0.16 to 2.25) mg/dL, and the median estimated creatinine clearance (CL_{cr}) (range) was 112 (39 to 182) mL/min. Acute kidney injury (AKI) was detected in 29 subjects (6.7%) after 4 to 20 days of vancomycin therapy. Data from before the change in sCR were included for these subjects.

The first dose values ranged from 500 to 2,000 mg, with one-third receiving 1,000 mg or lower and the remaining two-thirds receiving 1,250 mg or higher. A median of 4 doses (range, 1 to 21) were administered prior to obtaining the first SVC, with the last pre-SVC dose time averaging 40.8 ± 22.8 h. The average daily dose was 2,297 ± 782 mg, with a range of 744 to 5,125 mg. An additional median (range) of 14 (2 to 96) doses were tracked after the first SVC measurement. The average daily dose after the first SVC, 2,286 ± 870 mg/day, was almost identical to the dose prior to the first SVC. The numbers of repeat SVCs available per number of subjects were 2 (n = 223), 3 (n = 126), 4 (n = 64),

25/4/23 | 18:06 | 4/Color Fig: 3 | ArtID: 00172-23 | DOI:10.1128/aac.00172-23 | CE: KGL-cld

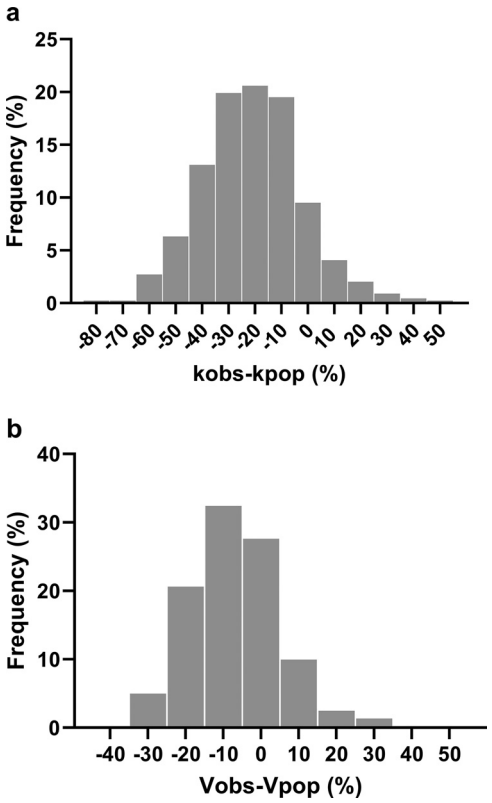

FIG 1 Percent differences in k_{obs} relative to k_{pop} estimates (a) and percent differences in V_{obs} relative to V_{pop} estimates (b).

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5 (n = 21), and 6 or more (n = 8). The majority of SVCs were obtained as troughs within 1 h of the next dose.

F1 Figure 1a and 1b show histograms of the percent differences in the observed k (k_{obs}) and V (V_{obs}) relative to the population estimates of k (k_{pop}) and V (V_{pop}), respectively. The population prior estimate of k was determined as the population estimate of clearance (CL_{pop}) divided by V_{pop}. It is useful to point out that if the observed serum vancomycin concentration (SVC_{obs}) is higher than the predicted SVC (SVC_{pred}) based on the prior estimates, both k and V values will need to decrease to achieve an SVC_{pred} equal to the SVC_{obs}. If SVC_{obs} is lower than SVC_{pred}, the values of k and V will need to increase to achieve an SVC_{pred} equal to the SVC_{obs}. For this method, we generated a family of pharmacokinetic curves that pass through a single point (SVC_{obs}), and these curves are characterized by specific k,V pairs. The table of k,V pairs consists of increasing values of k associated with decreasing values of V, with each calculated to result in an SVC_{obs} value equal to SVC_{pred}. The k,V pair associated with the lowest objective function value is then selected as the best estimate for k_{obs} and V_{obs}. Table 1 shows the predictive performance using the Bayesian estimation based on the first SVC. The first SVC is almost identical to the predicted value by design, with only a slight deviation due to rounding. The prediction is reasonable for the second SVC and then degrades further for subsequent SVC measurements. Table 2 shows the predictive performance for population estimates of pharmacokinetic parameters. Note that the predictions are poor for all SVC repeats. Only the first 5 SVC measurements are shown since the number of patients with >5 SVCs is small. A regression analysis for each subject's percent SVC deviation $[(C_{obs} - C_{pred})/C_{pred} \times 100\%]$ versus the sample time was used to look at trends in the prediction error over time starting with the first SVC for which the prediction error was near zero. A negative slope indicated a trend toward overestimation where the value of SVC_{obs} minus SVC_{pred} is negative. Eighty-four patients met the criteria for a slope of less than −0.1, and the median predicted (interquartile range) error was

