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Web-accessible critical limits and critical values for urgent clinician notification

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Abstract

Objectives: To survey the World Wide Web for critical limits/critical values, assess changes in quantitative low/high thresholds since 1990–93, streamline urgent notification practices, and promote global accessibility.
Methods: We identified Web-posted lists of critical limits/values at university hospitals. We compared 2023 to 1990–93 archived notification thresholds.
Results: We found critical notification lists for 26 university hospitals. Laboratory disciplines ranged widely (1–10). The median number of tests was 62 (range 21–116); several posted policies. The breadth of listings increased. Statistically significant differences in 2023 vs. 1990 critical limits were observed for blood gas (pO_2, pCO_2), chemistry (glucose, calcium, magnesium), and hematology (hemoglobin, platelets, PTT, WBC) tests, and for newborn glucose, potassium, pO_2, and hematocrit. Twenty hospitals listed ionized calcium critical limits, which have not changed. Fourteen listed troponin (6), troponin I (3), hs-TnI (3), or troponin T (2). Qualitative critical values expanded across disciplines, encompassing anatomic/surgical pathology. Bioterrorism agents were listed frequently, as were contagious pathogens, although only three hospitals listed COVID-19. Only one notification list detailed point-of-care tests. Two children's hospital lists were Web-accessible.
Conclusions: Urgent notifications should focus on life-threatening conditions. We recommend that hospital staff evaluate changes over the past three decades for clinical impact. Notification lists expanded, especially qualitative tests, suggesting that automation might improve efficiency. Sharing notification lists and policies on the Web will improve accessibility. If not dependent on the limited scope of secondary sources, artificial intelligence could enhance knowledge of urgent notification and critical care practices in the 21st Century.

Keywords: artificial intelligence (AI); cardiac biomarkers; Coronavirus disease 2019 (COVID-19); critical limits and critical values; ionized calcium; standards of care

Introduction

Urgent communication of dangerously abnormal test results began decades ago when lists of critical limits and critical values were used to trigger clinician warnings. The first national surveys published in *JAMA*, *Pediatrics*, the *Archives of Pathology and Laboratory Medicine,* and *Medical Laboratory Observer (MLO)* in 1990–93 codified this important practice in the United States [1–4].

Our goals are to report findings of a comprehensive search for open source (public domain) critical limit and critical value test lists posted on the World Wide Web (the "Web"); to identify changes in ionized calcium and other quantitative critical limit thresholds since 1993; to assess the current Web listings of cardiac biomarker critical limits; and to document notification priorities for qualitative and new listings, such as tests for Coronavirus disease 2019 (COVID-19).

Institutions adjust quantitative critical limits and select qualitative critical values to identify extremely abnormal findings that may trigger life-saving treatment. Caregivers use critical notifications to facilitate rapid evaluation and therapeutic decisions at the bedside, in emergency rooms, and when performing point-of-care testing (POCT). Accreditation agencies, such as the US Joint Commission, require hospitals to create and maintain appropriate policies for urgent notification of critical test results.

Artificial intelligence (AI) is accelerating access to and interpretation of Web-posted information that could play an important role in establishing and maintaining the quality of medical knowledge in the future [5–7]. Therefore, we hope that this research will encourage sharing of critical limits, critical values, and governing policies so that AI can assist emergency, clinical, and laboratory practitioners in setting

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decision thresholds and ultimately, enhancing standards of care.

Materials and methods

Definitions

A critical limit is defined as a low or high quantitative threshold of a life-threatening diagnostic test result. A critical value is defined as a qualitative result (e.g., a positive COVID-19 rapid antigen test) warranting urgent notification. Both demand rapid response, ideally within minutes [8, 9] and potentially life-saving treatment, isolation of the patient, or other timely medical intervention.

Open-source searches

PubMed articles and internet postings were identified using browser keywords (e.g., critical limits, critical values, critical-risk results, significant-risk results, alert values, hypercritical results, and panic values). This yielded 270 articles, editorials, letters to the editor, blogs, and peer-reviewed papers dealing with critical limits, critical values, urgent notifications, relevant artificial intelligence, urgent communication of critical results, and related topics.

Only those articles directly related to raw data, notification lists, national surveys, interpretation, and associated topics (please see *MLO* [10, 11]) were included in the final 70 selected. Raw data and policy retrievals from the Internet were parsed into university hospital and independent laboratory findings. Multiple search hits zeroed in on the same hospital documents thereby providing assurance that none were missed. This research was conducted April 2023 through April 2024.

Scope

We focused on hospital Web listings in the United States. All possible university and children's hospital critical notification lists were sought along with an equal number of independent laboratory postings to balance statistical analyses. The 28 states with postings were well distributed across America. Lists were analyzed for changes in the number of measurands, laboratory categories (i.e., disciplines), quantitative thresholds, and qualitative findings in relation to those observed in 1990–93 national surveys [1–4].

Databases

Summaries of critical limits and critical values for adults and children from past national hospital surveys have appeared in the *MLO Clinical Laboratory Reference* (*CLR*) annually from 1992 through 2023 [12] and for adults through 2024 [13]. Raw data from the United States national surveys [1–4] archived by Knowledge Optimization (Davis, CA) were used to compare 2023 Web listings. That is, we compared changes in raw data from 1990 to 1993 to Web-listed raw data in 2023. Measurands not found or documented in the 1990s surveys are marked by ellipses (…).

Changes over time

Changes in quantitative critical limits were determined by comparing the means and medians of quantitative critical limits in 1990–93 national surveys [1–4] to those listed on the Web in 2023. In addition to clinical chemistry, hematology, and other laboratory disciplines, notifications studied in detail comprised: (a) cardiac biomarkers – for their current importance in emergency and crisis care, (b) ionized calcium – to assess the impact of potential modifications of electrochemical methods since 1987 [3, 14], and (c) highly infectious diseases, such as COVID-19 – to update actionable tests used during the pandemic.

