Opinion Paper

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An evidence- and risk-based approach to a harmonized laboratory alert list in Australia and New Zealand

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Abstract: Individual laboratories are required to compose an alert list for identifying critical and significant risk results. The high-risk result working party of the Royal College of Pathologists of Australasia (RCPA) and the Australasian Association of Clinical Biochemists (AACB) has developed a risk-based approach for a harmonized alert list for laboratories throughout Australia and New Zealand. The six-step process for alert threshold identification and assessment involves reviewing the literature, rating the available evidence, performing a risk analysis, assessing method transferability, considering workload implications and seeking endorsement from stakeholders. To demonstrate this approach, a worked example for deciding the upper alert threshold for potassium is described. The findings of the worked example are for infants aged 0–6 months, a recommended upper potassium alert threshold of >7.0 mmol/L in serum and >6.5 mmol/L in plasma, and for individuals older than 6 months, a threshold of >6.2 mmol/L in both serum and plasma. Limitations in defining alert thresholds include the lack of well-designed studies that measure the relationship between high-risk results and patient outcomes or the benefits of treatment to prevent harm, and the existence of a wide range of clinical practice guidelines with conflicting decision points at which treatment is required. The risk-based approach described presents a transparent, evidence- and

consensus-based methodology that can be used by any laboratory when designing an alert list for local use. The RCPA-AACB harmonized alert list serves as a starter set for further local adaptation or adoption after consultation with clinical users.

Keywords: alert list; alert threshold; critical result; critical risk result; harmonization; hyperkalemia.

Introduction

Inconsistencies and gaps in laboratory practices for managing critical and significant risk results (collectively known as high-risk results) may expose patients to unnecessary harm. In response to this, the Clinical Laboratory Standards Institute and a working party of the Royal College of Pathologists of Australasia (RCPA) and the Australasian Association of Clinical Biochemists (AACB) published best practice recommendations to guide laboratories in the design and maintenance of their high-risk result procedures [1, 2].

Central to these procedures is the alert list, a list of tests and alert thresholds outside which results require timely notification. According to guidelines, the composition of the alert list is the responsibility of individual laboratories in consultation with their clinical users [1, 2]. Despite ongoing efforts to harmonize and standardize analytical methods and reference intervals or clinical decision limits, there is considerable variation in the tests and thresholds that laboratories include on their alert list. Clinical and patient organizations, including patient safety advocates and medical indemnity organizations, have voiced the need for a more uniform and agreed procedure on when and how high-risk results should be communicated [3]. To enable laboratories to apply a uniform and risk-based approach for the safe delivery of care to patients, the working party has decided to compose a harmonized alert list, at least for the most common analytes, based on the best available evidence.

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Approach to the development of a harmonized alert list

Minimum data set

Essential components of the harmonized alert list were determined by the RCPA-AACB working party to include the following:

- name of the tests as per national recommendation [4];
- measurement unit, as per national recommendation [4];
- sample type;
- alert (upper and lower, and/or delta change) threshold;
- source(s) and strength of evidence for the alert threshold;
- timeframe within which a result should be notified and acted upon; and
- clinical context such as patient age, gender, pregnancy status and patient setting (where relevant).

Selecting the tests

Thirty-eight tests were initially identified as possible candidates for the common alert list, based on the combined experience of working party members (Supplementary Data; Table 1). Consideration was given to whether the harmonized alert list should only contain tests that have demonstrated transferability of results across different methods, namely, analytes with reference intervals already harmonized at national level [5]. However, the consensus view of the working group was that this would eliminate a number of important tests. Instead, it was decided that analytes with alert thresholds transferable and non-transferable across different methods should be clearly distinguished, and that the suitability of method-specific decision limits for non-transferable analytes would be determined by reviewing their performance in external quality assurance program(s).

Process for deciding the alert thresholds

A six-step process for identifying and assessing the suitability of alert thresholds was devised and is summarized in Figure 1. This process is illustrated by an example of establishing the critical risk alert threshold in hyperkalemia.

Figure 1: Process for identifying and assessing the suitability of alert thresholds.

Establishing the upper alert threshold for potassium

Hyperkalemia has a detrimental impact on muscle and nerve cell excitation causing weakness, fatigue, paraesthesia, depression of deep tendon reflexes, palpitations and potentially life threatening cardiac arrhythmias [6].

Step 1: Review the literature on alert thresholds

A published systematic review of the literature on alert thresholds revealed 62 papers that reported upper thresholds for potassium ranging from 5.5 to 7.0 mmol/L with a median of 6.2 mmol/L [7].

