

Original Article

Heterogeneity of publicly accessible online critical values for therapeutic drugs

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Abstract

Introduction: Critical values are reported to clinicians when laboratory values are life threatening and require immediate attention. To date no definitive critical value limit recommendations have been produced regarding therapeutic drug monitoring. Some laboratories choose to publish critical value lists online. These publicly available values may be accessed and potentially utilized by laboratory staff, patient care providers, and patients. **Materials and Methods:** A web-based search of laboratories associated with the Accreditation Council for Graduate Medical Education pathology residency programs was initiated to determine which therapeutic drugs had critical values and to examine the degree of variation in published critical values for these institutions. **Results:** Of the 107 institutions with university-based pathology training programs, 36 had published critical values online for review. Thirteen therapeutic drugs were investigated and the number of institutions reporting critical value limits for the drug, as well as the median, range, standard deviation, and the coefficient of variation of critical value concentration limits for each drug were determined. A number of the online critical value limits were deemed to be erroneous, most likely due to incorrectly listed units of measurement. **Conclusions:** There was a large degree of heterogeneity with regard to the chosen critical value limits for therapeutic drugs. This wide variance in critical values appears to be greater than that observed in interassay proficiency testing. Institutions should reexamine the rationale for their current critical value parameters and ensure that critical value limits and associated units are accurately published online.

Key words: Critical value, internet, therapeutic drug monitoring, web 2.0, webpage

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INTRODUCTION

Clinical laboratory results continue to be a vital component of patient management. While most laboratory results are not life threatening, certain results need to be promptly reported to the individuals managing patient care.^[1] These urgent laboratory results are called “critical values” and are defined as an abnormal

value that suggests a life-threatening pathophysiologic state unless urgent care is provided.^[2,3] Critical values have been shown to be associated with adverse patient events in the clinical setting.^[4] In recent years, the Joint Commission has promoted proper reporting of critical values as a requirement for quality healthcare.^[5] Efficient application and reporting of critical value limits positively impact patient outcomes by ensuring that

laboratory results with potentially rapid morbid and/or life-threatening consequences reach the clinician in a timely manner. The College of American Pathologists (CAP) Q-probe study concluded that 65% of reported critical values resulted in a change in therapy.^[2]

Although guidelines for determining critical values have been proposed, a 1997 survey revealed that almost half of laboratories do not have any formal policies for establishing and reviewing critical value parameters.^[6] More recent surveys have identified a variety of modalities that are utilized in establishing critical values which include, but are not limited to, published literature, medical staff recommendations, manufacturer recommendations, internal validation of critical value limits, and adoption of values from other laboratories.^[2,7-9] The Joint Commission's designation of critical value reporting as a national patient safety goal has increased focus on proper critical value utilization.^[10] Therapeutic drugs have become a mainstay in patient treatment and monitoring their levels represents a significant portion of laboratory testing. Adverse effects associated with inappropriate drug dosing and subsequent toxicity range from mild to potentially lethal. Thus, critical values provide a safety net to clinicians striving to avoid prolonged exposure of patients to inappropriate drug concentrations. In the case of therapeutic drugs, critical value limits are often established with regard to dangerously high drug concentrations. In this study, the critical value concentration limit refers to the lowest drug concentration that is reported as a critical result.

While many laboratories utilize critical values in the reporting of therapeutic drug levels, there is limited literature available regarding absolute levels and interlaboratory variation. One study reviewed nine United States Veterans Administration medical centers and summarized the marked variation in therapeutic drug critical values.^[11] A study of 19 pediatric institutions in Canada also demonstrated large variation in pediatric therapeutic drug critical values.^[12] Not only is there wide variation in the reported critical value drug concentration limits, but there is also disparity in the therapeutic drugs that are associated with critical values.^[7] In response to these discrepancies, there have been calls for the adoption of more standardized critical values.^[9,11]

Although critical values should be clearly defined in laboratory operating procedures and medical record reporting, some laboratories also choose to publish online critical value lists. While these values can be accessed by laboratory staff, patient care providers, and patients, it is not entirely clear how this information is being utilized. For better or worse, physicians and medical staff have been demonstrated to utilize public web-based resources and search engines for assistance in clinical decision making.^[13-15] The degree to which web-based

publications of critical value limits influence clinical practice or result interpretation is unknown. Furthermore, Internet accessible critical values allow for interlaboratory comparison when establishing or altering one's critical value limits. Various laboratories have reported using critical values from established laboratories as a factor in setting their own critical value limits.^[7] Thus, reference to critical value limits in a public online setting may influence the establishment of critical value limits in other institutions. It has been suggested that surveying critical value limits could assist in the establishment of more uniform and safe critical value limits, as well as in the optimization of effective critical value reporting systems.^[7,9,11]

