Laboratory Monitoring: Back to Basics

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PROLOGUE
For a variety of reasons, students often consider themselves unprepared to interpret common laboratory values on clerkship rotations. The preceptor, and usually the student, realizes that a general understanding of common laboratory values is needed to practice in settings where such values are available. There is a tremendous amount of information concerning laboratory monitoring, but the information is often overwhelming and the student seems to lose track of the most common causes of abnormal values. The purpose of this article is to provide an overview of laboratory parameters that are routinely ordered in settings where monitoring is performed. The parameters include serum sodium, chloride, potassium, bicarbonate, blood urea nitrogen (BUN), and creatinine. The intent is not to make the pharmacy student a diagnostician, but rather to enable the student to have a basic understanding of laboratory value interpretation that is important when recommending and monitoring medication regimens.

INTRODUCTION
As a clerkship preceptor in a hospital setting, it is not uncommon that I encounter pharmacy students who do not feel capable of assessing common laboratory values. There are a number of possible explanations for this finding but three are particularly common. First, the important points were discussed but simply not learned (other than on a short-term basis for an examination). Second, the material was not discussed to a sufficient degree, often due to an erroneous presumption that students would learn this material piecemeal throughout the curriculum. Finally, the information was presented in such detail that the most important overreaching concepts were not learned. Considering the number of textbooks and handbooks devoted exclusively to laboratory values, it is not surprising that students would tend to feel overwhelmed with the sheer volume of information in the medical literature. Regardless of the explanation for the deficiency, a general understanding of common laboratory values is needed for any student who will be practicing in settings where such values are available.

The intent is not to make the pharmacy student a diagnostician. However, a basic degree of laboratory value interpretation is needed when recommending and monitoring medication regimens. I have found that one does not need to convince clerkship students that this information is important- it is usually obvious to them within the first few days of my elective rotation in the surgery area (which includes learning the basics of parenteral nutrition). Therefore, with help from pharmacy residents, and a colleague who coordinates our nutritional support team, we routinely review basic laboratory monitoring for all students taking my rotation. The verbal and written feedback associated with this interactive learning environment has been uniformly positive.

The purpose of this article is to review the basic components of the information that is discussed on my rotation. The focus will be on those serum laboratory parameters that are commonly ordered on admission and throughout the patients' hospital stays: sodium, chloride, potassium, bicarbonate, blood urea nitrogen (BUN), and creatinine. In discussions of this topic with students, important points that apply to a variety of patient care settings are stressed, but admittedly my perspective is from the standpoint of a hospital pharmacist. Clinicians will be quick to point out some other commonly ordered, and important, parameters are not listed above. However, I have found many of the parameters likely to be mentioned are best taught with specific disease states. For example, the white blood cell count is well suited for a discussion of infectious...
Table I. Goals and objectives pertaining to discussion of common laboratory values

Goal 1: Understand the general principles involved in laboratory monitoring.
   T.O. 1.1 (Comprehension) Explain the problems associated with the interpretation of single or isolated laboratory variables.
   E.O.0.1.1.1 (Knowledge) List four examples of how an intervention to normalize a laboratory value that is outside of the usual stated range may be detrimental with regards to patient outcome.

Goal 2: Understand how to interpret the most common causes of abnormal serum sodium, potassium, bicarbonate, blood urea nitrogen (BUN), and creatinine concentrations.
   T.O.2.1 (Comprehension) Discuss the association between sodium and chloride concentrations.
   E.O.2.1.1 (Comprehension) Give examples of how sodium and chloride concentrations may be high, normal, or low in patients with fluid deficiencies or excess.
   T.O.2.2 (Comprehension) Describe the relationship between potassium concentrations and acid-base disturbances.
   T.O.2.3 (Comprehension) Describe at least one situation in which a low or high bicarbonate concentration may not require any intervention to normalize the value.
   T.O.2.4 (Comprehension) Explain when the BUN and creatinine concentrations may rise together and when the BUN alone may be increased.

*T.O. refers to a terminal objective while E.O. refers to an enabling objective (i.e., the enabling objective is a subset of a terminal objective

Table II. Basic concepts pertaining to laboratory monitoring

| Patients have died with "normal" laboratory values. |
| Many patients have lived (quite well) with abnormal laboratory values. |
| Laboratory values outside the listed normal range may not be abnormal (e.g., laboratory error) or may not be abnormal for a particular patient. |
| The goal should not be to make all laboratory values normal; resist the urge to do something in a clinically stable patient. |
| Trends (not single, isolated values) that are most important. |
| Laboratory values should never be interpreted in isolation (i.e., without other available information such as history of present illnesses, past medical history, medication history, physical examination). |

...diseases, while other components of the complete blood count are important relative to the topic of anemia. Similarly, blood glucose monitoring is particularly applicable when caring for the patient with diabetes.

