Total Arsenic Screening Prior to Fractionation Enhances Clinical Utility and Test Utilization in the Assessment of Arsenic Toxicity

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Key Words: Arsenic speciation; Arsenic fractionation; Heavy metals; Test utilization; Inductively coupled plasma mass spectrometry

ABSTRACT

Objectives: The objective was to evaluate the utility of a screen with reflex-to-fractionation testing compared with direct-to-fractionation testing for suspected toxic exposure.

Methods: This study was based on a retrospective data analysis of urine arsenic results from previously tested samples (n = 12,960). Total urine arsenic by inductively coupled plasma mass spectrometry was used as a screening method to identify elevated arsenic concentrations. Arsenic fractionation was the speciation assay to differentiate toxic and benign arsenic species.

Results: Screening samples based on total arsenic concentration resulted in less than 10% of samples requiring arsenic fractionation, with a final positivity rate of less than 1% for toxic arsenic. Samples with fractionation ordered directly had a positivity rate for toxic arsenic of 3.3%. The overall positivity rate for exposure to toxic arsenic was less than 1%.

Conclusions: A total arsenic screen before fractionation reduces the number of samples requiring fractionation by more than 91%, supporting the use of a screen with a reflex-to-fractionation approach for urine arsenic.

The use of screening assays with reflex to confirmation or quantification is a commonly used testing strategy. A screen with reflex-to-quantification approach may be warranted when investigating trace metal exposure due to the non-descript and often overlapping symptoms of toxicity, such as gastrointestinal distress and neuropathy, making it difficult to correlate with a specific exposure incident. In addition, exposure to arsenic may occur through routine dietary ingestion of certain foods, such as rice,¹ thus eliminating the necessity for a specific incident to be connected with potential toxic exposures. Investigation of arsenic toxicity may involve a total arsenic screen with reflex to a fractionation assay to distinguish toxic and benign forms of the element, thus providing an ideal case study for the utility of a screen with reflex algorithm in trace metal analysis.

Arsenic exists as a number of species, only some of which are associated with toxicity. Upon completion of this activity you will be able to:
• interpret arsenic results with respect to the American Conference of Governmental Industrial Hygienists biological exposure index criteria.
• discuss the various species of arsenic and their potential for toxicity.
• compare the utility of a screen with reflex approach and direct to arsenic fractionation for assessment of possible toxic exposures.

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[As(III)], arsenate [As(V)], and the metabolites monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) are the most toxic forms and also known carcinogens. Organic arsenic species, most commonly arsenobetaine and arsenocholine, are generally considered benign and not associated with toxicity. The concentration of 35 μg/L has been set by the American Conference of Governmental Industrial Hygienists (ACGIH) as the Biological Exposure Index (BEI) for the sum of inorganic and methylated arsenic in urine. Speciation, or fractionation, to identify individual arsenic species is required to distinguish the presence of toxic and benign arsenic.

The symptoms of arsenic toxicity may be nonspecific and often overlap with symptoms of other toxicants. Acute arsenic toxicity can be characterized by gastrointestinal distress, including vomiting and diarrhea, and also cardiac arrhythmias. Chronic toxicity may be characterized by renal failure, cardiac arrhythmias, liver dysfunction, and peripheral neuropathy. Arsenic in urine is often evaluated using one of two possible tests, either a total arsenic with reflex to fractionation or directly to arsenic fractionation without a prior total arsenic concentration. These two tests can be obtained through three distinct laboratory test ordering possibilities: (1) a total arsenic concentration with reflex to fractionation, (2) direct arsenic fractionation, or (3) heavy metal panels that include total arsenic with reflex to fractionation in addition to other commonly encountered heavy metals (eg, lead and mercury) Figure 1. Test orders 1 and 2 offer a targeted investigation for arsenic, whereas test order 3 is broader and evaluates additional heavy metals in addition to arsenic. In each of these three tests, elevated arsenic concentrations will undergo fractionation to identify the contributing arsenic species. However, in the two test order options that include total arsenic with reflex to fractionation (total arsenic and heavy metal panels), samples without elevated arsenic do not undergo fractionation. This reflex approach allows a total arsenic concentration to function as a screening test to determine which samples necessitate further evaluation for potential arsenic toxicity.

