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EDITORIAL

Promptly reporting of critical laboratory values in pediatrics: A work in progress

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Abstract

In the 21st century, the determination of alert thresholds remains the most challenging and controversial issue in clinical pediatrics. Pre-analytical, analytical, and post-analytical matters will consolidate or undermine the fate of any laboratory process. Pre-analytical issues need to be cleared off before the laboratory physician can dispatch the result to the pediatrician in charge. Once it is cleared off, the classification of essential laboratory results is paramount. It is more than an academic exercise and may be subdivided in the order of priority we handle it to inform promptly and safely the primary physicians. Currently, we are applying new modes of making sure relevant information is transmitted without interrupting the standard workflow of the primary physicians in charge for the child, who eventually need a fast line of action for results that may be life-threatening.

Key words: Communication; Laboratory; Healthcare; Prioritization; Quality

Core tip: Communication is crucial in pediatrics, not only in the emergency departments. A fast line of action needs to be in place but needs to rely on pediatric laboratory physicians. The interaction between pediatrics and pediatric laboratory will build a center of excellence identifying critical values that need to be transmitted promptly from the bench to bedside.

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INTRODUCTION

Children's hospitals are very busy healthcare institutions that have targets to meet regarding quality

Table 1 The Sydney Triage to Admidssion Risk Toll examples in pediatrics

Critical (must know now): Amniotic fluid, blood culture, hemoglobin, pH, sodium, potassium
Urgent (must know): Coombs test for newborn hemolysis
Important (should know): Sideremia (iron)

care and waiting list probably not comparable to any other healthcare institutions. Children's hospitals are unique institutions and provide immediate attention to thousands of newborns and kids every year. The application of correct triage protocols is crucial to avoid chaos[1-5]. Risk-stratification is essential for the accurate management of diseases. The term triage has been used, and we are accustomed to using it in several disciplines to better manage sick patients. In clinics, triage is the assignment in a determinate time frame of degrees of urgency to a different degree of body/mind illnesses or wound/damage to choose the appropriate order of treatment of patients in non-war settings or casualties in a disaster or war setting. Triage has its origin during the wars of Napoleon Bonaparte arising from the terrific work of Dominique Jean Larrey (1766, Baudéan, France - 1842, Lyon). Further, the term "triage" was used during World War I (WWI)[6]. At this war, the personnel classified the wounded soldiers into three categories according to the degree of injury and potential outcome. The first category entailed victims "who are likely to survive", probably irrespective of what kind of therapy they receive. The second category addressed the victims who were "unlikely to survive", apparently unrelatedly of what therapy they could receive, and, finally, the third category included injured soldiers for whom immediate care might make a positive difference in the outcome. It is paramount to understand that the third category is critical. Many emergency medical services (EMS) systems, worldwide, still use a similar model[7-13]. First responders may use START, which is an acronym for simple triage and rapid treatment[14-18]. Although criticized and, sometimes, vehemently discussed, the START is a relatively proper procedure. It is used by first personnel to rapidly classify victims during a mass casualty incident according to the severity of the injury (immediate/red, delayed/yellow/walking wounded/minor/green, and deceased/expectant/black)[18-21]. Since 1983, the year when staff members of Hoag Hospital and Newport Beach Fire Department located in California, developed START, this triage protocol or its modified version is currently widely used in the United States and Canada[16,21-24]. Similarly, laboratory diagnostics has faced the importance to establish laboratory triage system. Doubtlessly, laboratory diagnostics play a significant role in the correct triage of sick children. Values associated with imminent danger/death of the child (unless acted upon promptly) require to be identified as critical values and need to be punctually referred to the EMS personnel or attending physicians.