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25/4/23 | 18:06 | 4/Color Fig: 3 | ArtID: 00172-23 | DOI:10.1128/aac.00172-23 | CE: KGL-cld

TABLE 1 Predictive performance of model-predicted SVCs compared to SVC_{obs} values using Bayesian-predicted pharmacokinetic parameters and the first SVC[a]

SVC	Mean error	MAE	Scaled MAE	RMSE	Scaled RMSE
1	−0.00183	0.00189	−0.0135	0.0104	0.0769
2	1.26	3.67	8.95	5.15	36.5
3	2.47	4.55	18.3	5.82	43.0
4	3.24	4.84	26.0	6.26	50.2
5	3.18	5.11	24.8	6.59	51.4

[a]MAE, mean absolute error; RMSE, root mean squared error.

−21.3% (range, −30.4 to −15.9%) at the last measurement time according to the regression equation. A positive slope indicates a trend toward underestimation where the value of SVC_{obs} minus SVC_{pred} is positive, and this criterion was met by 241 patients. The median (interquartile range) percent error determined according to the regression lines at the last measurement time was 42.2% (range, 21.5 to 75.3%). The number of persons with SVC measurement errors trending upward outnumbered those with concentrations trending downward by 3 to 1, and the magnitude of the change was also higher for those trending upward. This is evidence of time-dependent changes in pharmacokinetics that are often neglected with vancomycin TDM. These patients had no evidence of increasing sCR to explain the change. The mean 24-h AUC before the first SVC was determined to be 485 ± 149 mg · h/L. The 24-h AUC after the results from the first SVC were available was 490 ± 102 mg · h/L, indicating less variability after the SVC was available. Histograms of the AUC distributions before and after the first SVC are shown in Fig. 2a and b. The hospitals had no policy for dosing based on the AUC during the conduct of this study; however, the target trough SVC trended downward. Prior to the first SVC, 170 (38.4%) patients had a 24-h AUC of <400 mg · h/L, 186 (42.1%) had a 24-h AUC within the target range, and 86 (19.5%) had a 24-h AUC of >600 mg · h/L. After the first SVC was reported, 322 (72.9%) had a 24-h AUC within the target range, 68 (15.4%) had low values, and 52 (11.8%) had high values based on the model simulation. Figure 3 shows the relationship between the 24-h AUC post-SVC and the trough SVC.

DISCUSSION

Vancomycin TDM was conducted using a trough-only concentration for about 2 decades. Recent findings demonstrated that some patients develop excessive 24-h AUCs when targeting trough concentrations of between 10 and 20 μg/mL (6–8), and a major risk factor is the low ratio of the half-life to the dosing interval (9). This is particularly evident in children, who commonly exhibit a vancomycin half-life of <3 h. Even when a 6-h interval is utilized, some investigators suggested decreasing the target trough concentration to 7 to 10 μg/mL (10, 11). There are several issues that need to be considered with AUC targets. A suggestion has been made to measure SVCs early to ensure the rapid achievement of the target AUC (1, 12); however, many patients undergo hydration within the first 24 h, and this can sometimes improve vancomycin clearance. Guidelines suggest obtaining two SVCs for the accurate determination of the AUC (1); however, this will require more SVCs overall, with increased costs (13). The time-dependent changes in pharmacokinetics that we describe require that TDM be performed at least once weekly, although the optimal frequency of monitoring has not been determined. We prefer the judicious use of resources (one concentration over