The objective of this study was to evaluate the clinical utility of the three possible ordering options for urine arsenic in identifying arsenic toxicity, based on (1) clinical and analytical positivity rates between the three orders, (2) analytical equivalence between the two available tests, and (3) the cost-effectiveness of including a reflex component to the testing compared with direct fractionation for all samples.

Materials and Methods

Use of Clinical Samples and Human Participants

This project and its protocols were approved by the University of Utah Institutional Review Board (IRB 00007275).

Data Collection

Data from samples previously analyzed for urine arsenic at ARUP Laboratories (Salt Lake City, UT) were included in this retrospective analysis. The initial data set included 13,013 orders for urine arsenic testing. Samples sent for arsenic analysis for which no result was available, due to the presence of interfering substances, submission of inappropriate specimen type, or order cancellation (n = 53), were excluded from the data set, producing a final data set containing 12,960 urine samples.

Summary of Relevant Arsenic Species

<table>
<thead>
<tr>
<th>Classification</th>
<th>Species</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inorganic</td>
<td>Arsenite</td>
<td>Highly toxic</td>
</tr>
<tr>
<td>Organic</td>
<td>Arsenobetaine</td>
<td>Benign</td>
</tr>
<tr>
<td>Methylation</td>
<td>Dimethylarsinic acid</td>
<td>Moderately toxic</td>
</tr>
<tr>
<td>Organic</td>
<td>Arsenocholine</td>
<td>Benign</td>
</tr>
</tbody>
</table>

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**Figure 1** Example testing algorithm for urine arsenic. As, arsenic; Cd, cadmium; Co, cobalt; Hg, mercury; Pb, lead; Zn, zinc.
arsenic results from all three order options (total arsenic with reflex, direct to arsenic fractionation, and heavy metal panels with arsenic reflex). Patient name, date of birth, and result verification date were used to match total and reflexed arsenic results for a given sample prior to deidentification for data analysis. For analysis of the reflexive portion of the testing algorithm, only samples with a total arsenic level of 35 µg/L or higher were included. Samples with a total arsenic level of less than 35 µg/L on which fractionation was performed at the request of the physician were excluded from the analysis of reflex to fractionation. Direct-to-fractionation samples were analyzed separately from the total arsenic with reflex-to-fractionation samples.

Urine Total Arsenic Assay

Urine total arsenic samples were analyzed by inductively coupled plasma mass spectrometry (ICP-MS). Samples were mixed with one equivalent of 1% nitric acid and diluted 1:50 with diluent (0.5% nitric acid and 0.05% Triton X-100), to which yttrium was added as an internal standard. Samples were analyzed on a SCIEX ELAN 9000 or DRC II ICP-MS instrument (PerkinElmer, Waltham, MA) connected to a Cetac 510 HS autosampler (Teledyne Cetac Technologies, Omaha, NE). Masses at m/z of 75 (arsenic) and 89 (yttrium) were monitored, with yttrium used as the internal standard for quantification. To confirm arsenic results were free of polyatomic interferences (eg, argon chloride [ArCl] at m/z 75), we tested all results greater than 35 µg/L by using m/z 91 (arsenious acid) and a PerkinElmer DRC II ICP-MS. The limit of quantification for total arsenic was 10 µg/L, and the imprecision of the assay, based on current performance of quality control (QC) in the laboratory, was calculated as the coefficient of variation (CV) and was less than 5% at 31.7 µg/L.