Statistics

The normality of 2023 data was determined by applying the Shapiro-Wilk test (https://www.statskingdom.com/shapiro-wilk-test-calculator.html) and confirmed by inspecting histograms. Very few 2023 quantitative critical limits were normally distributed. Therefore, we used primarily the Kruskal–Wallis non-parametric test to determine if differences over three decades were statistically significant (https://www.socscistatistics.com/tests/kruskal/default.aspx).

Differences were considered significant when $p<0.05$, or if $p<0.01$, then highly significant. Cell entries in the Tables are boldface when significantly different. Please note that the Kruskal–Wallis test does not directly compare medians, but instead the raw data distributions and therefore can generate a significant p-value even if two medians are equal.

In the case where both 1990s and 2023 data were normally distributed, the significant difference was determined using Student's t-test for the means with unequal variances (https://www.omnicalculator.com/statistics/t-test) and identified with a superscript "ND" (for normally distributed) next to the footnoted p-value.

The order of measurands in the tables was determined from frequencies of 2023 Web survey listings. Listing frequencies were determined by dividing by 26 (2023 Web survey), 92 (1990 adult national survey [1]), or 100 (1993 national survey of ionized calcium critical limits [3]).

Units for critical tests

The percentages of university hospital notification lists using conventional units were: 64 % for chemistry, 100 % for blood gas, 98 % for hematology and coagulation, 89 % for newborn, and 78 % overall for quantitative tests. We report tabulated results in conventional units to allow facile access to statistical summaries without the need for healthcare providers to use conversion factors in the United States or in other countries still using conventional units.

Ethics

The UC Davis IRB deemed this research exempt (ID 2078118-1). Data for the Web survey were extracted from public domain open sources accessible on the Internet. No hospitals or organizations were contacted. There were no interviews. Results are reported anonymously.

Results

Table 1 summarizes the number of critical limits and critical values discovered on Web-posted notification lists in 2023 for 26 university hospitals and 26 independent laboratories. The median numbers of all tests listed was 62 (range 21–116) for university hospitals and 56.5 (range 21–119) for independent laboratories. The difference was not significant. All university hospital Web postings were included and analyzed in detail. Independent laboratory lists were summarized.

Analysis of potential calling burden (see Table 1) showed that if notifications for critical drug and toxicology critical results were automated, then the volume of calls in university hospitals could decrease 25 %, and for independent laboratories, 32 %. The difference in the median number of tests (62) listed by university hospitals vs. the number (46.5) without drug and toxicology tests was statistically significant ($p<0.01$).

Numbers of disciplines identified as headings on university hospital notification lists varied widely from 2 to 10 with median 5 and mean 5.3 (SD 2.1), while at independent laboratories, the median was 4 (range 1–10) and mean, 4.5 (SD 2.6).

Table 2 compares clinical chemistry critical limits in 2023 vs. 1990. Statistically significant differences over the past three decades were identified for the following quantitative measurands: glucose (median low critical limit, $p<0.05$), calcium (median low, $p<0.01$), and magnesium (median high, $p<0.05$). Please consult the tables for the directions (i.e., higher or lower) of the statistically significant changes. The p values for the differences in the median low critical limits for magnesium ($p=0.0506$) and phosphorus ($p=0.0753$) were marginal.

In 1993, 57 % of general hospitals listed ionized calcium critical limits. In 2023, 77 % of university hospitals listed ionized calcium critical limits, which have not changed significantly over three decades (Table 2). Ionized calcium non-critical spans remained nearly the same at 0.74 mmol/L (mean) and 0.75 (median) for 2023 compared to 0.73 mmol/L (mean) and 0.70 (median) for 1993.

Fourteen university hospitals listed troponin (6 hospitals), troponin I (3), hs-TnI (3), or troponin T (2). One that listed hs-TnI, also identified troponin I with i-STAT POCT. A few (3) listed CK-MB (creatine kinase MB isozyme). Only one university hospital and one independent laboratory listed BNP (brain or B-type natriuretic peptide). Eighteen independent laboratories listed cardiac biomarkers.

Table 3 presents blood gas and pH critical limits. Statistically significant differences ($p<0.05$) were observed in the critical limits for median low arterial pO_2 and arterial pCO_2, although significance for median low arterial pCO_2 was caused by dissimilar histograms underlying nonparametric analysis. Compared to the 1990s national surveys, more hematology measurands were listed, including venous pH and pCO_2 and capillary pCO_2 and pH.

Table 4 shows hematology and coagulation findings. International Normalized Ratio (INR) was a new listing and also the most frequent one. The median low critical limit for platelets ($p<0.05$), median high critical limit for hemoglobin ($p<0.05$) and partial thromboplastin time ($p<0.01$), and both low ($p<0.01$) and high ($p<0.05$) median critical limits for white blood cell count displayed statistically significant change over three decades.

Table 5 summarizes the most frequently listed qualitative critical values in microbiology, virology, parasitology, blood bank, hematology, anatomic pathology, clinical microscopy, surgical pathology, and urinalysis in 2023. Three university hospitals and one independent laboratory listed a positive COVID-19 test result as a qualitative critical value. The SARS-CoV-2 detection methods were not identified. Two listed RSV. Please see Table S1 in the Supplementary Material for qualitative critical values unique to 2023 web listings.

Table 1: Number of critical limit and critical values on web-posted notification lists.

Statistic	University hospitals (n=26)			Independent laboratories (n=26)		
	CL and CV results notified	Drugs and toxicology automated	Burden added if not automated	CL and CV results notified	Drugs and toxicology automated	Burden added if not automated
Median	62	46.5	25.0 %	56.5	38.5	31.9 %
Mode	52	35	–	53 (central)	37	–
Range	21–116	17–99	–	21–119	21–79	–
Mean	67.8	50.6	25.4 %	57.6	41.7	27.6 %
SD	26.3	20.4	–	20.4	15.2	–

CL, critical limit (quantitative); CV, critical value (qualitative).