CRITICAL VALUES IN LABORATORY DIAGNOSTICS

The procedures of laboratory diagnostics do play a central role in clinical decision making and managing the care of numerous pediatric disorders, particularly life-threatening diseases. A mixture of issues is entailed in the total quality of the testing process, beginning with the appropriateness of test ordering in pre-analytical phase of the process and concluding with the timely and efficient communication of test results to the physicians who oversee the pediatric patient in the post-analytical phase of the process[25]. Numerous studies point to the sensitive time's frames of the pre-analytical and post-analytical phases for most of the diagnostic errors[26-30]. The identification and effective communication of the "highly abnormal" values have raised the threshold of attention of numerous physicians because this activity is essential to good laboratory practice and for the accreditation of the hospitals. Despite several efforts in improving laboratory standardization using several accreditation models, the improvement of laboratory standardization, effectiveness, and efficiency is an ongoing quality process, and the list of the harmonized critical values in pediatrics is a continuing debate. Probably, first and foremost risk-stratifying patients regarding sepsis is a mandatory process because of the cardiovascular dysfunction associated with sepsis[31]. A serum test of lactate is often established in the emergency to diagnose enteral ischemia and as a serological marker of end-organ perfusion. However, it seems to be highly nonspecific. Lactate level is a classic example of critical values. In fact, values more or equal to 4 mmol/L are considered to require early and aggressive resuscitation procedures, whereas values less than 4 mmol/L are associated with patients who do not require the typical interventions in the early management of sepsis. The use of serum lactate should probably be addressed in patients who have signs of a septic infection. This test should be based on the degree of suspect specific diseases[32]. Substantially, critical values may be segmented into tiers of severity, including the critical at a high level "must know now" results, the "must know" results with less critical value, and the "should know" results or, also called, "courtesy" calls by Dietzen[33,34]. The last category entails the least severe results. Although there are numerous references for adults, sources are quite scarce in Pediatrics. In the following table, we list some examples of START in Pediatrics (Table 1).

The first tier, *i.e.*, the life-and-death critical values of

the original Lundberg's definition[35] need to be referred to as "must know now" results. The second tier, those values with highly significant data of a severe disease without the burden of an immediate response need to be referred to as "must know" results. The "should know" results or "courtesy" calls may include abnormal results that incorporate a specific intervention as a mandate but remain dependent from the context where are generated. Despite the controversy raised recently, we agree that the lactate level is a "must know now" result. Other pediatric examples of critical values with "must know now" level of the critical setting include total bilirubin and ammonia, while the conjugated bilirubin concentration may be considered a "must know" result. Critical values are also analytes such as potassium and TCO_2, which is an amount of carbon dioxide in several states total carbon dioxide. In an emergency, the measurement of TCO_2 is key because it is part of an electrolyte profile, which is advantageous in evaluating HCO_3^- concentration. TCO_2 and HCO_3^- are mandatory elements to properly assess the acid-base imbalance along with pH and PCO_2 partial pressure of carbon dioxide and electrolyte imbalance. The Coombs test for newborn hemolysis is an urgent value that often has been part of litigation because it has been classified as "important" but not "urgent". Maternal alloimmunization toward antigens of erythrocytes causes hemolytic Disease of the Fetus and Newborn (HDFN). In severe cases, HDFN may lead to life-threatening fetal anemia and severe forms of neonatal hyperbilirubinemia with a risk for the baby developing kernicterus. In the most severe cases, there is an etiology linked to anti-D, despite the introduction of antenatal and postnatal anti-D immunoglobulin prophylaxis. Erythrocytes antibody screening programmes are aimed to detect maternal alloimmunization early in pregnancy with the aim to identify high-risk cases to timely start antenatal and postnatal treatment[36-38]. An abnormal result in an indirect Coombs test means that the patient has circulating antibodies to any erythrocytes that are considered foreign to the body. Depending on the age and events, this circumstance may indicate erythroblastosis fetalis, an incompatible blood match for receiving a blood transfusion, or hemolytic anemia due to an autoimmune reaction or drug toxicity. There is a visible risk for kernicterus, and this critical value needs to be reported urgently.

Another abnormal result that needs particular attention is the ferritin value in the setting of hemophagocytic lymphohistiocytosis or lymphohistiocytic syndromes (HLH syndromes) ("must know now" value). Hyperferritinemia, which is usually with a value greater than 10000 ng/mL, is a crucial hallmark in HLH. It is used as an indicator triggering a macrophage activation syndrome leading to HLH. Measurement of serum ferritin can be used in both diagnosis and prognosis in the setting of HLH. Hyperferritinemia is a significant contributor to manage appropriately critically ill children and should be communicated urgently to the pediatric emergency team or a professional team of a pediatric intensive care unit.