Fractionated Arsenic Assay

Urine arsenic fractionation samples were analyzed using high-performance liquid chromatography (HPLC) coupled to ICP-MS (HPLC-ICP-MS). The internal standard used for arsenic fractionation was lead (m/z 208). Samples were diluted 1:20 with Agilent Technologies (Santa Clara, CA) Speciation Diluent (4 mmol/L sodium phosphate monobasic, 0.4 mmol/L EDTA, 20 mmol/L sodium acetate trihydrate, 6 mmol/L sodium nitrate, 1% [v/v] ethyl alcohol, 50 µg antimony/L, and 50 µg lead/L, pH 11.0), and samples were analyzed using an Agilent Technologies model 7700x ICP-MS instrument with a 1200 Series HPLC system. Samples were injected onto a 4.6 × 150-mm arsenic speciation anion exchange column from Agilent Technologies, and the following HPLC system settings were used: injection volume, 50 µL; flow rate, 1.0 mL/min; and column oven temperature, 40°C. The limit of quantification for each arsenic species was 5 µg/L. The imprecision of the assay (%CV), based on current performance of QC in the laboratory, was as follows: less than 11% for As(III) at 21 µg/L, less than 10% for As(V) at 13 µg/L, less than 8% for MMA and DMA at 15 µg/L, and less than 6% for arsenobetaine at 52 µg/L. The ICP-MS was operated in collision mode using helium gas to remove polyatomic interferences (eg, ArCl) at m/z 75.

Analytical and Clinical Performance of Urine Total and Fractionated Arsenic Assays

Analytical performance of the total and fractionation assays was assessed based on quantitative agreement between the two assays. This analysis used the subset of samples that were reflexed to fractionation (n = 1,110), since both total arsenic and fractionation results were available for the same samples. For arsenic fractionation, the total arsenic measured was equal to the sum of quantitated species [As(III), As(V), MMA, DMA, and arsenobetaine]. A scatter plot with linear regression was used to determine the correlation between the two assays. Assay bias was evaluated based on the percent difference between the assays, calculated as 100 × [total arsenic – sum of fractionated arsenic species]/total arsenic, and visually represented using a Bland-Altman relative difference plot. Analytical positivity was defined as the sum of fractionated arsenic species at 35 µg/L or higher. Clinical positivity was defined as the sum of inorganic and methylated arsenic species at 35 µg/L or higher, consistent with ACGIH guidelines.

Cost Analysis

A cost analysis was conducted to determine the approximate testing costs for the two testing approaches: screen with total urine arsenic (including use of a heavy metals panel) or direct to fractionation. For this analysis, the average list prices from three reference laboratories were used for the price of a total urine arsenic assay as well as the fractionated urine arsenic assay. The average list prices were $104.55 for a total urine arsenic assay and $188.23 for fractionated arsenic, when measured by ICP-MS or HPLC-ICP-MS.

Results

Analytical and Clinical Positivity

Since the goal of arsenic testing is to identify possible arsenic exposure, arsenic positivity was evaluated separately for the three possible ordering patterns: total arsenic with reflex, direct to fractionation, and heavy metal panels. In this analysis, analytical positivity was defined as the sum of all fractionated arsenic species 35 µg/L or higher, and clinical positivity was defined as the sum of inorganic and methylated arsenic species 35 µg/L or higher, consistent with the ACGIH guidelines.
BEI. This data set included 12,960 urine arsenic results, including 365 results that were ordered directly as arsenic fractionation. Of the remaining 12,595 total arsenic results, 10,623 were ordered through heavy metal panels and 1,972 were ordered as stand-alone total arsenic.

In our laboratory, three available heavy metal panels can be ordered that include arsenic analysis. In addition to arsenic, panel 1 includes lead and mercury; panel 2 includes lead, mercury, and cadmium; and panel 3 includes lead, mercury, cadmium, cobalt, and zinc. Data were combined for all three panels for subsequent analyses with a total of 10,623 ordered tests and 900 total reflexed to arsenic speciation (8.5%).

Overall, less than 1% (114 of 12,960) of urine arsenic results were clinically positive. For arsenic results from heavy metal panel orders, 7.3% were analytically positive and 0.6% were clinically positive. Results from total arsenic orders showed similar positivity rates, with 8.6% of samples being analytically positive and 1.8% being clinically positive. To compare positivity between the total arsenic orders (heavy metal panels and stand-alone total arsenic) and the direct-to-fractionation orders, we calculated the percent positivity based on the number of samples that were reflexed to fractionation. Heavy metal panel orders resulted in an analytical positivity of 86.7% and clinical positivity of 7.3%. For stand-alone total arsenic orders, 80.5% were analytically positive and 17.1% were clinically positive. Finally, for samples that were ordered directly to fractionation, 13.7% were analytically positive and 3.3% were clinically positive.