TABLE 2 Predictive performance of model-predicted SVC values compared to SVC_{obs} values using population prior estimates of pharmacokinetic parameters[a]

SVC	Mean error	MAE	Scaled MAE	RMSE	Scaled RMSE
1	3.45	4.77	47.3	6.27	62.1
2	4.26	6.09	54.7	7.56	67.8
3	5.33	6.42	60.2	7.92	74.2
4	5.63	6.83	67.9	8.43	83.7
5	5.51	7.19	68.5	8.66	82.5

[a]MAE, mean absolute error; RMSE, root mean squared error.

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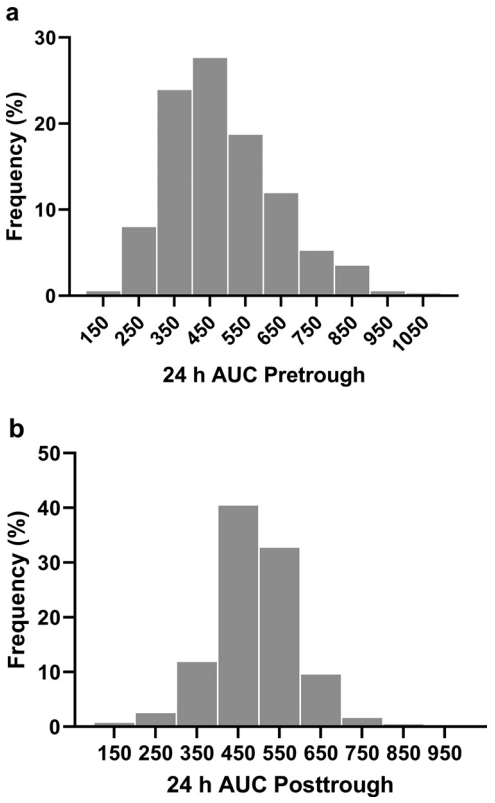

FIG 2 Histogram of 24-h AUC values before (a) and after (b) the results of the first SVC.

two) and monitoring at least weekly given the changes that occur over time. Finally, the method of analysis is a consideration. Bayesian analysis has been considered the only reliable method to estimate vancomycin pharmacokinetics using a single concentration; however, another suitable approach may be to use a one-compartment model with a covariate-adjusted population estimate for *V* followed by solving for *k* such that C_{pred} is equal to C_{obs} (14).

Several publications have described the use of a two-compartment model with Bayesian estimation and one SVC (15, 16). Such analyses will produce a result, but there is insufficient information to guide the estimation of four parameters. Software packages use an algorithm to search for values of the four parameters required to characterize a two-compartment model based on covariate-adjusted prior estimates (prior means and standard deviations). There is limited information about the individual curves, and the starting values are based on mean prior values. The most direct parameter that correlates with C_{pred} is V_c. The program will start iterating values for the other three parameters and primarily change V_c systematically to minimize the C_{obs} minus

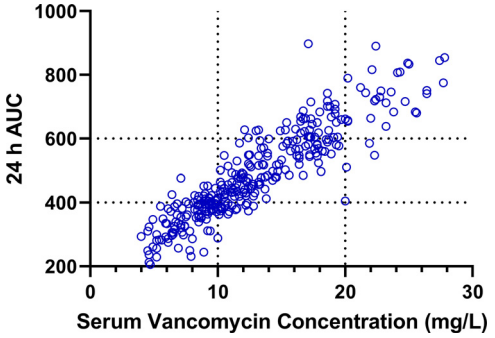

FIG 3 Twenty-four-hour AUC estimated before the first SVC versus the value of the first SVC (trough).