In 1991, Kost *et al*[39] reviewed critical limits of 39 children's hospital across the United States. These authors listed glucose, potassium, calcium, and sodium as high critical limits in children, whereas critical limits for newborns were glucose, potassium, hemoglobin, platelets, hematocrit, and white blood cell counts. Both the presence of blasts on the blood smear and abnormal cerebrospinal fluid findings are qualitative critical results. Children's hospitals target foremostly critical limits for surveillance in the setting of the evaluation of kidney function, coagulation, and potassium. In the 39 children's hospitals reviewed, the number of tests ranged from 3 to 50. Currently, the number of critical values may easily go over 100, and, indeed, it may become a nightmare for a laboratory physician. The increase in the number of critical values is due to the improvements in health care, transplantation program, and stem cell therapy protocols. Indeed, there is a high subjectivity in addressing tests and thresholds in several hospitals, and the specialization of the hospital may condition the choice of level of critical value. About a decade ago, Dietzen evaluated four pediatric institutions, in addition to three adult hospitals. The results are part of the critical tests of the 4th edition (now adjourned 6th edition) of "Tietz Textbook of Clinical Chemistry and Molecular Diagnosis"[34,40]. The number of tests ranged from 12 to 45. Eleven values, including total bilirubin, conjugated bilirubin, ammonia, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sweat chloride, iron, gamma-glutamyl-transferase (GGT), fibrinogen, and lactate dehydrogenase (LDH), were identified as unique in a pediatric setting. The high variability of critical values identified by Kost *et al*[39], Dietzen[34] and others[41,42] point to the high variability of the critical value assignment. Prompt interventions to prevent kernicterus include phototherapy and exchange transfusion total bilirubin concentrations are values that physicians must know now. A mildly increased value of unconjugated hyperbilirubinemia may be found in the neonatal period, but an increased value of conjugated bilirubin almost always indicates pathology and surgically correctable diseases need to be ruled out[43-45]. The diagnosis of biliary atresia, which is a perinatal necroinflammatory process involving the extra- and intrahepatic biliary system with progressive ductopenia and obliterative cholangiopathy needs to be targeted properly. The failure to recognize within 30-45 d after birth determines an irreversible liver damage and cirrhosis. The child's fate is, then, linked to liver transplantation. As indicated by Dietzen[34], conjugated bilirubin rates are critical values that pediatricians must know. However, these results may not necessarily be communicated "now", because biliary atresia is a life-threatening disease but not imminently. The course of action should be straightforward, but not instantaneous. Many inborn errors of metabolism may result in life-threatening

