Screening Strategies for Hemochromatosis

TO THE EDITOR: The article by Phatak and colleagues (1) is timely and should encourage physicians to follow a logical approach in the screening and diagnosis of hemochromatosis. The authors recommend screening for a condition with substantial morbidity and mortality rather than not screening because of fears of psychological harm and discrimination due to genotype analysis. However, even if screening for hemochromatosis becomes accepted, physicians may choose *HFE* mutation studies as the initial test rather than the pragmatic method of phenotypic screening suggested in the article. Phatak and colleagues recommend measurement of fasting transferrin saturation and unsaturated iron-binding capacity as the initial test in phenotype screening, but checking serum ferritin has some merit in individuals suspected to have hemochromatosis. This is especially true because of the substantial biological variability of transferrin saturation and unsaturated iron-binding capacity demonstrated in a recent study (2). Including serum ferritin in the screening would help avoid genetic testing in individuals with normal ferritin levels and transferrin saturation and also identify those with normal transferrin saturation and high serum ferritin levels, in whom *HFE* mutation tests may be appropriate. In contrast, transferrin saturation should be tested in situations in which a high serum ferritin level is an incidental finding during initiation of blood tests for other reasons (an increasingly common hospital practice), which would help in deciding to proceed to genotype analysis.

In summary, phenotype analysis should be the first step in screening for hemochromatosis, and screening strategies should include measurement of serum ferritin and transferrin saturation before resorting to genetic testing.

Jecko Thachil, MBBS
University of Liverpool
Liverpool L69 3BX, United Kingdom

Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We appreciate Dr. Thachil’s comments regarding the value of serum ferritin measurement as an adjunctive test to serum transferrin–iron saturation in the diagnostic algorithm for hereditary hemochromatosis. We agree that the serum ferritin level is the most useful noninvasive measure of body iron stores in patients with hemochromatosis and can help determine the need for therapeutic intervention. Waalen and colleagues (1) have recommended a ferritin-only screening approach, using a relatively high serum ferritin threshold value of 1000 µg/L (1). Of 59 patients identified in a primary care clinic by using this serum ferritin threshold during a population screening study, 20 were C282Y homozygotes. However, we believe that a threshold serum ferritin level of 1000 µg/L will miss many cases with phenotypic expression and that a lower threshold will increase the likelihood of finding nonspecific elevations. The multitude of causes other than iron overload for high serum ferritin levels make this test less valuable when used as part of a targeted screening strategy. Although serum transferrin saturation may also demonstrate variability (2), a persistently elevated serum transferrin saturation, as defined in our article, remains the best predictive phenotypic test for the homozygous C282Y mutation (3, 4). Thus, although serum ferritin may be a useful adjunctive test in screening strategies and is certainly important to determine the degree of iron overload and risk for hepatic fibrosis once *HFE* hemochromatosis is confirmed, we remain convinced that serum ferritin is sufficiently nonspecific to be a useful initial screening test to diagnose hemochromatosis.

Pradyumna D. Phatak, MD
Rochester General Hospital
Rochester, NY 14621

Herbert L. Bonkovsky, MD
Carollinas HealthCare System
Charlotte, NC 28232

Kris V. Kowdley, MD
Virginia Mason Medical Center
Seattle, WA 98101

Potential Financial Conflicts of Interest: None disclosed.

References
ponents are included in composite outcomes. This is consistent with the primary motivation for most uses of composite outcomes: to reduce sample size requirements to achieve the desired statistical significance (4). Second, a plot of the P values of the composite outcome revealed marked asymmetry around the midpoint of the plot, suggesting reporting bias: Researchers may have selected components to include in the composite that favored statistical significance.

Overall, Lim and colleagues’ study supports views that we have expressed elsewhere (3–6). Although the use of composite end points is appropriate in some instances (4), they can potentially provide misleading impressions about the nature and magnitude of treatment benefits. This occurs when the composite outcome includes components of widely varying importance to patients, but the less important components are primarily responsible for the observed effect (6). These instances create serious challenges for the interpretation of results and their application in clinical practice and can mislead both patients and physicians.

Iñacio Ferreira-González, MD, PhD
Gaietà Permanyer-Miralda, MD, PhD
Vall d’Hebron Hospital, CIBER de Epidemiología y Salud Pública
08035 Barcelona, Spain

Jason W. Busse, MSc
P.J. Devereaux, MD, BSc, PhD
Gordon H. Guyatt, MD, MSc
McMaster University
Hamilton, Ontario L8N 3Z5, Canada

Pablo Alonso-Coello, MD
Iberoamerican Cochrane Center, Hospital de la Santa Creu i Sant Pau, CIBER de Epidemiología y Salud Pública
08025 Barcelona, Spain

Víctor M. Montori, MD, MSc
Mayo Clinic
Rochester, MN 55905

Potential Financial Conflicts of Interest: None disclosed.

References

CLINICAL OBSERVATIONS

Gallbladder Carriage of Salmonella paratyphi A May Be an Important Factor in the Increasing Incidence of This Infection in South Asia

Background: Enteric fever is a burden in developing countries, in which poor sanitary conditions facilitate its persistence. Most cases are attributed to the bacterium Salmonella typhi. However, S. paratyphi A is an emerging agent of enteric fever. This trend is apparent in Kathmandu, Nepal, where the proportion of enteric fever cases at Patan Hospital caused by S. paratyphi A increased from 17.5% in 1993 to 34% in 2003 (1).