25/4/23 | 18:06 | 4/Color Fig: 3 | ArtID: 00172-23 | DOI:10.1128/aac.00172-23 | CE: KGL-cld

C_{pred} (2) residual. The value of C_{obs} is not even accepted as true. There are countless local minimums for the objective function, so convergence is readily obtained. Although the model appears to be stable functionally, ~~it works by the random simulation of three parameters based on the prior mean distribution and minimization by changing V_d.~~ The program converges as soon as a local minimum in the objective function is found. ~~This is almost the same as fixing three parameters and allowing the fit to be governed by V_c.~~ The availability of only one SVC begs for simplification to a one-compartment model. Even then, allowing measurement error for SVC is overcomplicated. There is no information in the data to guide the magnitude or direction of the measurement error. Consequently, we think that it is important to exclude measurement error unless one has 3 or more SVCs.

A simplified one-compartment Bayesian method for interpreting vancomycin pharmacokinetics using a single SVC is described. This analysis was implemented using Microsoft Excel given the tools available, including graphical presentation. The medication administration record (datetimes and doses) can be copied from the electronic health record into a worksheet, avoiding transcription errors. There is no requirement for single-dose or steady-state data as the analysis involves the full dosing record and superposition principles. All doses are given before the SVCs are entered along with the SVC datetime and SVC result. Bayesian priors are individualized based on creatinine clearance (CL_{CR}) for CL_{pop} and weight for V_{pop}; k_{pop} is determined as CL_{pop}/V_{pop}. Due to sarcopenia, increased tubular secretion, or augmented renal function, some patients will have very high calculated CL_{cr} values, and some are substantially overestimated. For determining the Bayesian estimate for CL, we restricted the value of CL_{cr} to 130 mL/min/1.73 m^2. This was done to prevent the Bayesian prior from driving an overestimate of CL. If the trough concentration is underpredicted, the *k* and *V* values for the individual will still be selected based on the measured concentration. We have extended the method to allow reevaluation each time an SVC is obtained, and the prior estimates are updated based on the result of the previous evaluation. This research has the same limitations as any retrospective study in that recorded information is assumed to be correct. The facilities use barcodes and computerized time stamps for documenting medication administration and blood collection times, which is a marked improvement over studies conducted before such technology was in use. The other limitation is that the timing of TDM and dose adjustments were not controlled by the investigators; however, there is a general practice plan in place for vancomycin TDM.

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Conclusion. A one-compartment Bayesian method is described for vancomycin pharmacokinetic analysis using a single (usually trough) SVC. The method results in an improved predictive performance for the next SVC, but the predictive performance degrades over time. Dose adjustments based on the trough concentration were shown to improve target AUC attainment after the first SVC. The most likely reason for the degrading performance is time-dependent pharmacokinetics, which are not associated with significant trends in sCR. Regular monitoring of SVCs is needed to detect increased vancomycin exposure in an attempt to prevent an increased risk of nephrotoxicity.

MATERIALS AND METHODS

This multicenter study used data obtained from a retrospective record review between 1 January 2021 and 31 December 2021, inclusive. Institutional review board approval, a waiver of informed consent, and private health information authorization were obtained from the University of Arizona Human Subjects Protection Program. The patients (adults ≥18 years of age) were from Banner Health facilities, including Banner University Medical Center—South, Banner University Medical Center—Tucson, and Banner University Medical Center—Phoenix. Criteria for patient selection included a prescription for vancomycin therapy, the availability of a trough concentration from at least two different dosing intervals, serum creatinine (sCR) with a fluctuation of <0.3 mg/dL, and a body mass index (BMI) of <35 kg/m^2. Patients were excluded if they presented with acute kidney injury (AKI) or if sCR varied by >0.3 mg/dL during the pharmacokinetic observation period. There were no exclusions for gender or ethnicity and no upper limit cutoff for age. Patients aged >89 years were assigned an age of 93 years to avoid age being considered a HIPAA identifier. Electronic data (dose and administration datetime) were extracted from the medication administration records and checked manually to ensure accuracy. Demographic

25/4/23 | 18:06 | 4/Color Fig: 3 | ArtID: 00172-23 | DOI:10.1128/aac.00172-23 | CE: KGL-cld

and laboratory data were entered into Excel, including datetimes that were necessary to calculate time intervals. Datetimes were used temporarily to determine times in hours relative to the time of the first dose, and once each case was entered, only deidentified data (without the date or datetime) were saved. The Excel program performed all calculations for estimating *k* and *V* based on the dose information and first serum vancomycin concentration (SVC).