Table 2: Clinical chemistry critical limits.

Mesurand	Listing frequency, %		Units	Low mean (SD)		Low median (range)		High mean (SD)		High median (range)	
	2023	1990		1990	2023	1990	2023	1990	2023	1990	2023
Glucose	100	100	mmol/L	2.6 (0.4)	2.7 (0.3)	**2.5 (1.7–3.9)**	**2.78[a] (2.2–3.3)**	26.9 (8.0)	24.9 (2.6)	27.8 (6.1–55.5)	25.0 (19.4–27.8)
			mg/dL	46 (7)	49 (6)	**45 (30–70)**	**50[a] (40–60)**	484 (144)	449 (46)	501 (110–1,000)	450 (350–500)
Potassium	100	100	mmol/L	2.8 (0.3)	2.8 (0.2)	2.7 (2.5–3.6)	2.8 (2.5–3.0)	6.2 (0.4)	6.1 (0.2)	6.0 (5.0–8.0)	6.0 (6.0–6.5)
Sodium	100	100	mmol/L	120 (5)	121 (2)	120 (110–137)	120 (120–125)	158 (6)	159 (2)	160 (145–170)	160 (155–160)
Calcium	96	100	mmol/L	1.65 (0.17)	1.56 (0.10)	**1.62 (1.2–2.15)**	**1.56[b] (1.25–1.75)**	3.22 (0.22)	3.19 (0.12)	3.24 (2.62–3.49)	3.24 (2.99–3.49)
			mg/dL	6.6 (0.7)	6.3 (0.4)	**6.5 (5.0–8.6)**	**6.3[b] (5.0–7.0)**	12.9 (0.9)	12.8 (0.5)	13.0 (10.5–14.0)	13 (12–14)
Magnesium	81	33	mmol/L	0.41 (0.16)	0.43 (0.03)	0.41 (0.21–0.74)	0.41 (0.41–0.49)	2.02 (0.82)	2.10 (0.53)	**1.75 (1.03–5.02)**	**2.02[a] (1.44–3.70)**
			mg/dL	1.0 (0.4)	1.0 (0.08)	1.0 (0.5–1.8)	1.0 (1.0–1.2)	4.9 (2.0)	5.1 (1.3)	**4.3 (2.5–12.2)**	**4.9[a] (3.5-9.0)**
Ionized calcium	77	57	mmol/L	0.82 (0.14)	0.81 (0.05)	0.80 (0.50–1.07)	0.8 (0.75–0.90)	1.55 (0.19)	1.55 (0.09)	1.50 (1.30–2.00)	1.55 (1.41–1.80)
Phosphorous	77	33	mmol/L	0.39 (0.10)	0.35 (0.05)	0.32 (0.26–0.65)	0.3 (0.29–0.48)	2.87 (0.48)	2.92 (0.22)	3.22 (2.26–3.23)	2.89 (2.58–3.23)
			mg/dL	1.2 (0.3)	1.1 (0.1)	1.0 (0.8–2.0)	1.0 (0.9–1.5)	8.9 (1.5)	9.0 (0.68)	10.0 (7.0–10.0)	9.0 (8.0–10.0)
CO_2 content	69	75	mmol/L	11 (2)	10.5 (1.1)	10 (5–20)	10 (10–14)	40 (3)	41 (4)	40 (35–50)	40 (36–50)
Lactate	58	5	mmol/L	…	…	…	…	3.4 (1.3)	4.1 (1.0)	3.0 (2.3–5.0)	4.0 (2.0–5.0)
			mg/dL	…	…	…	…	30.6 (11.7)	36.8 (8.96)	27.0 (20.7–45.0)	36.0 (18.0–45.0)
Osmolality	38	20	mmol/kg	250 (13)	243 (19)	250 (230–280)	250 (190–251)	326 (18)	333 (22)	320 (295–375)	325 (320–390)
Cerebrospinal fluid glucose	38	16	mmol/L	2.1 (0.6)	1.8 (0.4)	2.2 (1.1–2.8)	1.9 (1.1–2.2)	24.3 (11.4)	18.3 (5.4)	16.7 (13.9–38.9)	16.7 (13.9–27.8)
			mg/dL	37 (10)	33 (7.7)	40 (20–50)	35 (20–40)	438 (206)	330 (97)	301 (250–700)	300 (250–500)
Chloride	31	20	mmol/L	75 (8)	77 (4)	80 (60–90)	78 (70–81)	126 (12)	123 (4.6)	120 (115–156)	121 (119–130)
Creatinine	23	10	µmol/L	…	…	…	…	654 (380)	698 (218)	884 (177–1,326)	769 (442–884)
			mg/dL	…	…	…	…	7.4 (4.3)	7.9 (2.5)	10 (2.0–15.0)	8.7 (5.0–10.0)
Urea nitrogen	15	20	mmol/L	…	…	…	…	37.1 (21.1)	34.4 (3.92)	33.9 (14.3–107.1)	35.9 (28.6–37.1)
			mg/dL	…	…	…	…	104 (59)	96 (11.0)	95 (40–300)	101 (80–104)
Uric acid	8	20	µmol/L	…	…	…	…	773 (119)	773	892 (595–892)	773
			mg/dL	…	…	…	…	13 (2)	13	15 (10–15)	13
Bilirubin	0	25	µmol/L	…	…	…	…	257 (86)	…	257 (86–513)	…
			mg/dL	…	…	…	…	15 (5)	…	15 (5–30)	…

[a]p<0.05: differences were considered significant, [b]p<0.01: differences were considered highly significant. Cell entries in the Table are boldface when significantly different.

Table 6 summarizes the frequency of listings of bioterrorism threats and pathogens as qualitative critical values. Table 6A reports bioterrorism agents listed and groups threats by dissemination capability and potential mortality. Table 6B shows pathogens deemed important enough to warrant urgent notification of their presence and identifies the US Centers for Disease Control and Prevention [15], World Health Organization [16], and US National Institute of Allergy and Infectious Diseases [17] priorities for detection.