As reflected in the goals and objectives (Table I), this discussion with students is not intended to replace literature reviews or other reference materials concerning laboratory parameters. Rather, it is intended to be an overview of the topic with the presumption that ongoing learning will take place. While multiple sources of more detailed information are available, one particularly useful resource is published by the American Society of Health-System Pharmacists. It is a practical, yet comprehensive reference, which discusses laboratory parameters in a manner understandable to students as well as other health professional (1).

GENERALIZATIONS PERTAINING TO LABORATORY MONITORING

There are a few basic concepts that are fundamental to laboratory monitoring (see Table II). The first three generalizations listed in the table pertain to the issue of what is normal. Every laboratory has a list of normal ranges based on the specific assays being used. However, patients die every day of disease states that are not reflected by abnormal laboratory tests. The flip side of this issue is that many patients have abnormal laboratory values and have no perceptible disease. The analogy of a bell-shaped curve in statistics is useful for understanding this point. Let’s take the example of a population of healthy patients with serum sodium concentrations. While the majority of subjects in the sample will fall within 1 or 2 standard deviations of a curve reflecting the normal range of values of sodium concentrations (i.e., 135-145 mMol/L), there are individuals whom by chance have values that are in the tails of the curve. For whatever reason, these healthy individuals just happen to have values that are quite different from the majority of individuals.

The fourth generalization in Table II follows the above discussion regarding normality. Given that a subset of healthy patients will have laboratory values outside of the usual normal range, the clinician must resist the attempt to make everything normal through interventions to raise or lower the number. This is the classic principle of treating the number, not the patient. While the temptation to treat a number may be resisted when the laboratory value was ordered for screening purposes, the issue becomes more complicated when treating patients who appear to have some disease. In the latter setting, there is an even greater temptation to make all laboratory values normal, particularly when there are difficulties relative to identifying the true disease process. The clinician needs to resist the temptation, since patient harm may result from an intervention that does not treat the true problem. First, do no harm.

Another fundamental concept of laboratory value interpretation concerns the importance of trends relative to single values. An isolated sodium value of 155 mMol/L (normal 135-145 mMol/L) may be clinically unimportant if the value has been relatively stable over a period of a few days. On the other hand, if the concentration had been much lower (e.g., < 130mMol/L) for more than week and was then rapidly increased to 155 mMol/L in less than a few hours, the change could be life threatening. It is also possible that an isolated, abnormal laboratory value may be due to improper patient identification, specimen handling, specimen analysis, or data entry.

There are several examples from both the literature and from my clinical experience that are used to demonstrate the concerns with treating isolated laboratory values, not the patient. In one example reported in the literature, a physician expressed his regret over an incident in which a patient died when her admission serum sodium concentration of 98 mMol/L was rapidly increased to a concentration greater than 120 mMol/L. The physician was interpreting the best evidence at the time that suggested such an approach was appropriate. The physician went on to say how the literature had changed over the years and how a more conservative management approach may have prevented the neurologic complications attributable to the rapid escalation in the sodium concentration. In a personal example, I informed a physician of a critically
low phosphate concentration (0.5 mg/dL, normal range 2.5-4.5 mg/dL) in a patient with respiratory failure in the intensive care unit. When the physician went to check the laboratory value for himself on the computer, the concentration was reported as being 3.2 mg/dL, so he did not order phosphate supplementation. When I called the laboratory, I was informed that the originally reported low concentration was correct and that somehow the value of another patient was inadvertently entered into my patient's record. At this point I had to page the physician, who had left the intensive care unit, and inform him that the original report was correct. Given this sequence of events, he wanted to see the concentration for himself before he ordered a supplement. Eventually the patient received the necessary phosphate infusion but the delays attributable to data entry were disconcerting to say the least.

Finally, laboratory values should never be interpreted apart from other important assessment parameters such as the patient history and physical examination, assuming such information is available. In many cases, clerkship students on my rotation learn this lesson through inappropriate blood draws through IV lines containing parenteral nutrition solution. When students see this happen for the first time, they usually come to my office with a panicked, perplexed look on their faces. They explain that the patient looks fine, but many of a patient's laboratory parameters such as glucose and potassium are much higher than the normal range. They can't understand how the values could change so dramatically in one day. Although they sense something is missing from their analysis of the situation, they are usually quick to offer a variety of interventions aimed at reducing the elevated concentrations back to the normal range. While contaminated blood draws may be a source of frustration and concern for students who encounter this situation for the first time, it provides a valuable lesson with regards to laboratory monitoring that is usually well remembered.