Step 2: Rating the evidence for alert thresholds

The quality of the evidence from the literature review was rated using an adaptation of a previously reported approach [8]. The highest level of evidence is derived from outcome studies (Level 1), followed by recommendations from professional bodies (Level 2), then thresholds sourced from laboratory or clinician surveys (Level 3), with

thresholds reported by individual laboratories ranking the lowest (Level 4). Thresholds derived by collaboration between the laboratory and clinicians are rated higher (subgroup a) than thresholds decided by one of these key stakeholders alone (subgroup b).

Out of the 62 papers identified for hyperkalemia, three were outcome studies (Evidence Level 1). Only one of the three involved collaboration between the laboratory and clinicians (Level 1a). In this 5-year retrospective hospital inpatient study, an upper potassium alert threshold of 6.2 mmol/L was deemed appropriate [9]. Among other findings, the study showed a time-dependent association between the degree of abnormality in the potassium results and increased rates of death. The 48-h in-hospital death rates of patients with potassium concentrations of 5.8–5.9, 6.0–6.1, 6.2–6.3 and >6.4 mmol/L were 2.5%, 2.7%, 3.2% and 3.9%, respectively; the overall in-hospital death rate was 2.0%. The second outcome study (performed by clinicians) evaluated the effectiveness of intervention by a rapid response team when potassium reached 6.3 mmol/L [10]. Over the 5-year study period, 890 patients with a discharge diagnosis code of “hyperkalemia” died, but only four of these deaths were found to be attributable to hyperkalemia (i.e. potassium >6.3 mmol/L within 8 h of death and no other likely cause of death). The third outcome study (performed by a laboratory) retrospectively investigated causes, outcomes and timeliness of clinical response for hyperkalemia [11]. In this 1-year study, the frequency of cardiac arrest/shock at various potassium levels was as follows: 10 of the 116 patient episodes (9%) with potassium between 6 and 7 mmol/L, 10 of the 38 patient episodes (26%) with potassium between 7 and 8 mmol/L and 11 of the 12 patient episodes (92%) with potassium >8 mmol/L. These researchers determined that an alert threshold of 7 mmol/L was optimal to prevent harm in a timely manner.

Six of the 62 papers identified for hyperkalemia were recommendations by professional bodies (Evidence Level 2). Three of these recommendations were developed in collaboration between the laboratory and clinicians (Evidence Level 2a; endorsing thresholds of 6.0, 6.2 and 6.5 mmol/L), whereas the other three were produced by laboratory professionals alone (Evidence Level 2b; with thresholds of 6.0, 6.2 and 6.2 mmol/L).

Step 3: Risk analysis to assess threshold suitability

Risk analysis, as described by the Clinical and Laboratory Standards Institute in the GP47 Guideline, has been performed to assess the suitability of the alert thresholds identified by the evidence review process [1]. This analysis involved the following:

- identification of the potential harm and clinical intervention associated with a critical risk result;
- estimation of the likelihood and severity of the potential harm (in absence of intervention) and the urgency of clinical intervention to reduce the risk of harm;
- evaluation of whether routine reporting of the result exposes the patient to an unacceptable risk of harm.

The most significant adverse outcome of hyperkalemia is immediate death due to cardiac arrest. Given this, even asymptomatic patients with mild hyperkalemia are treated. Procedures for potassium elimination (e.g. loop diuretics, ion-exchange resin delivered to the colon or dialysis) are generally slow to act. Therefore, patients with symptoms, electrocardiogram (ECG) changes or moderate to severe hyperkalemia require faster acting (albeit temporary) treatment to stabilize the myocardium (by calcium gluconate) and shift potassium into the cells (e.g. insulin or β -2 agonists) [12–16]. The laboratory should report moderate to severe hyperkalemia immediately to allow initiation of prompt and aggressive treatment, whereas routine reporting of mild hyperkalemia is adequate for less-urgent management. Unfortunately, there is little agreement on the threshold that distinguishes mild from moderate hyperkalemia, with various authors defining moderate hyperkalemia at as low as 6.0 mmol/L and mild hyperkalemia at as high as 7.5 mmol/L [17]. Common decision points for more aggressive treatment are either >6.0 mmol/L or >6.5 mmol/L [5, 12, 13, 15–18]. Some experts suggest a higher threshold (>7.0 mmol/L) for patients with chronic kidney disease and on potassium sparing medication assuming that cardiac mortality is associated with more acute rise in blood potassium concentration [19].