Since this analysis compares positivity across two different tests (total arsenic and arsenic fractionation), the analytical equivalence of these two assays was evaluated. The quantitative agreement was determined using the total arsenic concentration and the sum of quantified arsenic species in the fractionation assay [As(III), As(V), MMA, DMA, and arsenobetaine]. The linear regression of the sum of arsenic species compared with total arsenic showed similar positivity rates, with 8.6% of samples being analytically positive and 1.8% being clinically positive. To compare positivity between the total arsenic orders (heavy metal panels and stand-alone total arsenic) and the direct-to-fractionation orders, we calculated the percent positivity based on the number of samples that were reflexed to fractionation. Heavy metal panel orders resulted in an analytical positivity of 86.7% and clinical positivity of 7.3%. For stand-alone total arsenic orders, 80.5% were analytically positive and 17.1% were clinically positive. Finally, for samples that were ordered directly to fractionation, 13.7% were analytically positive and 3.3% were clinically positive.

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### Table 2
**Summary of Positivity Rates for Urine Arsenic Based on the Initial Ordering Pattern**

<table>
<thead>
<tr>
<th>Ordering Pattern</th>
<th>Heavy Metal Panels</th>
<th>Urine Arsenic</th>
<th>Direct to Arsenic Fractionation</th>
<th>Total Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ordered, No.</td>
<td>10,623</td>
<td>1,972</td>
<td>365</td>
<td>12,960</td>
</tr>
<tr>
<td>Fractionated, No. (% of ordered)</td>
<td>900 (8.5)</td>
<td>210 (10.6)</td>
<td>365 (100)</td>
<td>1,475 (11.4)</td>
</tr>
<tr>
<td>Analytically positive, No. (% of fractionated) (% of total)</td>
<td>780 (86.7) [73]</td>
<td>169 (80.5) [8.6]</td>
<td>50 (13.7)</td>
<td>999 (67.7)</td>
</tr>
<tr>
<td>Clinically positive, No. (% of fractionated) (% of total)</td>
<td>66 (7.3) [0.6]</td>
<td>36 (17.1) [1.8]</td>
<td>12 (3.3)</td>
<td>114 (7.7) [0.9]</td>
</tr>
</tbody>
</table>

*Analytical positivity is defined as a sum of all arsenic species (inorganic, methylated, and organic) 35 μg/L or higher, and clinical positivity is defined as a sum of toxic arsenic species (inorganic and methylated) 35 μg/L or higher. Samples that were reflexed to fractionation but were not analytically positive contained organic arsenic species that are not identified and quantified in this assay.*
35 to 5,511.6 µg/L. The total arsenic assay had a mean relative bias of 10.5%. This overall positive bias exists because the total arsenic assay quantifies all arsenic present in the sample, while the fractionation assay quantifies only the toxic (inorganic and methylated as MMA and DMA) and major organic (arsenobetaine) species, which means the presence of additional organic arsenic species that may be present in a sample is not quantified by this assay.

Cost Analysis

The low rate of positivity of arsenic testing supports the inclusion of a screen with reflex approach with respect to laboratory test utilization; however, the economic impacts of this approach were also investigated. A cost analysis was conducted to estimate the financial impact of arsenic testing using a screen with reflex approach compared with direct to fractionation for the analytically positive and analytically negative results. Table 3. For the 949 analytically positive results, the cost per patient from the screen with reflex approach was $292.78 and $188.23 with direct to fractionation. In the analytically positive group, the use of the screen with reflex approach resulted in a net loss of $99,217.95. For the 11,646 analytically negative results, the cost per patient was $104.55 with the screen with reflex approach and $188.23 with direct to fractionation. In the analytically negative group, the use of the screen with reflex approach resulted in a net savings of $974,537.28. In total (n = 12,595), use of the screen with reflex approach resulted in a net savings of $875,319.33 or $69.53 per patient.