In order to evaluate the degree in variation and consistency of existing online critical values for therapeutic drug monitoring, a web-based review of laboratory critical value limits for therapeutic drugs was initiated. While a significant proportion of commercial, government, and university-based laboratories publish critical value limits online, the target population of this study was all United States clinical laboratories associated with the Accreditation Council for Graduate Medical Education (ACGME) pathology residency programs. These accredited laboratories were selected for a systemic online examination of the variation of posted therapeutic drug critical values. Academic institutions with pathology residency programs play a significant role in training the next generation of physicians and laboratory directors, and often also serve as commercial referral resources for community-based laboratories and medical institutions.

MATERIALS AND METHODS

In August 2009, personal computers of the authors were used to investigate a set of 107 university-based core clinical laboratories that were associated with United States pathology residency programs. This study was limited to academic hospitals with pathology residency programs. Commercial reference laboratories without associated pathology residency programs were not surveyed; however, many of the academic institutions in this study concurrently offer reference laboratory services. The search engine Google was used to identify these university-based core clinical laboratories and the publicly available critical values were collected by searching the laboratory websites. This study was performed at the University of Arkansas for Medical Sciences. Of the 107 programs, 36 of the clinical laboratories had Internet accessible published critical value limits for therapeutic drugs. The critical values were manually recorded into Excel using each individual program's units. These values were then converted to the International System of Units (SI) by applying commonly used conversion factors. To further analyze these values, Excel was utilized to

calculate the median, range, standard deviation, and percent coefficient of variation for each therapeutic drug.

During the process of collecting data and converting the published critical value limits to uniform units for comparison, it became apparent that certain reported values were absurd due to mislabeled units of measurement mentioned in the Results section. These values were deemed erroneous and were not utilized in further analysis. For the 36 institutions, the percentage of laboratories reporting each drug and the percentage of laboratories with absurd results were calculated.

Variation in critical value limits between laboratories could represent true differences in practice or could be reflective of assay-specific analytical differences. In order to account for such analytical potential variation, the CAP 2009 Participant Summary "B" Survey of Chemistry/Therapeutic Drug Monitoring was utilized as a reference to gauge interassay variation. For this approach, a single CAP survey challenge sample was selected for each analyte that measured values closest to the critical value limit concentration for each therapeutic drug. By identifying the variability in survey challenge samples, the acceptable intrinsic laboratory assay variability was established and provided a measure of variation in

therapeutic drugs due to assay differences. For a single challenge sample, both the range of all assay reported instrument means and the mean coefficient of variation between all reported instruments were determined. These values were compared to the range and coefficient of variation for published critical values collected in this study.

RESULTS

There was wide variation among the 36 laboratories that published Internet accessible critical values for therapeutic drugs, see Table 1. Multifold differences were observed for many therapeutic drugs, indicating a high degree of variance and a lack of standardization. In most cases, the relative coefficient of variation was greater than or equal to 20%.

Nearly all programs with online published critical values reported critical values for antiepileptics and other commonly toxic drugs such as digoxin, lithium, salicylate, and theophylline. Fewer institutions had critical values for antibiotic monitoring with vancomycin being the most frequently reported. The percentage of total institutions reporting critical values for each analyte and specified sample type is provided in Table 2.

Table 1: Therapeutic drug concentration critical value distribution for 36 institutions with publicly available critical values lists and accredited pathology residency training programs