INTERPRETATION OF SPECIFIC LABORATORY PARAMETERS

Sodium and Chloride

Although chloride may be involved in acid/base disorders (which is beyond the scope of this discussion), concomitant movements of serum sodium and chloride concentrations either upwards or downwards is usually reflective of extracellular fluid changes. Therefore, for the remainder of this section, the emphasis will be on serum sodium changes with the presumption that chloride concentrations are changing in a proportional manner.

One of the more important points for students is that there are very few pure sodium or pure water disturbances. For example, it is possible that a patient has hyponatremia due to inadequate sodium intake or hypernatremia due to excessive ingestion of sodium (e.g., in the form of salt tablets). Similarly, relatively pure free water disturbances include hyponatremia caused by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or hypernatremia caused by diabetes insipidus. However, in the majority of cases, there are changes in both sodium and water and the resulting sodium concentration depends on the degree of change in each.

In chronic disease states such as congestive heart failure, cirrhosis, and nephrosis both sodium and water are retained, but water is retained in excess of sodium. The result is hyponatremia. Hypernatremia is a relatively common occurrence in the hospital or urgent care setting when hypovolemic patients are resuscitated with normal or isotonic saline solution, which contains 154 mMol/L of sodium and 154 mMol/L of chloride (for monovalent ions such as sodium, potassium, chloride, and bicarbonate, one mMol equals one mEq). Given the normal serum sodium concentration of 135-145 mMol/L, vigorous resuscitation with this solution commonly increases the serum sodium concentration as the ability of the kidneys to excrete the excessive sodium load becomes overwhelmed. The student may be confused by references that list certain problems such as diarrhea and excessive sweating as causing both hyponatremia and hypernatremia(3). This is a good opportunity to explain that such losses rarely occur in the absence of fluid intake. Therefore, the resulting sodium concentrations depend on the type of fluids being ingested by the patient or administered by clinicians. Fluid replacement with low (tap) water or no (five percent dextrose in water) sodium containing solutions will frequently result in hyponatremia since losses of sodium will be in excess of losses of water. Fluid replacement with high amounts of sodium (normal saline) will frequently result in hypernatremia since losses of sodium are less than losses of water (although the metabolic acidosis that commonly occurs from the high concentration of chloride in normal saline is usually a more important clinical problem)(4).

There are a number of medications that may cause hyponatremia or hypernatremia. Examples of products commonly dispensed in inpatient and outpatient settings that may result in hyponatremia are thiazide diuretics and morphine, while lithium and loop diuretics may result in hypernatremia. The degree of change in the sodium concentration from the normal range of values depends on the patient's ability to compensate for the effects of the offending medication, as well as the type of fluid (i.e., high or low sodium) that is being ingested.

Although an in-depth discussion of the causes and management of hyponatremia and hypernatremia is usually beyond the introduction of the topic to students, excellent reviews are available for those wishing to obtain more information on the subject(5,6). Similarly, resources are available concerning related topics such as tonicity, osmolality, and use of urine electrolytes(7-9).

Potassium

One of the most important concepts concerning potassium relates to its intracellular distribution. Students who have seen relatively normal potassium concentrations in the range of 3.5 to 5.5 mMol/L often greatly under-estimate total potassium stores in the body. Let's presume we are trying to calculate the total potassium stores in an 80 kg adult male. This male has approximately 60 percent total body water (i.e., 48 L) of which two-thirds (32 L) is in the intracellular and one-third (16 L) in the extracellular fluid compartments of the body. None of this will surprise a student with a basic knowledge of fluid distribution, however, the student often does not realize that potassium is predominantly an intracellular cation with a concentration of approximately 150 mMol/L inside the cell. Therefore, an incredible 4800 mMol (150 mMol/L x 32 L) is located intracellularly. Compare this to the paltry 72 mMol (assuming a potassium concentration of 4.5 mMol/L x 16 L) of potassium residing in this male's extracellular stores, which is what the student sees when looking at a normal serum potassium concentration.

Many of the other important issues related to potassium revolve around its distribution characteristics. For example, a patient with a metabolic acidosis will have potassium movement to the extracellular compartment as the excessive hydro-
Some important points:

- Correcting acid/base disturbances rapidly (e.g., over minutes) may not have time to shift intracellularly where the majority of the deficit resides. In this case, more than 50% of this male's normal extracellular potassium will be given as a bolus and carried directly to vital organs, including the heart with possible cardiac arrest.