The full dose history was collected for each subject as long as sCR remained stable. If sCR increased by >0.3 mg/dL above the baseline, AKI was documented, and subsequent data on doses and serum concentrations were not collected. Simulations were performed using the dosing history and estimated parameters with a one-compartment model implemented in SAS (SAS version 9.4; SAS Institute, Cary, NC). The simulation was displayed graphically, showing the pharmacokinetic profile and all SVCs performed. For the first measured concentration, the predicted concentration was always very close by design. For all subsequently measured concentrations (SVC_{obs}), the predicted SVC (SVC_{pred}) and difference ($SVC_{obs} - SVC_{pred}$) were calculated.

Creatinine clearance (CL_{cr}) was estimated using the Cockcroft-Gault equation. For obese patients (actual body weight [ABW] >120% of the ideal body weight [IBW]), an adjusted body weight (AdjBW) was used, where AdjBW = IBW + 0.4 (ABW − IBW). A factor of 0.85 was used for females. Population priors were vancomycin clearance (CL_{van}) = 0.0474 × CL_{cr} + 0.942 (17) and volume of distribution (*V*) = 0.7 L/kg (18) × ABW (or AdjBW if applicable). The coefficient of variation for both parameters was 0.3. The maximum CL_{cr} allowed was 130 mL/min/1.73 m^2, and if the calculated value exceeded this value with correction for body surface area (BSA), the maximum value was used. For example, if an individual with a BSA of 1.5 m^2 was calculated to have a CL_{cr} of 215 mL/min, a value of 130 × 1.5/1.73 mL/min or 113 mL/min was used for the Bayesian prior.

A range of *k* values with a resolution of 0.001 was created (e.g., 0.050 to 0.150 h^{-1}). Based on a one-compartment model and equations for the concentration of the drug in the body at a specified time, there is a unique companion value of *V* that will pair with each value of *k* and result in an SVC_{pred} equal to the SVC_{obs}. The parameter pairs define a family of pharmacokinetic curves that pass through the SVC_{obs}. The Bayesian objective function is

$$Obj = \frac{(k_i - k_{pop})^2}{(\mathrm{CV}\, k_{pop})^2} + \frac{(V_i - V_{pop})^2}{(\mathrm{CV}\, V_{pop})^2}$$

where *k* is the elimination rate constant, *V* is the volume of distribution, and CV is the coefficient of variation. The subscript "i" refers to the individual estimate, and "pop" refers to the population prior value. One notable term missing is a term that accounts for measurement error ($SVC_{obs} - SVC_{pred}$). In the case of a single concentration, no information is available to help characterize the direction and magnitude of the measurement error as there would be with three or more concentrations. Parameter estimates were obtained from a table of candidate parameter pairs by selecting the *k*,*V* pair with the minimum Bayesian objective function value. Detailed pharmacokinetic methods are described in Appendix SA in the supplemental material.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, DOCX file, 0.1 MB.

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AUTHOR QUERIES

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AQF—Is the running title at the top of p. 3 OK? The length limit is 54 characters and spaces.

AQG—Sentence "Figure 1a and b show histograms. . ." as meant? If not, please rewrite for clarity.

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AUTHOR QUERIES

Below are queries from the copy editor indicating specific areas of concern. Please respond in-line in the main text above, either by marking a change or indicating "ok."

2

AQH—If "C_{obs}" is an abbreviation, please define it at first use in the text.

AQI—"median predicted (Q_1 to Q_3) error" as meant? If not, please rewrite for clarity. See also similar wording below.

AQJ—"based on CL_{cr} (CL) weight (V)" as meant?

AQK—Please make sure that the page numbers in reference 18 (formerly 7) are correct.

AQL—Please check label b missing in Figure 1 caption.