Table 3: Blood gas and pH critical limits.

Measurand	Listing frequency, %		Units	Low mean (SD)		Low median (range)		High mean (SD)		High median (range)	
	2023	1990		1990	2023	1990	2023	1990	2023	1990	2023
pH	85	35	pH	7.21	7.21	7.20 (7.00–7.35)	7.20 (7.15–7.30)	7.59	7.59	7.60 (7.50–7.65)	7.60
			Units	(0.06)	(0.03)			(0.03)	(0.02)		(7.55–7.60)
Arterial pO_2	81	26	mm Hg	43 (6)	46 (6)	**40 (30–55)**	**44[a] (39–60)**	…	…	…	…
			kPa	5.7 (0.8)	6.1 (0.8)	**5.3 (4.0–7.3)**	**5.9[a] (5.2–8.0)**	…	…	…	…
Arterial pCO_2	73	30	mm Hg	19 (3)	20 (3)	**20 (9–25)**	**20[a] (9–25)**	67 (6)	65 (4)	70 (50–80)	65 (60–70)
			kPa	2.5 (0.4)	2.7 (0.4)	**2.7 (1.2–3.3)**	**2.7[a] (1.2–3.3)**	8.9 (0.8)	8.7 (0.5)	9.3 (6.7–10.7)	8.7 (8.0–9.3)
Venous pH	23	…	pH	…	7.16	…	7.19 (7.00–7.23)	…	7.56	…	7.57 (7.52–
			Units		(0.08)				(0.03)		7.59)
Capillary pCO_2	12	…	mm Hg	…	23 (4)	…	23 (20–25)	…	65 (5)	…	65 (60–70)
			kPa	…	3.1 (0.5)	…	3.1 (2.7–3.3)	…	8.7 (0.7)	…	8.7 (8.0–9.3)
Capillary pH	12	…	pH	…	7.20	…	7.20 (7.15–7.25)	…	7.58	…	7.60
			Units		(0.05)				(0.03)		(7.55–7.60)
Venous pCO_2	12	…	mm Hg	…	24 (5)	…	24 (19–28)	…	71 (12)	…	65 (64–85)
			kPa	…	3.2 (0.7)	…	3.2 (2.5–3.7)	…	9.5 (1.6)	…	8.7 (8.5–11.3)

[a]p<0.05: differences were considered significant, [b]p<0.01: differences were considered highly significant. Cell entries in the Table are boldface when significantly different.

Table 4: Hematology and coagulation critical limits.

Measurand	Listing frequency, %		Units	Low mean (SD)		Low median (range)		High mean (SD)		High median (range)	
	2023	1990		1990	2023	1990	2023	1990	2023	1990	2023
INR	92	…	…	…	…	…	…	…	4.9 (0.7)	…	5 (4–7)
Platelets	92	45	10^9/L	37 (21)	27 (13)	**30 (10–100)**	**20[a] (10–50)**	894 (206)	941 (112)	1,000 (100–1,000)	1,000 (600–1,000)
Hemoglobin	92	42	g/dL	7 (2.2)	6.2 (0.7)	7 (4–15)	6 (5–7)	19 (4.4)	20.7 (1.1)	**20 (20–30)**	**20[a] (20–22.5)**
Partial thromboplastin time	89	33	Sec	50 (–)	18 (–)	50 (–)	18 (–)	80 (33)	120 (32)	**80 (40–150)**	**120[b] (70–200)**
Fibrinogen	77	27	g/L	0.85 (0.26)	0.88 (0.16)	1 (0.08–1)	1 (0.6–1)	7.8 (2.6)	…	8 (5–10)	…
WBC	73	42	10^9/L	2.02 (0.7)	1.33 (0.5)	**2 (1–5)**	**1.25[b](0.5–2.0)**	37 (22)	52 (32)	**30 (9.5–100)**	**50[a] (15–149)**
Hematocrit	65	29	%	20 (8.1)	18 (2.5)	18 (41)	20 (15–21)	60 (12.8)	59.4 (3.8)	60 (20–80)	60 (54–65)
Absolute neutrophil count	31	…	10^9/L	…	0.56 (1.8)	…	0.5 (0.5–1.0)	…	…	…	…
WBC count in CSF	23	…	WBC/mm^3	…	…	…	…	…	70 (71)	…	45.5 (0.01–200)
Band count	15	…	%	…	…	…	…	…	20 (7)	…	22.5 (10–25)

[a]p<0.05: differences were considered significant, [b]p<0.01: differences were considered highly significant. CSF, cerebrospinal fluid; INR, international normalized ratio; WBC, white blood cell count. Cell entries in the Table are boldface when significantly different.

University hospitals often have maternity wards and therefore, must provide urgent notifications of critical newborn test results (Table 7). Among clinical chemistry measurands for newborns, 88 % listed high bilirubin critical limits; 73 %, low and high glucose; 31 %, low and high potassium; and 31 %, low and high pH. About one quarter listed hemoglobin and hematocrit.

Since the 1990s, median low glucose (p<0.01) and arterial pO_2 (p<0.05), median high potassium (p<0.05), and mean high hematocrit (p<0.01) differed significantly for newborns. Only two children's hospital notification lists were retrieved. The median number of tests listed was 68 (range 56–80). The two children's hospitals did not list COVID-19 or cardiac biomarkers.

Table 5: Qualitative critical values.

