Only the conjugated form of bilirubin appears in urine. Unconjugated bilirubin, such as that produced during intravascular hemolysis, is not water soluble and cannot be excreted by the kidneys. Conjugated bilirubin can appear in the urine when bile ducts are obstructed or when the integrity of the liver is compromised such that bilirubin is released directly into the bloodstream. Therefore, urine bilirubin reflects increased levels of conjugated bilirubin in the serum. The presence of bilirubin in human urine is consistent with hepatitis, cirrhosis, gall bladder disease, and various hepatocellular cancers. Urine bilirubin levels are commonly assessed with the urinalysis dipstick test; this test involves use of a pad that produces a diazotization color reaction in the presence of bilirubin. Urine bilirubin testing became common when a colorimetric bilirubin test pad was included in common urinalysis test strips. The goal of urine bilirubin screening is to potentially reveal a pathologic liver or gall bladder condition early, before jaundice is apparent. However, urine bilirubin does not appear to add significant information toward the diagnosis of most patients.
test uses a solid diazonium salt that gives a purple reaction in the presence of bilirubin. Our laboratory uses urinalysis strips that detect bilirubin via a coupling reaction of the diazonium salt 2,6-dichlorobenzene-diazonium-tetrafluoroborate with bilirubin in an acidic medium. If present, this reaction with bilirubin produces a pink to red-violet color proportional to the total bilirubin concentration.4

Recently, supplier shortages of the Ictotest tablets have made it necessary for our laboratory to stop confirming positive urine bilirubin results. This change prompted us to question the usefulness of the test in general. Although a few studies have been published concerning the use of urine bilirubin testing, those that we reviewed demonstrated the limitations of this type of testing. Binder et al5 showed that the presence of urine bilirubin correlated strongly with serum bilirubin elevations but was not highly predictive of abnormal liver function test (LFT) results.6 Kupka et al6 also showed that urine urobilinogen and urine bilirubin have only approximately a 50% negative predictive value for at least 1 abnormal LFT result.

An informal survey of physicians in our system revealed nearly unanimous consensus; when a positive urine bilirubin test result is found, follow-up testing is seldom warranted. The healthcare professionals who do follow up on positive urine bilirubin results stated that the only action they take is order a liver function panel (albumin, total bilirubin, alkaline phosphatase [ALP], alanine transaminase [ALT], and aspartate aminotransferase [AST]). The general opinion of our health care professionals was that a urine bilirubin result was not likely to add new information to a case and would be even less likely to be helpful if a positive result was not confirmed. Based on these attitudes, we conducted a retrospective analysis of patient charts to help gauge the usefulness of urine bilirubin testing in our practice. In our system, we use Chemstrip 10 UA dipsticks (F. Hoffmann-La Roche Ltd., Basel, Switzerland). We queried records to determine how many positive samples had abnormal LFT results in the 2 weeks before the positive urine-bilirubin results were obtained (LFTs included AST, ALT, gamma-glutamyl transpeptidase [GGT], and total bilirubin). We considered positive results on these tests to constitute expected positives. The positive urine bilirubin test results from patients who did not also have abnormal LFT results within the 2 previous weeks were considered to be unexpected positives.

For the unexpected positive samples, we noted how many LFTs had been ordered subsequent to the positive urine-bilirubin results. During a 20-month period, we performed 241,929 urinalysis tests (Table 1) on samples from inpatients and outpatients. Of these, 831 tested positive for urine bilirubin (0.3%). All of these positive results were confirmed using the manual Ictotest. Of these positive results, 60% were from patients who had also had abnormal LFT results or a previously positive urine bilirubin test result in the previous 2 weeks. These positive urine bilirubin results we labeled as expected positives. For these patients, the urine bilirubin result did not add clinical value because they already had been proven to have abnormal liver function or elevated serum bilirubin concentrations before a positive urine bilirubin result was obtained. However, 40% of the positive results derived from patients who had had no previous abnormal LFT results; thus, we deemed these results to be unexpected positives. Of these, 80% had liver function tests ordered with 2 weeks after the positive urine bilirubin result was obtained. An obvious shortcoming of our study is that we could not discriminate the reason for the original urinalysis order. An order that is placed to investigate a urinary tract infection would be less likely to produce an unexpected positive bilirubin result than would an order for a patient who has abdominal pain. In this way, our sample was biased against finding abnormal LFT results.