- Hypokalemia typically occurs when gastrointestinal (vomiting, diarrhea) or urinary losses of potassium are not adequately replaced. However, there are conditions that may increase so-called insensible losses through sites such as the skin (e.g., excessive sweating and large open wounds). In general, students are typically aware of the major medication classes that may alter potassium concentrations such as thiazide and loop diuretics that increase the urinary loss of potassium, or potassium sparing diuretics that may decrease urinary losses. In some cases, the effects of medications are influenced by potassium concentrations. One particularly notable example is the increased risk of digoxin cardiotoxicity in patients with hypokalemia. It is worth mentioning that a few medications that affect serum potassium concentrations are used in a beneficial manner. A patient with hyperkalemia may receive sodium bicarbonate (which causes the opposite effect of the metabolic acidosis example earlier), or glucose and insulin, to drive the potassium inside the cell. It should be stressed that these interventions usually cause a transient decrease in serum potassium concentrations since the potassium is not actually eliminated from the body. Other interventions such as the administration of sodium polystyrene sulfonate (a potassium binding resin) or the institution of dialysis may be employed for permanent removal.

- The student should be aware of one cause of pseudohyperkalemia, hemolysis, since it is not an uncommon occurrence when tourniquets are used during phlebotomy or when improper handing of a blood sample causes a breakdown of the cells. Both of these factors cause potassium to be released from the inside to the outside of the cell leading to spurious measurements of the serum potassium concentration. Most laboratories let the clinical know when hemolysis has taken place, but it doesn’t hurt to give the laboratory a call when a markedly elevated potassium concentration is seen in a patient who has had relatively stable, low to normal serum concentrations.

**Bicarbonate**

The major importance of the serum bicarbonate concentration lies in its association with acid/base disturbances, which as mentioned earlier, are beyond the scope of this discussion. A few general statements can be made regarding the interpretation of abnormal bicarbonate concentrations (normal serum range 24-32 mMol/L). Some defined disorders may cause consistent changes in the direction of bicarbonate concentrations when concomitant disease states are not present. For example, a metabolic acidosis (a lactic acidosis to be more specific) with a decreased bicarbonate concentration will occur in virtually every patient with substantial losses of blood volume due to hyperfusion of vital organs with the ensuing anaerobic metabolism that takes place. In this case, correction of the underlying problem by fluid administration will correct the acid/base disturbance. There is little evidence that therapies such as sodium bicarbonate will improve patient outcomes in such situations.

Bicarbonate concentrations may also be changed as a result of compensation for primary respiratory problems such as hypoventilation (respiratory acidosis) or hyperventilation (respiratory alkalosis). In this case, the altered serum bicarbonate concentrations are reflective of the body’s attempt to maintain a normal pH. Interventions by the clinician to raise or lower the bicarbonate concentrations to the usual normal range are likely to be counterproductive with regards to acid/base balance.

There is one final note with regards to bicarbonate concentrations. Many laboratories report the serum bicarbonate concentration in terms of total carbon dioxide content. This is because the great majority of carbon dioxide in the body is in the form of bicarbonate and only a small amount is in the form of carbonic acid. When the bicarbonate is reported in this fashion, there is a tendency for students to refer to bicarbonate as carbon dioxide. Particularly in the hospital setting this can be misleading, since the clinician may erroneously assume the student is referring to the carbon dioxide values associated with arterial blood gas measurements. Therefore, it is best if the student uses the term bicarbonate when referring to serum concentration monitoring of the electrolyte.

**Blood Urea Nitrogen (BUN) and Creatine**

As with the sodium and chloride concentrations, it is useful to consider the BUN (normal range 9-20 mg/dL) and creatinine (normal range 0.3-1.3 mg/dL) laboratory parameters together. The most common cause of an elevated serum BUN to creatinine ratio (i.e., the BUN concentration divided by the creatinine concentration) is intravascular depletion. For a patient who has lost plasma volume, regardless of the cause, the initial response of the body is to increase sodium and water retention by the kidneys. As this retention occurs, urea is passively absorbed back into the bloodstream in the kidneys, while the creatinine is excreted in the urine. The result of these changes is decreasing urine output and an increasing BUN to creatinine ratio. If the reduced plasma volume is not replaced, the creatinine value will eventually be to rise once the kidneys and other organs can no longer compensate for the reduced plasma volume. The rising creatinine is a harbinger of possible renal failure and indicates a need for prompt resuscitation. Whenever students see an increasing serum creatinine concentration, their first consideration should be that of impending renal failure.