accumulation of toxic intermediates. A critical value that pediatricians need to know now is the ammonia level. In consideration that hyperammonemia occurs in defects of the urea cycle or secondary to hepatocellular dysfunction and is extremely toxic to the newborn brain, an immediate and straightforward line of action must be put in place to prevent irreversible neurologic damage. The number of new devices, including digital droplet PCR, has increased in the last decade and accuracy and precision are the criteria to receive Food and Drug Administration approval[46]. Chief instances are disorders of the urea cycle, phenylketonuria, and galactosemia. Physicians "must know" about the rates of the substances "now" to prevent calamitous sequelae for the child. Fatty acid oxidation defects include medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. MCAD may remain asymptomatic for a long time. Nevertheless, a severe hypoglycemia may result in neuro-disability and death in case of a prolonged fast,. In such situations, parents may be unaware of this catastrophic cascade. In case of such a tragedy, the pediatric pathology services will play a substantial role in helping the family to find the etiology and eventually target the specific genes. In newborn screening programs, some diseases progress slowly, whereas some others eventually lead to severe multi-organ dysfunction. The result of mucoviscidosis is not a critical value that pediatricians need to know now. Mucoviscidosis or cystic fibrosis (CF) entails insufficiency of the exocrine pancreas and chronic pulmonary disease leading to failure of the lung in the 3rd or 4th decade of life. Acute life-threatening complications may occur in newborns but are highly infrequent. Another similar endocrinological disorder that does not reach the level of highest priority is congenital hypothyroidism. A different value is given to lysosomal storage diseases, such as sialidosis[47]. In sialidosis, there is a deficiency of the enzyme neuraminidase, which ends in the abnormal accumulation of toxic compounds in several organs, mainly brain and liver, although other organs are also affected[48,49]. In fact, sialidosis may be considered a critical diagnosis that physicians must know now. In inborn errors of metabolism with target organs, including brain, heart, and liver, priority is the highest. Finally, drug monitoring and toxicology results are results with the most top priority because life-threatening imbalances can occur at any time. The pharmacological history is mandatory in evaluating the interaction of drugs with herbals or food in pediatrics more than in any other medical area[50,51]. Metabolomics is playing a central role in inborn errors of metabolism[52-54]. The severe potential of these disorders dictates that physicians know about these conditions at the time the value of the test becomes known to the laboratory physician. My clinical and research experience in several countries (Italy, Germany, United Kingdom, Austria, Canada) has been crucial in understanding the role of communication of critical values to emergency physicians or to a professional team of pediatric intensive care units. Although a table would be beneficial, it does not fit all children's hospital priorities, because some institutions have different priorities with some providing primary care and some tertiary care. However, I am a strong advocate in considering that the laboratory physician team liaise with the clinical physicians to create a list that is specific for that specific institution. In my experience, critical values come to the list once they are set by the laboratory physicians in collaboration with the clinicians. It is not a one-off activity, but it is under continuous review at regular intervals, which is crucial for the accreditation of the institution. It is a dynamic process. Critical values may change over time if critical incidents or "near misses" occur and are discussed in the setting of a comprehensive quality assurance.

Finally, the pre-analytical process is critical because it may require the clinical team to liaise with the laboratory to identify the best way to gather and deliver the sample for analysis (*e.g.*, saline, transport medium, formaldehyde, glutaraldehyde). Another point that remains crucial is the age of the patient. A serum bilirubin value over 300 μmol/L is critical (must know now) for a child during the first 15 d of life, but it is less critical (must know) for older children. Also, even for the same unit or even the same patient, the significance of an abnormal value may change over time. The presence of blastic cells in the peripheral blood is critical at the first diagnosis, but its presence will be less essential once the diagnosis of leukemia has been established. The analytical phase is complicated as it encompasses a whole list of devices and steps in clinical and surgical pathology. The postanalytical phase remains probably the most evolving at this time. The complexity of modern hospitals and inter-disciplinary works may favor the use of electronic ways to communicate the results. Advances in electronics, wireless communication, and personal communicative devices have changed the way we work along with others. Laboratory data can be accessed anytime and anywhere giving the clinical team an opportunity to act immediately on critical values. The next level of essential values in patient care will be dictated by improving the level of communication of the information and, probably, through an interpretation of the value. The phone conversation may remain crucial to discuss and interpret correctly critical values.

CONCLUSION

The original concept of critical value was defined in the 70's of the last century as a value representing an imminent danger on which a physician needs to act promptly[35]. In pediatrics, failure to provide this value means loss of life or development of mostly neurologic disabilities. Thus, the mandatory prompt intervention infers that the result is communicated precisely very close to the precipitating event. The medical/surgical intervention upon it is unambiguous and abrupt raising the need for an objective treatment. In the 21st century,

the determination of alert thresholds remains the most challenging and controversial issue in clinical pediatrics. In any case, pre-analytical matters need to be cleared off before the laboratory physician can dispatch the life-threatening result. Classification of essential laboratory results is more than an academic exercise. Prioritizing critical calls should be part of the excellent educational training of the resident. In this setting, life hangs in the balance, and life-death decisions need to be taken in seconds not minutes. A phone conversation may be substituted using other alternative alerting functions, including inserting data into the database of electronic medical records or communicating by e-mail. These new methods are modes of making sure relevant information is transmitted without interrupting the standard work-flow of the primary physicians in charge of the child.

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