Laboratory disciplines and critical values	Detection method(s) (if identified)	Frequency, %
Microbiology		
Blood, cerebrospinal fluid, or body cavity fluid	Culture	85
Cryptococcus species	Culture, RAgT	65
Blood, cerebrospinal fluid, or body cavity fluid	Gram stain	62
Acid-fast Bacillus (AFB)	Culture, stain	54
Dimorphic fungal pathogens (e.g., *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides* species)	Culture, PCR, smear	31
Group A *Streptococci*	Culture, RAgT	19
Mycobacterium tuberculosis	Culture, PCR	19
Neisseria meningitidis	Culture, RAgT	19
Bordetella pertussis (any specimen from a neonate)	Culture, PCR	15
Neisseria gonorrhea	Culture, probe	15
Haemophilus influenzae B	Culture, RAgT	12
Legionella pneumophilia	Culture, RAgT	12
Group B *Streptococci*	Culture, RAgT	8
MRSA (Methicillin Resistant *Staph Aureus*)	Culture	8
Vancomycin Intermediate/Resistant *Staphylococcus*	Not listed	8
VRE (Vancomycin Resistant *Entercoccus*)	Not listed	8
Positive India Ink preparation	–	4
Virology		
Herpes simplex virus (HSV) in newborns or term pregnant mothers	Culture, PCR	35
Herpes simplex virus (HSV) in CSF	PCR	31
HIV (Human Immunodeficiency virus)	PCR, RAgT	23
Cytomegalovirus (CMV)	PCR, RAgT	19
Varicella zoster virus (VZV)	PCR	19
Epstein-Barr virus (EBV)	PCR	15
COVID-19 (SARS-CoV-2) detected	Not listed	12
Influenza A&B	Culture, PCR, RAgT	12
Hepatitis A, B, or C	PCR, RAgT	12
Syphilis	RPR, VDRL	12
Respiratory Syncytial virus (RSV)	PCR	8
Parasitology		
Malarial parasites	Smear	35
Parasites in sterile body fluid	Smear	23
Microfilaria	Smear	15
Babesia	PCR, smear	12
Blood Bank		
Positive transfusion reaction	–	27
Positive direct coombs test/direct antiglobulin test (DAT)	–	23
Maternal titers of significant red cell antibodies during pregnancy	–	15
Blood product associated with a transfusion reaction	Culture	12
Incompatible crossmatch	–	12
Indirect Coombs positive/Indirect antiglobulin test (IAT)	–	12
Crossmatches unable to locate compatible red cells	–	8
Blood product associated with a transfusion reaction	Gram stain	8
Hemoglobinemia in post-transfusion reaction specimen	–	8
Hematology		
Presence of blasts in blood	Smear	27
Positive Heparin-induced platelet antibody	–	23
New diagnosis or findings of leukemia	Smear	4
Presence of band cells	Smear	4
Presence of sickle cells or aplastic crisis	Smear	4
Anatomic pathology		
Unexpected diagnosis of malignancy (as determined by the clinical information provided)	–	15
Significant disagreement between the frozen section and final diagnosis	–	12
Significant discrepancy between outside diagnosis and the review diagnosis	–	12
Pneumothorax	X-ray	12
All revised or amended reports reflecting a significant change in diagnosis with potential to impact treatment or outcome	–	8
Clinical microscopy		
Presence of malignant cells, blasts, or microorganisms in cerebrospinal fluid or body fluids	Smear	15
Presence of organisms by microscopic examination	Smear	8
Surgical pathology		
Any findings likely to reflect unrecognized perforation of an organ (e.g. fat in endometrial curettage or endoscopic polypectomy specimen)	–	12
Significant discrepancy between the FNA rapid assessment diagnosis and the final diagnosis	–	12
Crescents in kidney biopsy specimens	–	8
Unexpected absence of chorionic villi in uterine curetting		8

Table 5: (continued)

Laboratory disciplines and critical values	Detection method(s) (if identified)	Frequency, %
Fungi in FNA of immunocompromised patients	–	4
Urinalysis		
Combination of strongly positive test results for glucose and for ketones in urine	–	12
Presence of RBC casts	–	12
Presence of reducing substances	–	12

COVID-19, Coronavirus disease 2019; CSF, Cerebrospinal fluid; FNA, fine needle aspiration; PCR, polymerase chain reaction; RAgT, rapid antigen test; RBC, red blood cells; RPR, rapid plasma reagin; SARS-CoV-2, severe acute respiratory syndrome-Coronavirus-2; VDRL, Venereal Disease Research Laboratory.

Table 6: Frequency of listings of bioterrorism threats and pathogens.

Categories and threats				Frequency, %
A. Bioterrorism threats listed as critical values				
Category A: Detection of threats that are easily disseminated, result in high mortality, cause public panic, and require special action[a,b]				
Tularemia (*Francisella tularensis*)				27
Anthrax (*Bacillus anthracis*)				23
Plague (*Yersinia pestis*)				23
Botulism (*Clostridium botulinum* toxin)				15
Smallpox (*Variola major*)				12
Viral hemorrhagic fever				8
Category B: Detection of threats that are moderately easy to disseminate, low mortality rates, and require enhanced disease surveillance[a,b]				
Brucellosis (*Brucella* species)				23
Escherichia coli O157:H7 or shiga-toxin tests				19
Burkholderia mallei or *pseudomallei*				15
Epsilon toxin of *Clostridium perfingens*				8
Salmonella species				8
Shigella				8
Cholera (*Vibrio cholerae*)				8
Q fever (*Coxiella burnetii*)				8
Pathogens (and resistance)	**CDC**	**WHO**	**NIH**	**Frequency, %**
B. Pathogens deemed critical for rapid detection and listed as critical values with federal classifications				
Tuberculosis, including drug-resistant tuberculosis			X	58
Coccidioides species			X	27
Meningitis	X	X		27
Human immunodeficiency virus			X	23
Plague (*Yersinia pestis*)		X	X	23
Streptococcus, group A			X	19
Bordetella pertussis			X	15
Listeria	X		X	15
Antimicrobial resistance			X	12
Coronavirus disease 2019 (COVID-19)	X			12
Viral hemorrhagic fever		X	X	8
Salmonella	X		X	8
Cholera (*Vibrio cholerae*)		X		8
Shigellosis (*Shigella* species)		X	X	8
Influenza A		X	X	8
Hepatitis A	X		X	8
Hepatitis C	X		X	4
Cyclospora cayatanensis			X	4
Rubeola (measles)	X		X	4
Monkeypox		X		4
Norovirus	X			0
Ebola virus disease		X	X	0
Marburg virus disease		X	X	0
Zika virus disease		X	X	0