In our review, we considered positive urine bilirubin results from patients who had had an abnormal LFT result within 2 weeks of a new finding of urine bilirubin positivity to be unexpected positives. Of these unexpected positives, 85% had had abnormal LFT results within 2 weeks of the positive bilirubin result. This finding is consistent with results reported by Kupka et al., who found that positive urine bilirubin predicted the presence of at least 1 LFT abnormality.

Table 1. Results of Urinalysis Tests by Subcategory

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of UA tests</td>
<td>241,929 (100)</td>
</tr>
<tr>
<td>UA results positive for urine bilirubin</td>
<td>831 (0.3)</td>
</tr>
<tr>
<td>Expected positives</td>
<td>502 (0.2)</td>
</tr>
<tr>
<td>Unexpected positives</td>
<td>329 (0.1)</td>
</tr>
<tr>
<td>Positives that were followed up</td>
<td>264 (0.1)</td>
</tr>
<tr>
<td>Unexpected positives from patients who had had abnormal LFT results</td>
<td>205,156 (84.8)</td>
</tr>
</tbody>
</table>

*UA results positive for urine bilirubin includes samples from patients who had had abnormal LFT results in the previous 2 weeks.

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83% of the time. However, our criteria for unexpected positives are not rigorous. The ordering of LFTs after a positive urine bilirubin result assumes that only the urine bilirubin result prompted the ordering of the LFTs. In reality, subsequent orders for LFTs were likely triggered by factors such as patient symptoms, verbal history, and patient medication monitoring, rather than merely a positive urine bilirubin test result. Nevertheless, we counted these unexpected positives as evidence that supported the value of urine bilirubin testing. Thus, our unexpected positives likely overestimate the influence of the positive urine bilirubin results on clinical care.

We concluded the following: First, although it can be argued that urine-bilirubin testing may have some value in uncovering liver pathologic manifestations, our data suggest that it plays a minor role, given the way it is currently used and ordered. Because we could not discriminate results based on presentation or previous diagnosis, our criteria for unexpected positives are generous. However, only 0.1% of all confirmed-positive urine bilirubin results were classified as unexpected positives. Furthermore, we believe that most of the subsequent LFTs were probably ordered based on patient history and other signs and symptoms, rather than due to positive urine bilirubin results. Hence, the number of actual unexpected positives is likely to be considerably lower than 0.1%. Therefore we conclude that the test has limited value in routine screening. From the standpoint of laboratory usage, we conclude that urine bilirubin results do not add significant information for the vast majority of patients.

Given the shortage of confirmation (Ictotest) reagent, releasing positive urine bilirubin results that were not confirmed would have significantly added to the potential for unnecessary follow-up of patients. We experienced this briefly during the initial week after discontinuing the Ictotest confirmation procedure. For a brief period, we labeled positive urine bilirubin dipstick results as potential positives. We chose this phrase to reflect the fact that we were unable to confirm the positive result. This resulted in 2 patients (treated by a nurse practitioner and a physician assistant) being sent to the Emergency Department of our health system, for investigation of positive urine bilirubin results. The physicians in the Emergency Department quickly discharged these patients.

Laboratory use and stewardship are becoming increasingly important in our current era of rising healthcare costs, managed care organizations, accountable care organizations, and the Affordable Care Act. Our practice is interested not only in eliminating unnecessary test orders but more importantly, reducing unnecessary downstream medical costs and patient anxiety. Our practice decided to cease confirmation of positive urine bilirubin results and also to refrain from releasing the results. We now suppress the results from the urine bilirubin component of the urinalysis test strip. No laboratorians or other health care professionals have voiced any concerns about this action, to our knowledge. We believe that this action decreases unneeded follow-up and anxiety among patients and does not compromise patient care. LM

References

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