Therapeutic drug	Median critical value limit	Range	Standard deviation	Coefficient of variation (%)	N	Surveyed units of measurement
Acetaminophen unspecified (mcg/ml)	50	20-250	67.5	81.1	26	mcg/ml, mg/l, g/ml, mg/ml, mcg/dl
Acetaminophen 4 hours (mcg/ml)	150	150-200	25.8	15.2	10	mcg/ml
Acetaminophen 12 hours (mcg/ml)	50	40-50	5.2	11.1	6	mcg/ml
Amikacin peak (mcg/ml)	35	25-75	9.9	27.3	23	mcg/ml, mg/l
Amikacin trough (mcg/ml)	10	8-75	16.3	117.5	16	mcg/ml, mg/l
Carbamazepine (mcg/ml)	15	11-20	2.5	16.7	36	mcg/ml, mg/l
Digoxin (ng/ml)	3	2-4	0.6	23.2	35	ng/ml, mcg/l, ng/dl
Gentamicin peak (mcg/ml)	12	8-25	3.1	25.7	26	mcg/ml, mg/l
Gentamicin trough (mcg/ml)	2	1.5-25	6.1	134.4	17	mcg/ml, mg/l
Lithium (mEq/l)	2	1.2-3	0.4	19.7	33	mmol/l, ng/dl mEq/l, mmol/dl
Phenobarbital (mcg/ml)	50	40-70	8.1	15.7	36	mcg/ml, mg/l
Phenytoin (mcg/ml)	30	20-40	6.9	23.3	36	mcg/ml, mg/l
Free phenytoin (mcg/ml)	3	1.6-4	0.7	21.8	16	mcg/ml, %, mg/l, mg/ml
Salicylate (mg/dl)	31	20-50	8.3	23.2	31	mg/ml, mg/dl, mg/l, mcg/ml
Theophylline (mcg/ml)	25	20-40	5.0	19.8	33	mcg/dl, mcg/ml, mg/l
Tobramycin peak (mcg/ml)	12	8-25	3.2	26.6	24	mcg/ml, mg/l
Tobramycin trough (mcg/ml)	2	2-25	6.5	120.3	16	mcg/ml, mg/l
Valproic acid (mcg/ml)	150	100-200	32.7	21.1	33	mcg/ml, mg/l
Vancomycin peak (mcg/ml)	60	30-100	18.2	29.3	28	mcg/ml, mg/l
Vancomycin trough (mcg/ml)	20	15-100	27.8	88.2	14	mcg/ml, mg/l

This table displays the therapeutic drugs researched, the number of the 36 institutions reporting each drug, and the types of units of measurement used in reporting. Additionally, the median critical values, range of critical values, standard deviation, and coefficient of variation for the lowest concentration considered to be critical for each therapeutic drug (critical value limit) are listed. The final column lists all units used by the surveyed institutions; however, the concentrations in the rest of the table are listed in the units given in the first column.

Table 2: Percentage of laboratories publishing critical values for each therapeutic drug

Therapeutic drug	Percentage of laboratories reporting a valid critical value	Percentage of laboratories reporting a critical value deemed "absurd"	Total percentage of laboratories reporting a critical value
Acetaminophen unspecified	72.2	8.3	80.6
Acetaminophen 4 hours only	11.1	0	11.1
Acetaminophen 12 hours only	0	0	0
Acetaminophen 4 and 12 hours	16.7	0	16.7
Amikacin peak only	25.0	0	25.0
Amikacin trough only	5.6	0	5.6
Amikacin peak and trough	38.9	0	38.9
Carbamazepine	100	0	100
Digoxin	97.2	2.8	100
Gentamicin peak only	30.6	0	30.6
Gentamicin trough only	5.6	0	5.6
Gentamicin peak and trough	41.7	0	41.7
Lithium	91.7	5.6	97.2
Phenobarbital	100	0	100
Phenytoin	100	0	100
Free phenytoin	44.4	2.8	47.2
Salicylate	86.1	11.1	97.2
Theophylline	91.7	2.8	94.4
Tobramycin peak only	27.8	0	27.8
Tobramycin trough only	5.6	0	5.6
Tobramycin peak and trough	38.9	0	38.9
Valproic acid	91.7	0	91.7
Vancomycin peak only	41.7	0	41.7
Vancomycin trough only	2.8	0	2.8
Vancomycin peak and trough	36.1	0	36.1

The actual published critical values deemed "absurd" are listed in Table 3. The total percentage of the 36 laboratories included in this study which published a viable or absurd critical value is given in the third column.

Several analytes in this study exhibited critical value limits linked to the time of specimen collection. While some institutions reported both peak and trough critical values for antibiotics, others specified only peak or trough critical values. Another example was the reporting of acetaminophen critical values. Although all 36 institutions reported critical values for acetaminophen, 26 did not specify the time after acetaminophen ingestion, four only reported a value for 4 hours postingestion, and six reported values for both 4 and 12 hours postingestion.

As described previously, several absurd critical values were reported on the websites of the laboratories and were not included in further data evaluation. Most of these values appeared to result from the publication of erroneous units of measurement. All critical value limits deemed absurd are listed in Table 3.