Discussion

This study investigated the utility of a screening assay for heavy metal analysis using urine arsenic as a case study. Urine arsenic results were analyzed retrospectively to determine ordering patterns and positivity rates indicating possible arsenic toxicity. The analytical performance of urine total arsenic and arsenic fractionation assays was compared and demonstrated acceptable correlation and agreement, with a slight positive bias toward the total arsenic assay. This positive bias is expected since the fractionation assay does not identify and quantify all arsenic species that may be present but only the toxic [As(III), As(V), MMA, and DMA] and major organic (arsenobetaine) species. This agreement indicates that analysis of arsenic by either total or fractionation assays will each provide an accurate assessment of arsenic and potential for toxicity.

In terms of arsenic positivity, 7.7% of results showed elevated urine total arsenic, based on the ACGIH BEI of 35 µg/L. Most of these samples were analytically positive (ie, quantifiable organic arsenic) but not clinically positive (ie, quantifiable inorganic and/or methylated arsenic species). Less than 1% of all samples analyzed for urine arsenic were clinically positive, with a sum of inorganic and methylated arsenic species 35 µg/L or higher. When the positivity rates are broken down based on ordering patterns, the lowest rates of both analytical and clinical positivity upon fractionation were observed in the samples that were ordered directly to arsenic fractionation (13.7% and 3.3%, respectively). The use of a screening assay prior to fractionation, either through the use of a heavy metals panel or stand-alone urine total arsenic, increased the yield of elevated arsenic results upon fractionation. Due to the increased assay cost and low rates of positivity observed when ordered directly, the use of a screen prior to fractionation resulted in overall decreased testing costs.

One nuance of evaluating suspected arsenic toxicity is appreciating the most common sources of arsenic exposure. A likely cause of elevated total arsenic, predominantly due to organic arsenic, is the recent ingestion of seafood; however, the association of diet with benign organic arsenic cannot be generalized to all dietary forms of arsenic since seafood consumption may also cause an increase in methylated arsenic species. Inorganic arsenic is present throughout the environment, is found in drinking water, and is a by-product of copper smelting. In addition, inorganic and methylated forms of arsenic are found in rice. The presence of toxic arsenic species in an individual, however, does not automatically indicate exposure to sources of contamination. Toxic inorganic arsenic is used as a therapeutic agent for the treatments of some cancers, particularly acute promyelocytic leukemia. Due to these varied sources of potential exposure to arsenic, a clinical and dietary history is required to provide context for arsenic concentrations in a given individual.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Analytically Positive (n = 949)</th>
<th>Analytically Negative (n = 11,646)</th>
<th>Per Patient</th>
<th>Total</th>
<th>Total</th>
<th>Per Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen with reflex</td>
<td>292.78</td>
<td>277,849.22</td>
<td>104.55</td>
<td>1,217,589.30</td>
<td>1,498,437.52</td>
<td>118.70</td>
</tr>
<tr>
<td>Direct to fractionation</td>
<td>188.23</td>
<td>178,630.27</td>
<td>188.23</td>
<td>2,192,126.58</td>
<td>2,370,756.85</td>
<td>188.23</td>
</tr>
<tr>
<td>Net savings</td>
<td>(104.55)</td>
<td>(99,217.95)</td>
<td>83.68</td>
<td>974,537.28</td>
<td>875,319.33</td>
<td>69.53</td>
</tr>
</tbody>
</table>

* Values are costs in US dollars, calculated using the average list prices from three reference laboratories.
The data presented here indicate that direct ordering of arsenic fractionation results in a clinical positivity rate of 3.3%. However, screening samples for elevated total arsenic prior to fractionation reduces the number of negative samples requiring fractionation by 91.3%. This raises the possibility that heavy metal panel screens for a wider array of toxic metals may be more efficient and cost-effective in identifying possible exposures than ordering individual heavy metals directly.

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