Aligning the laboratory’s alert threshold with the decision limit used locally for aggressive treatment to prevent a dangerous clinical outcome rather than on limits linked to severe pathophysiological changes is a sensible and pragmatic approach as it harmonizes laboratory and clinical practice and guides timely medical intervention. In the absence of such local treatment protocols, the working party recommends the literature sourced threshold of 6.2 mmol/L (see Steps 1 and 2).

Step 4: Transferability and pre- and postanalytical aspects of the alert threshold

Determining whether different thresholds should be used for specific patient subsets or clinical settings is essential and offers an opportunity for customizing alert thresholds. In some cases, pre- or postanalytical factors may impact on the use of the alert threshold and its harmonization.

Population-specific alert thresholds

Patients receiving dialysis, if reliably identified by the laboratory, could reasonably have a higher hyperkalemia threshold. Acceptable identification could include a clear statement of “predialysis” on the pathology request form. Identifying predialysis patients purely based on ward location is inadequate, as this does not provide certainty that dialysis treatment is imminent.

Renal excretion of potassium is low during the first months of life, resulting in higher blood potassium levels in the neonatal period and early infancy [20]. The Australasian harmonized upper reference limit for serum potassium is 6.5 mmol/L from age 0 to 1 week and 6.7 mmol/L from the 2nd to the 26th week of age [4]. Babies often tolerate potassium of 7.5–8.0 mmol/L without ECG changes [21]. The UK National Health Service neonatal guidelines for management of hyperkalemia recommend administration of salbutamol (β -2 agonist) at serum potassium >7.0 mmol/L, and calcium gluconate when potassium exceeds 7.5 mmol/L and ECG changes are present [21]. On this background, the working party recommends an upper alert threshold of 7.0 mmol/L for infants aged between 0 and 6 months.

Preanalytical considerations – effect of sample type

Potassium is 0.3–0.4 mmol/L higher in serum compared to plasma, due to its release from platelets and white blood cells during clotting [4]. Clinicians are generally unaware of this issue, and it is rarely considered when treatment guidelines are formulated. Laboratories may have a preferred sample type, but they are unlikely to reject samples collected in alternate tubes. In the lack of specific information, it is reasonable to assume that retrospective outcome studies are commonly based on a mixture of sample types. A conservative approach is needed to set potassium alert thresholds when studies do not report the sample type for which their decision thresholds apply. The recommended adult upper potassium threshold of >6.2 mmol/L is conservative enough for use with serum or plasma, considering that 6.5 mmol/L is a commonly used treatment decision point. Due to the lack of preanalytical information in studies and guidelines, laboratories may consider lowering the infant threshold from >7 to >6.5 mmol/L if plasma is the preferred specimen.

Pseudohyperkalemia

The possibility of pseudohyperkalemia should be investigated and eliminated before a high-risk potassium result

is communicated to clinicians. Some laboratories that receive samples collected from remote locations extend their upper reference limit for potassium to 5.5 mmol/L to allow for cellular leakage of potassium [4]. It is not advisable to apply a similar offset to the upper alert threshold because missed diagnosis of moderate hyperkalemia has more serious consequences than missed mild hyperkalemia.

Step 5: Impact of the selected threshold on the frequency of critical alerts

To assess the practical and organizational consequences of proposed alert thresholds, the frequency of alerts should be investigated. As the harmonized thresholds may flag differing number of cases in primary, secondary or tertiary care, this impact assessment is best performed on local databases. If the frequency of alerts presents an unmanageable workload both to the laboratory and the clinical recipients, the utility of the threshold and the preanalytical error rate for potassium measurements needs to be reevaluated and the risk-assessment revisited and refined (Step 3), in consultation with the clinicians involved (Step 6).

Potassium results were analyzed over a 3-month period within a network of seven laboratories servicing nine public hospitals in the Sydney metro and its catchment area. Of the 21 potassium results per day measured on infants (aged 0–6 months), one result per 1.4 days was >6.2 mmol/L, one result every 2.5 days was >6.5 mmol/L and one result every 10 days was >7.0 mmol/L. Therefore, lowering the infant alert threshold to match the adult threshold, if required, would not be a burden on workflow. There were 1789 potassium results per day across the nine hospitals on patients older than 6 months, of which 45 results per day were >5.5 mmol/L (i.e. the upper nationally harmonized reference limit), 13 results per day were >6.0 mmol/L, eight results per day were >6.2 mmol/L and four results per day were >6.5 mmol/L. Thus, for this laboratory network, adoption of the recommended upper alert threshold (i.e. >6.2 mmol/L) would produce an undemanding one hyperkalemia alert per laboratory per day. If local preferences dictated a lowering of the threshold to >6.0 mmol/L, the number of hyperkalemia alerts would still be manageable at two per laboratory per day.