CDC, Centers for Disease Control and Prevention; COVID-19, Coronavirus Disease 2019; NIH, National Institutes of Health; WHO, World Health Organization. [a]Centers for Disease Control and Prevention (CDC), Bioterrorism Agents/Diseases (by category)|Emergency Preparedness & Response. Published May 15, 2019. https://emergency.cdc.gov/agent/agentlist-category.asp#catdef [Accessed March 16, 2024]. [b]Homeland Security. Biological Attack Fact Sheet. Department of Homeland Security. Published July 8, 2015. https://www.dhs.gov/publication/biological-attack-fact-sheet [Accessed March 16, 2024].

One university hospital listed notification thresholds for more than 20 point-of-care tests and at another "point-of-care testing" appeared as part of the title on the same line with chemistry tests without any further distinguishing details. One listed gluocse critical limits for POCT. Otherwise, separate notification lists for point-of-care testing were not encountered.

Most policies posted on the Web defined what a critical value is and said that a licensed provider needed to be telephoned immediately. Many mentioned needing a read back of critical values and/or a notification answering machine policy. Ten hospitals listed critical limits for outpatients. The average number of measurands listed was 4.1 (SD 5.0) with 76 % unique to outpatients. Five institutions had policies related to calling outpatient critical values, consisting of providing information to assist with contacting outpatients, differences in how frequently critical values should be called between inpatients and outpatients, or only contacting outpatients during business hours.

Twenty-three university hospital notification lists were titled "critical values" or "critical result(s)." Several used the terms interchangeability. Two used "alert values" or "alert

Table 7: Newborn critical limits.

Measurand	Listing frequency, %		Units	Low mean (SD)		Low median (range)		High mean (SD)		High median (range)	
	2023	1990		1990	2023	1990	2023	1990	2023	1990	2023
A. Clinical chemistry											
Bilirubin	88	9	µmol/L	…	…	…	…	239 (34)	257 (34)	257 (171–308)	257 (205–342)
			mg/dL	…	…	…	…	14 (2)	15 (2)	15 (10–18)	15 (12–20)
Glucose	73	42	mmol/L	1.8 (0.4)	2.2 (0.4)	**1.7 (1.1–2.8)**	**2.2[b] (1.7-3.1)**	18.1 (6.0)	14.5 (5.3)	16.7 (11.1–38.9)	12.5 (8.3–27.8)
			mg/dL	32 (7)	39 (7)	**31 (20–50)**	**40[b] (30–55)**	326 (108)	261 (95)	301 (200–700)	225 (150–500)
Potassium	31	32	mmol/L	2.6 (0.2)	2.7 (0.3)	2.5 (2.5–3.5)	2.8 (2.0–3.0)	7.7 (0.7)	7.1 (0.7)	**8.0 (5.5–8.0)**	**7.0[a] (6.0-8.0)**
Calcium	15	…	mmol/L	…	1.46 (0.35)	…	1.56 (0.95–1.75)	…	2.95 (0.19)	…	2.99 (2.74–3.12)
			mg/dL	…	5.8 (1.4)	…	6.3 (3.8–7.0)	…	12 (0.8)	…	12 (11–13)
Sodium	12	…	mmol/L	…	120 (9)	…	125 (110–125)	…	155 (9)	…	160 (145–160)
B. Blood gas and pH											
pH	31	…	…	…	7.16 (0.11)	…	7.20 (7.00–7.25)	…	7.57 (0.07)	…	7.60 (7.50–7.65)
Arterial pO_2	23	8	mm Hg	37 (7)	47 (5)	**35 (30–50)**	**50[a] (40–50)**	92 (12)	94 (5)	100 (70–100)	90 (90–100)
			kPa	4.9 (0.9)	6.3 (0.7)	**4.7 (4.0–6.7)**	**6.7[a] (5.3-6.7)**	12.3 (1.6)	12.5 (0.7)	13.3 (9.3–13.3)	12.0 (12.0–13.3)
Arterial pCO_2	23	2	mm Hg	35 (7)	28 (4)	35 (30–40)	30 (20–30)	55 (7)	66 (11)	55 (50–60)	65 (50–80)
			kPa	4.7 (0.9)	3.7 (0.5)	4.7 (4.0–5.3)	4.0 (2.6–4.0)	7.4 (0.9)	8.8 (1.5)	7.4 (6.7–8.0)	8.7 (6.7–10.7)
C. Hematology											
Hemoglobin	27	7	g/L	95 (35)	87 (23)	85 (50–150)	81 (60–120)	223 (23)	226 (10)	210 (210–250)	225 (211–240)
Hematocrit	23	7	%	33 (6)	25 (7)	30 (24–45)	21 (20–36)	**71 (4)**	**66[bND] (4)**	70 (65–75)	68 (60–70)

[a]p<0.05: differences were considered significant, [b]p<0.01: differences were considered highly significant. Cell entries in the Table are boldface when significantly different.

levels" as their primary nomenclature. Six institutions had the term "alert values" or "alert levels" present, and all institutions used the terms interchangeably with critical values. Three institutions used the term "panic value" (which for obvious reasons should not be used) in initial definitions [e.g., "Notification by the Laboratory of Critical (Panic) Values"] but then used "critical value" as the primary nomenclature.

Terms such as "critical-risk results," found in the Clinical Laboratory and Standards Institute guideline, "Management of Critical- and Significant-Risk Results (GP47)," [18] were not encountered, although one university hospital used a mixed terminology, "Critical Risk Alert Thresholds." GP47 does not recommend how many tests should be listed for urgent notification and does not differentiate unique notification requirements for critically low or high point-of-care test results.