Interassay differences for each drug are a potential cause of the observed wide variation in therapeutic drug monitoring critical value limits. To evaluate this possibility, the CAP 2009 Participant Summary "B" Survey of Chemistry/Therapeutic Drug Monitoring was utilized. This document details the reported values for

Table 3: Absurd Internet-published critical value limits

Therapeutic drug	Absurd values
Acetaminophen (mcg/ml)	150 g/ml, 100 mg/ml, 50 mcg/dl
Digoxin (ng/ml)	2.4 ng/dl
Lithium (mEq/l)	1.5 mmol/dl, 0.9 ng/dl
Salicylate (mg/dl)	20 mg/ml, 30 mg/ml, 40 mg/ml, 30 mg/l
Theophylline (mcg/ml)	20 mcg/dl
Free phenytoin (mcg/ml)	4%

These therapeutic drug critical values were published on laboratory websites. The values were deemed absurd and were not included in the analyzed data presented in Tables 1 and 4.

each analyte as determined by different instruments. Table 4 illustrates that the range and coefficient of variation of critical values reported for each drug by the different university-based institutions were often substantially greater than the interinstrument mean values demonstrated by CAP proficiency testing.

DISCUSSION

While many of the laboratories in our study consistently

Table 4: Range of reported means and coefficients of variation for different instruments in CAP proficiency testing

Therapeutic drug	CAP range of reported instrument means	Range of surveyed critical values	Mean coefficient of variation between instrument means (%)	Mean coefficient of variation of surveyed critical value limits (%)
Acetaminophen unspecified (mcg/ml)	84.43-99.61	20-250	5.2	81.1
Acetaminophen 4 hours (mcg/ml)	84.43-99.61	150-200	5.2	15.2
Acetaminophen 12 hours (mcg/ml)	84.43-99.61	40-50	5.2	11.1
Amikacin peak (mcg/ml)	21.69-25.13	25-75	4.8	27.3
Amikacin trough (mcg/ml)	11.45-12.53	8-75	3.6	117.5
Carbamazepine (mcg/ml)	14.61-18.77	11-20	6.5	16.7
Digoxin (ng/ml)	2.20-2.70	2-4	6.9	23.2
Gentamicin peak (mcg/ml)	8.34-10.65	8-25	6.5	25.7
Gentamicin trough (mcg/ml)	1.34-1.98	1.5-25	11.2	134.4
Lithium (mEq/l)	1.85-2.21	1.2-3	6.4* See footer	19.7
Phenobarbital (mcg/ml)	47.73-59.18	40-70	5.7	15.7
Phenytoin (mcg/ml)	28.23-36.33	20-40	6.4	23.3
Free phenytoin (mcg/ml)	1.428-1.749	1.6-4	10.1	21.8
Salicylate (mg/dl)	28.68-32.66	20-50	4.0	23.2
Theophylline (mcg/ml)	17.12-23.96	20-40	10.5	19.8
Tobramycin peak (mcg/ml)	7.75-10.72	8-25	12.1	26.6
Tobramycin trough (mcg/ml)	2.96-4.70	2-25	15.3	120.3
Valproic acid (mcg/ml)	82.24-97.64	100-200	5.0	21.1
Vancomycin peak (mcg/ml)	20.84-39.56	30-100	14.5	29.3
Vancomycin trough (mcg/ml)	11.32-20.72	15-100	14.1	88.2

The CAP 2009 Participant Summary "B" Survey for Chemistry/Therapeutic Drug Monitoring was utilized (C-B). Summary data for a single challenge that had a mean best approximating published critical limits were utilized for each therapeutic drug. The table displays the range of mean values and the coefficient of variation reported for all instruments. For comparison, the range of published critical values and coefficients of variation observed in Table 1 are also given. A CAP survey-published "all methods" coefficient of variation of 6.4% was available for lithium.

reported critical values on similar sets of therapeutic drugs, there was a large degree of observed heterogeneity in critical value limits. Previous studies have indicated significant variation in critical values limits for chemistry and hematology analytes.^[5,7,9,12] Although fewer publications have focused on therapeutic drug monitoring critical values, the small number of existing targeted surveys have also indicated a gross lack of standardization.^[11,12] Not only does our study support these previous results, but also demonstrates the presence of significant discrepancies between academic training hospitals.

This study yielded other notable observations regarding utilization of critical value limits [Table 1]. While acetaminophen critical values were reported by all institutions, they fell into three categories: 4 hours post-ingestion, 12 hours post-ingestion, and time unspecified. Time-dependent nomograms utilize serum concentrations to evaluate for acetaminophen toxicity. Yet in our study, 26 of 37 institutions do not utilize time of ingestion when establishing critical values limits. Additionally, multiple laboratories reported vancomycin critical value limits for both peak and

trough determinations. While utilized in the past, recent reports have concluded that peak serum vancomycin concentrations should not be used to monitor for nephrotoxicity with the determination of trough concentrations being preferable.^[15,16]