Step 6: Endorsement for selected thresholds from laboratories and clinical groups

Alert lists developed in consultation with clinical users have a higher likelihood of successful implementation. Senior clinicians in various Australian hospitals in New South Wales are currently being surveyed through an

Table 1: Harmonized alert list for hyperkalemia.

Test name	Unit of measure	Sample type	Clinical context	Alert threshold	Notification timeframe	Level of evidence
Potassium	mmol/L	Serum	Age: 0–6 months	>7.0	Immediately	2b: NHS (UK) Neonatal guidelines 2015–2017
		Plasma	Age: 0–6 months	>6.5	Immediately	2b: NHS (UK) Neonatal Guidelines 2015–2017 ~ <i>Adjusted for sample type (Clin Biochem Rev 2014;35:213–35)</i>
		Serum/plasma	Age: >6 months	>6.2	Immediately	1a: Am J Clin Pathol 2014;142:617–28

online questionnaire regarding their acceptance of various alert thresholds. The survey has yet to be circulated to primary care physicians or their representative organizations, and endorsement of the list will be requested from a broad range of national colleges, patient and patient safety organizations such as the Clinical Excellence Commission.

For patients aged 0–1 month, 79% of survey respondents (53/67) agree with an upper alert threshold of >7.0 mmol/L. Among those that disagree, six have proposed a threshold of >6.2 mmol/L, whereas four suggested >6.5 mmol/L. For patients aged 28 days to 110 years, there was 71% agreement (57/79) for a threshold of >6.2 mmol/L. Alternative thresholds proposed by respondents for this age-group include >6.0 mmol/L (nine respondents) and >6.5 mmol/L (nine respondents). Fifty-five of 57 respondents (96%) thought that neonatal hyperkalemic critical risk results should be phoned immediately, whereas 58 of 69 respondents (84%) believed that hyperkalemic critical risk results on patients aged 28 days to 110 years require immediate phoning. However, overall clinician agreement for the proposed alert thresholds is strong.

Table 1 shows the harmonized alert list entry for the upper potassium threshold. It is important to emphasize that the Harmonized Alert List is only a recommendation that individual laboratories are advised to discuss with their clinical users. There remains the ability to modify and customize the alert list to align it with clinical practice guidelines used locally or when the local population has unique management requirements. Such deliberations and any deviations from the recommendations should be clearly documented.

Limitations and conclusions

In clinical research, randomized control trials are regarded as the strongest level of evidence. It is obviously unethical not to treat an individual's high potassium in order to measure the harm that it may cause. Consequently, outcome studies relevant to identification of alert thresholds are

restricted to retrospective observations. This makes it difficult to control for factors external to the laboratory result that have contributed to the outcome. Furthermore, the temporal relationship between the result and the outcome may be difficult to assess due to inadequate documentation. A well-designed retrospective study that incorporates detailed clinical information into the analysis can reduce the impact of confounding factors and, thus, strengthen the measured relationship between the high-risk result and the outcome. Given the complexity of the task, it is not surprising that a systematic literature review of common chemistry and hematology alert thresholds identified only a few outcome studies that assess the appropriateness of alert thresholds [6]. In fact, the review revealed a lack of any kind of evidence or explicit reasoning for the selection of alert thresholds. For many tests, the best available literature evidence is state of the art, captured by laboratory surveys on alert lists currently in use.

Even if a study successfully identified a strong cause-and-effect relationship between a laboratory result threshold and mortality, this may not be enough to define an alert threshold. The communication of a high-risk result must trigger medical action in time to prevent harm. For some tests, action may need to be taken before the result reaches a life-threatening level, so intervention can occur before it is too late.

There is no sense in rapidly communicating results if they do not impact clinical decisions [22]. Therefore, it is important to seek clinical approval of alert thresholds. However, many clinicians have personal preferences for result thresholds at which action must be taken, and laboratories cannot be expected to cater for idiosyncrasies of individual clinicians. Having a systematic, clinical risk-based approach to determining alert thresholds should be seen as good clinical governance and overcome such individual preferences.

This harmonization initiative by the RCPA-AACB working party aims to provide laboratories and clinicians with a starter set of recommended alert thresholds for some common analytes. The thresholds can be adapted to local circumstances and clinical protocols and should

be brought in line with clinical pathways and treatment recommendations. Laboratorians have an important role in mediating these discussions and ensuring that a joint policy and procedures are developed and implemented. Furthermore, the impact of joint policies and procedures must be followed up to ensure safer care to patients [23].

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