Discussion

Crisis intervention

Critical notifications should reflect life-threatening diagnostic test results, focus on treatable conditions and isolation of highly contagious patients, and avoid false positives. The responding clinical team may need to act immediately. Tests identifying serious abnormalities (e.g., elevated cardiac troponin) for which treatment is indicated or signaling need for isolation (e.g., positive COVID-19 test) take high priority. Published evidence presented next suggests that hospitals should re-evaluate critical limit thresholds that have changed since the 1990s.

Associations with mortality

Of the quantitative critical limits found in 2023 to have statistically significant differences since the 1990s, low and high white cell count; low glucose (adults and newborns), total calcium, and platelet count; high magnesium, partial thromboplastin time, and potassium (newborns); and high hematocrit (newborns) were among the top 15 tests associated with patient death within 24 h of reporting test results according to Yang et al. [19].

Arterial pO_2 (adults and newborns) and pCO_2 (adults) also had statistically significant differences but were not included in the Yang et al. [19] assessment. The new listing of

INR reflected standardization since the 1990s. Therefore, to maintain relevance to life-threatening conditions, we recommend that quantitative notification thresholds be reviewed now and updated annually.

Listing frequencies

Critical limits (including blood gases) that had significant changes in notification thresholds over the past three decades comprised 60 % of the top 20 tests ranked by individual institutions, laboratorians, or clinicians, and professional bodies based on the categorization of frequencies of observation documented in a 2016 review [20]. In all three categories (institutions, clinicians, and professional bodies), ionized calcium occupied the 21st rank in frequency of listings [20]. The non-critical span (high minus low critical limits) for ionized calcium agreed well with that originally documented in a 1993 national survey [3] despite technological advances, such as smaller and faster ion-specific Ca^{++} biosensors and processing for direct measurements used by whole-blood analyzers [21].

The magnesium median high critical limit increased. High and low magnesium thresholds should be re-evaluated in support of clinical management [22]. Ionized magnesium was not listed. Critical notifications for cardiac biomarker tests, which were listed by about half of the university hospitals (but not consistently), should meet the urgent needs of rule-in/rule-out protocols for the diagnosis of acute myocardial infarction [23].

Increase in listings

Three decades ago, 95 % of respondents at university hospitals listed only 16 chemistry, 4 blood gas, and 7 hematology quantitative critical limits with a total of 42 tests for adult patients [1], plus a relatively limited set of qualitative critical values. Web retrievals show that notification lists have expanded. The myriad qualitative notifications partially explain why the current totals of tests listed are high.

University hospitals in the top quartile listed 89–116 tests. Typically, these were large tertiary care academic medical centers with complex patients and several laboratory disciplines serving a broad spectrum of clinical specialties. We recommend that these hospitals assess whether critical results are diligently and timely notified to responsible clinicians, and importantly, if they trigger therapeutic actions that improve patient outcomes.

Infectious diseases and biothreats

Now endemic, COVID-19 variants are precipitating fall-winter surges [24]. Surprisingly, 88.5 % of university hospitals did not identify the detection of this pandemic threat as warranting urgent notification. Those that did (11.5 %) likely benefit from enhanced awareness, accelerated infection control, and mitigated contagion [25, 26]. In contrast to COVID-19, listings of bioterrorism agents (see Table 6A) and pathogens (see Table 6B) demanding rapid detection were encountered frequently. The latter aligned best with National Institutes of Health priorities.

Point-of-care testing

With one exception, urgent notification lists specific for POCT could not be retrieved, an unusual finding following worldwide expansion of POCT for the detection of COVID-19. Not explicitly listing point-of-care tests may increase liability if therapeutic delays occur. Also, actionable bedside critical results may not be communicated consistently to authorized decision makers capable of rapidly assessing and treating patients [27]. A survey abstract titled “POC Programs” stated that “glucometer” critical limits were listed by 95.2 % of 63 respondents; the abstract did not enumerate other measurands [28].

Children’s hospitals

We found only two children’s hospital notification lists on the Web. In 2023–2024 the *MLO CLR* [13] stopped publishing critical limits for children. Investigation of newborn and pediatric critical limits is necessary going forward because of innovative diagnostics (e.g., transcutaneous CO_2 and bilirubin monitoring), advances in the management of premature births, and updated life-saving therapeutic protocols. While not traditionally the purview of laboratorians, continuous monitoring has evolved to the point where rapid changes could trigger fast decisions and therefore merit notifications.

Trends and cautions

Investigators have addressed critical notifications in anatomic and surgical pathology, cytology, cytogenetics, molecular genetics, neonatology, pediatrics, radiology, surgery, virology, and other specialties. Some authors question the value of repeating critical results to confirm them

[29–31]. Others analyzed false positive critical value results [32]. With COVID-19 rapid antigen and molecular critical value notifications [33], both false positives and false negatives should be of concern, the former for triggering unnecessary isolation and possibly placing a patient in a high-risk ward, and the latter, for spreading disease by those unaware of infection [24–26].

Global awareness

Searches revealed relevant publications originating from Australia, Brazil, Canada, China, Croatia, Egypt, Ethiopia, Germany, India, Indonesia, Iran, Italy, Japan, Kenya, Korea, Kuwait, Nepal, Netherlands, Paraguay, Saudi Arabia, Singapore, Slovakia, South Africa, Spain, Taiwan, Thailand, Turkey, the UK, and other countries [20]. College of American Pathologists' Q-Probes provided insight into notification polices and tests in the United States in 2002 and 2007 [34, 35]. This year, the US Joint Commission 2024 safety goals continue to specify that United States hospitals must implement critical values policies, select tests for urgent notification, and monitor timeliness [36]. Ultimately, global awareness may facilitate harmonization [37].