Despite recommendations that phenytoin toxicity be preferentially monitored by assays for the free form, less than half of the studied institutions reporting a critical value for total phenytoin had a corresponding value for free phenytoin.^[16] This antiepileptic is almost completely protein bound with only a small fraction of the active free drug present. Renal failure, the alteration of albumin and total protein levels, and the presence of other highly protein bound drugs can affect the protein binding of phenytoin.^[17] This has been shown to occur in at-risk patient populations such as the critically ill and children.^[17,18]

Interassay differences are a potential contributor to variation in critical value limits. In almost all cases, the identity of the testing analyzer associated with specific critical value limits was not published online. Unlike many other common chemistry analytes, CAP proficiency reports (with the exception of lithium) do not

include “all method principles-all instruments” means and coefficients of variation for therapeutic drugs. The “all method” means and coefficients of variation are generated directly from data collected at all proficiency sites. These data could be used to compare the relative variation in proficiency testing to the variation observed in published critical value limits and would allow one to assess the degree to which interassay variation might contribute to critical value limit variation.

In the absence of the “all methods” variation metric, the CAP range of means and coefficient of variation for all instrument means calculated for a single proficiency challenge sample were compared to the data obtained from the web-based review of laboratories [Table 4]. For most drugs, the relative range and mean coefficient of variation of published critical values substantially exceeded relative differences observed in proficiency testing. This strongly implies that the observed variation in critical value limits is not predominantly due to differences in analytical methodology.

However, as is shown in Table 4, significant interinstrument differences do exist for some therapeutic drugs and this likely does contribute to a degree to the variation in critical value concentration limits. Reduction in interassay differences by the manufacturer may improve agreement of critical value concentration limits. Publication of “all method” means and coefficients of variation in proficiency testing reports may further encourage harmonization of assays.

There are several other potential causes of variation in critical value limits observed in our study, which include population diversity and tailored clinical standards of practice and notification.^[3] Extensive utilization and reporting of critical values requires significant investment of labor resources. Thus, some institutions may adopt relatively elevated critical values limits in order to reduce the volume of critical value calls.^[11] Additionally, institutions may adopt unusual critical values to reflect clinical predominance of certain disease states or to support specific treatment protocols. Clinical management philosophies for a particular condition may vary depending on a hospital’s expertise and familiarization with the disease and therapeutic agents. Further evaluation of the factors affecting the critical value heterogeneity between laboratories is essential in establishing an evidence-based standard.^[1,11]

To our knowledge, this study is the first to comment on public Internet-based accessible critical value limits. A significant portion (one-third) of the laboratories investigated in this study chose to publish online critical value limits for therapeutic drug monitoring. Multiple apparent errors in published lists of critical value limits were observed [Table 3]. Presumably, these errors are not incorporated into the formal reporting of patient

results. While the publication of critical value lists may provide an accessible reference to healthcare providers, the potential for error in the production of these online lists clearly does exist. The impact of these erroneous published critical value limits on patient care is not known, but it is plausible that clinical treatment might be inappropriately influenced by an incorrect web-based critical value limit. Institutions should consider the potential benefits of publishing web-based critical values versus deleterious effects related to the potential for erroneous reporting of these values. As pathology informatics continue to migrate toward direct reporting of laboratory data, accuracy must be maintained in supporting web-based documentation.

Our study illustrates that relatively little progress has been made in recent decades in implementation of more consistent critical value limits for therapeutic drug monitoring. A 1992 attempt to compile a comprehensive list of critical values in over 600 laboratories was discontinued due to “astounding” diversity, most notably in therapeutic drug monitoring.^[11,19] Diversity of critical value limits is not unique to the United States.^[9,12] For example, a report on a survey of critical limits in United Kingdom laboratories concluded that therapeutic critical value limits set by some laboratories “do not appear to be related to clinical toxicology.”^[8] Our study does not recommend specific critical value limits and does not indicate the practical presence of consensus-based recommendations for critical value limits in the laboratories surveyed. A wide body of literature has previously addressed the toxic concentrations and resulting clinical consequences for many therapeutic drugs.^[20] However, there is no current universal authoritative source for critical value limits.^[9]

In summary, the results of this web-based review demonstrate that publicly available established critical values for therapeutic drugs exhibit significant variation between academic laboratories. This variation does not appear to be predominantly caused by differences in assay methodology, as demonstrated by comparison to CAP proficiency testing results. Laboratories should consider the merits of publishing their critical values and work to eliminate errors in reporting online critical value limits. This study illustrates current interlaboratory discrepancies amongst academic laboratories with regard to published therapeutic drug critical value reporting, and may provide further impetus to calls for standardization of critical value limits.

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