There are a variety of formulas used to estimate a patient’s actual creatinine clearance based on serum creatinine concentrations. The Cockcroft and Gault equation in particular has relatively widespread use among pharmacists, although other equations more be more appropriate in patients with changing renal function. It is a good idea to tell the students to use such formulas to estimate creatinine clearance in any patient older than 65 years of age or anyone with a serum creatinine concentration greater than 1.3 mg/dL, since renally eliminated medications may need dosage adjustments. Unfortunately, using this approach will not catch all cases of overt or impending renal failure. A patient who has lost substantial lean mass after being immobile (e.g., bed rest) for prolonged periods of time may have a low serum creatinine due to a decreased production of creatinine from its precursor creatine is muscle. The formation of creatinine is an irreversible process that is a function of muscle mass (as well as age and sex), so if muscle wasting has occurred, the serum creatinine concentration may be low despite renal dysfunction.
In other words, the decrease in creatinine clearance due to renal dysfunction is offset by the decreased production of creatinine. Failure to recognize this issue could lead to excessive doses of renally eliminated medications.

The rate of rise of the serum creatinine concentration has implications beyond the choice of a formula to estimate creatinine clearance by the kidneys. In general, most clinicians consider a rise of 0.3 to 0.5 mg/dL/day as a clinically significant rise in the serum creatinine concentration. However, the serum creatinine concentration. However, the serum creatinine concentration is a relatively late indicator of renal dysfunction and it may take a number of days to reach a steady state concentration. This is another example of the importance of trends. A patient who has had her serum creatinine value rise from 0.8 mg/dL to 1.3 mg/dL to 1.8 mg/dL to 2.3 mg/dL over a four day period may actually be in complete renal failure, but the creatinine has not reached a steady state concentration. This concept is illustrated by telling the students to think of creatinine as a medication with all of the associated pharmacokinetic parameters such as half-life. Let’s presume the half-life of creatinine is three hours. Since the time to reach steady state concentrations is roughly 4 to 5 half-lives, as the half-life of the creatinine increased with worsening renal dysfunction, the time to reach steady state concentrations will be prolonged. Therefore, if the half-life of creatinine rose to 24 hours, the time to reach steady state concentrations would be 4 to 5 days.

While the major cause of clinically important increases in serum creatinine concentrations is renal dysfunction, there are causes of elevated BUN concentrations other than volume depletion and renal dysfunction. After volume depletion, the most common cause of an elevated BUN with a normal serum creatinine concentration (particularly in hospitalized patients) is protein administration by enteral or parenteral nutrition. Compared to the usual daily protein intake of an otherwise healthy adult (e.g., 0.8 g/kg/day), patients under sever stress may require more than twice this amount. This is often reflected in an elevated BUN to creatinine ratio. Typically, the rise in the BUN dose not exceed 30mg/dL, which is much lower than the trigger value (e.g., > 100 mg/dL) often used to indicate the need for dialysis in patient with renal failure. A summary of the key points regarding BUN and creatinine interpretation, as well as the other laboratory parameters discussed in this article, are listed in Table III.

**Table III. Key points regarding common laboratory values**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Proportional changes in these parameters generally reflects a fluid disorder</th>
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<tbody>
<tr>
<td>Sodium and chloride</td>
<td>Changes in sodium balance are usually associated with changes in water balance</td>
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<tr>
<td>Potassium</td>
<td>The great majority of potassium in the body is located in the intracellular compartment</td>
</tr>
<tr>
<td>Blood urea nitrogen (BUN) and creatinine</td>
<td>An elevated BUN to creatinine ratio usually indicates volume depletion</td>
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</table>

**CONCLUSION**

A basic understanding of the interpretation of common laboratory parameters is needed for any student who will practice in settings where such information is available. Particularly important general principles include the need for the student to consider the meaning of normal and abnormal concentrations. Furthermore, the focus should be on trends instead of isolated laboratory values, always taking into account other clinical information specific to the patient. The student needs to realize the importance of treating the patient not the laboratory value. For the instructor or preceptor introducing this topic, it is important to focus on the most common reasons for abnormal laboratory values, as well as common problems relative to laboratory value interpretation and associated interventions.

**References**

(3) Bakerman, S., ABC’s of Interpretive Laboratory Data, Interpretive Laboratory Data, Inc., Greenville NC (1984).