Guidelines

The Clinical Laboratory and Standards Institute guideline EP47 [18] equates critical limits with "alert thresholds" and "significant-risk results," which may confuse and may not prompt immediate therapeutic intervention. Only one notification list, which used a mixed terminology, "Critical Risk Alert Thresholds," was titled close to that suggested in EP47. A review [20] of notification practices concluded that outcomes studies and professional collaboration, which could be augmented by Web postings and AI, will be most useful for building future policies and test lists. Therefore, we briefly investigated the capabilities of Web-based AI answer engines.

Artificial intelligence

Artificial intelligence answer engines could help select decision thresholds and track the dynamics of changes, as well as synthesize knowledge bases, and if sufficiently granular, possibly enhance identification of highly infectious threats [38], timely responses to new outbreaks, and favorable quarantine outcomes. Open sourcing critical test lists on the Web would enable AI "data fusion," that is, heuristic integration of multiple data streams [39]. Sharing both critical test lists and notification policies could enhance acute care, AI-facilitated decision making, and consistency [10, 11, 37].

Please see Supplementary Material 2 for a Venn diagram mapping integration of AI and critical notification practices and Supplementary Material 3 for sample dialogues regarding critical results management and associations with mortality generated by Perplexity (https://www.perplexity.ai), a highly touted and heavily funded San Francisco start-up and answer engine [40]. Artificial intelligence currently appears weak at discovering original Web raw data but could help support laboratory professionals, including facilitating clinician communications and responding to questions [41]. Web postings of decisions thresholds would enable higher level AI responses to questions (Figure S2) and possibly also accelerate a shift from high volumes of urgent notifications to assessments that moderate their frequency and enhance their value [42].

Limitations

The sample of twenty-six university hospital notification lists represents all that were accessible online. Nonetheless, Web results revealed potential changes in mortality-associated critical limits over the past three decades, adequate reason for caution and re-evaluation. Some analyses of quantitative critical limits were affected by non-normal frequency histograms, but the medians did not change.

We found listings of new infectious threats, such as COVID-19, but did not contact hospital staff to determine why some threats were not listed more frequently. Conversely, we found numerous listings of qualitative critical values but cannot fully explain their urgency.

In 1984 in the United States, it was recommended to embed SI units in the digital outputs of instruments, including bedside monitoring devices, and display both SI and conventional units together when reporting results to initiate an educational process of conversion from conventional to SI units [43]. In a 1985 report, the Council on Scientific Affairs of the American Medical Association endorsed changing units to SI in America [44].

In 1986, the Editor of the *Journal of the American Medical Association (JAMA)* wrote an article promoting the conversion to SI units [45]. The article included tabulated conversion factors for diagnostic tests. Following publication of the first US national survey of critical limits and critical values, which was published in *JAMA* [1], frequencies of the use of conventional and SI units were extracted from the survey

data for a summary report the same year [46] in follow-up to the national initiative. We observe from the current Web survey that the majority of hospitals in the United States still are using conventional units.

Conclusions and recommendations

Outcomes

We recommend periodic review of quantitative thresholds and qualitative notifications. Rapid response to extremely abnormal test results helps prevent adverse adult and pediatric patient outcomes [19, 20, 47–68]. Secure messaging can improve efficiency by activating teams responding to hypercritical test results [69]. Automated messaging makes pharmacokinetic sense when alerting dynamic changes in drug levels, identifying the presence of toxic elements, quickly triaging patients with critical results, and improving efficiency.

Changes over time

We recommend that hospitals evaluate changes over the past three decades for clinical impact. Figure 1 summarizes changes in need of review, which could have resulted from assay modifications, calibration shifts, elimination of outliers, new therapies altering decision thresholds, or other factors, such as bias in the limited sample size. When assessing the impact of changes over time, both low and high critical thresholds should be evaluated because the non-critical span bracketing urgent treatment decisions may have changed.

Global threats

We recommend adding new notifications, such as positive COVID-19 test results, whether obtained in the laboratory or community, to urgent notification lists to speed mitigation of contagion and life-saving intervention. Sharing will advance transparency. Posting notification lists on the World Wide Web [70] and facilitating AI should help hospitals to identify new tests and critical values, adjust for changes in quantitative critical limits, and assess the status of bioterrorism agents and pathogens classified as high priority for rapid response.

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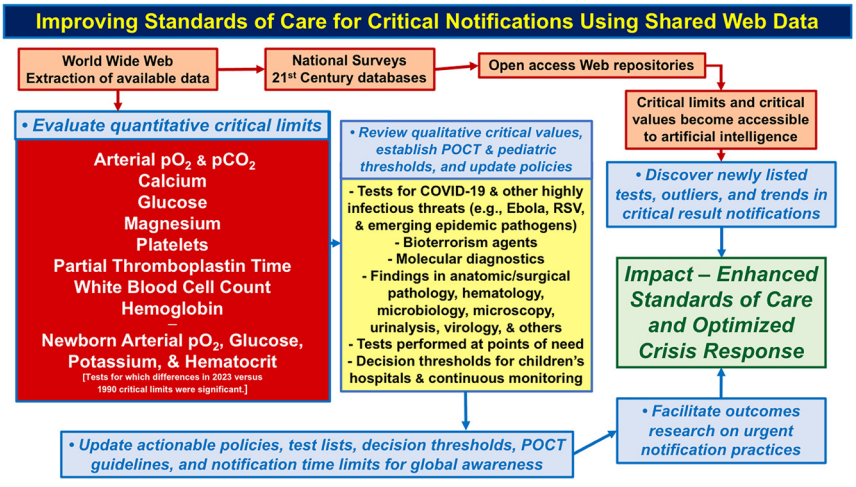

Figure 1: Recommended strategies for improving critical notification practices. This flowchart strategizes process steps that will enhance standards of care (green) for critical notification practices. The first steps are re-evaluation of quantitative critical limits that have changed since 1990–93 (red) combined with review of new and neglected qualitative notifications (yellow). Collaborative sharing (blue) combined with AI-facilitated discovery will produce high impact in the 21st Century. AI, artificial intelligence; COVID-19, Coronavirus disease 2019; POCT, point-of-care testing.

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