Salmonella typhi and S. paratyphi A are atypical with respect to the majority of the genus Salmonella because they can survive and replicate in deeper tissues. Systemic dissemination causes organisms to be found in the gallbladder. This ability of S. typhi to remain in the gallbladder is considered central to the transmission of typhoid fever (2). An estimated 10% of untreated patients continue to shed bacteria for up to 3 months after infection, and up to 4% for more than 1 year. Most carriers are asymptomatic, and around 25% have no history of enteric fever (3). The role of chronic carriage of S. paratyphi A has received little attention, and the extent to which it contributes to S. paratyphi A infection is unknown.

Objective: To identify the burden of Salmonella carriage in an area of Kathmandu with a high incidence of enteric disease.

Methods: We assessed the bile and gallbladder from 404 consecutive patients undergoing cholecystectomy between June 2007 and June 2008 at Patan Hospital. Patients were examined before surgery, and surgeons diagnosed the cause of gallbladder symptoms on basis of the preoperative assessment, appearance during surgery, and postsurgical histopathologic examination. Bile was extracted from all removed gallbladders and cultured to isolate enteric bacteria. The Nepal Health Research Council approved this study.

Results: The Table shows data collected from 404 patients undergoing cholecystectomy. We cultured invasive Salmonella from the bile of 22 patients, yielding a prevalence rate in this population of 5.4%. We confirmed 12 isolates to be S. typhi and 9 to be S. paratyphi A, for a ratio of S. typhi to S. paratyphi A of 4:3. The demographic characteristics of the population with Salmonella carriage were similar to the overall population undergoing cholecystectomy: 16 of 22 (72.7%) of Salmonella isolates were from women, and the median age in the female carriers was 35.9 years.

Six patients with Salmonella isolated from bile had histopathologic findings of acute inflammation. Patients with Salmonella infection were significantly more likely to have histopathologic findings of acute inflammation than were patients who had other organisms isolated or were culture negative.

Discussion: It is commonly thought that enteric fever due to S. paratyphi A is less severe than that caused by S. typhi. However, this is not the case in Nepal; a study of 609 patients (4) found no differences in clinical presentation or severity. The most comprehen-

www.annals.org
sive study of paratyphoid carriage (5) identified 35 S. paratyphi isolates from 1000 bile specimens taken during cholecystectomy; however, all but 5 were S. paratyphi B. We identified a 5.4% carriage rate of invasive Salmonella in our study population of 404 patients. Nine of 22 (2.2%) were S. paratyphi A.

Conclusion: These data highlight the problem of S. paratyphi A in Nepal, a pattern reflected in other parts of Asia. A population study is needed to assess the extent of the carriage of S. typhi and S. paratyphi A in this area and the contribution it makes to the disease burden. Strategies to prevent long-term carriage and identify those who do become carriers are needed to break the transmission cycle.

Nely Shrestha Khatri, MD
Pukar Maskey, MD
Sanjay Poudel, MD
Vijay Kumar Jaiswal, MD
Abhilasha Karkey, MSc
Samir Koirala, MD
Nikki Shakhya, MD
Krishna Agrawal, MD
Amit Arjyal, MD
Buddha Basnyat, MD
Patan Hospital
Lalitpur, Nepal

Acknowledgment: The authors thank the surgeons, operation theater staff, community medical workers, and microbiology and surgical staff for providing technical support.

Grant Support: Wellcome Trust.

Potential Financial Conflicts of Interest: None disclosed.

Corresponding Author: Buddha Basnyat, MD, Oxford University Clinical Research Unit, Patan Hospital, Lalitpur, Nepal; e-mail, rishibas@wlink.com.np.

References

Isolation of Mycobacterium kyorinense in a Patient With Respiratory Failure

Background: Isolation of nontuberculous mycobacterial species from clinical specimens is becoming more common.

### Table. Clinical Data and Bile Culture Results

<table>
<thead>
<tr>
<th>Bacterial Isolate</th>
<th>Patients, n (%)</th>
<th>Women</th>
<th>Med. Age (Range), y</th>
<th>Patients, n (%)</th>
<th>Men</th>
<th>Med. Age (Range), y</th>
<th>Patients, n (%)</th>
<th>Enteric Fever History, n (%)</th>
<th>Salmonella†</th>
<th>Elective</th>
<th>Acute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. typhi</td>
<td>12</td>
<td>31.9</td>
<td>(23–39)</td>
<td>8</td>
<td>40</td>
<td>(30–40)</td>
<td>4</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>S. paratyphi A</td>
<td>9</td>
<td>40</td>
<td>(33–59)</td>
<td>8</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Group C</td>
<td>1</td>
<td></td>
<td>50</td>
<td>1</td>
<td></td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>22 (5.4)</td>
<td>35.9</td>
<td>(23–59)</td>
<td>16 (72.7)</td>
<td>38</td>
<td>(28–50)</td>
<td>6 (27.3)</td>
<td>3 (13.6)</td>
<td>0 (0)</td>
<td>16 (72.7)</td>
<td>6 (27.3)</td>
</tr>
<tr>
<td>Non-Salmonella</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>25</td>
<td>45</td>
<td>(23–84)</td>
<td>21</td>
<td>58</td>
<td>(43–68)</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>13</td>
<td>51.5</td>
<td>(25–65)</td>
<td>11</td>
<td>73</td>
<td>(70–77)</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>13</td>
<td>43.5</td>
<td>(30–66)</td>
<td>12</td>
<td>72</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>11</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>8</td>
<td>44</td>
<td>(21–64)</td>
<td>4</td>
<td>41</td>
<td>(25–41)</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>2</td>
<td>51.5</td>
<td>(40–63)</td>
<td>2</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>1 (1.6)</td>
<td>50 (82)</td>
<td>10 (16.4)</td>
</tr>
<tr>
<td>Culture negative</td>
<td>321 (79.2)</td>
<td>39</td>
<td>(9–81)</td>
<td>250 (78.1)</td>
<td>44</td>
<td>(11–87)</td>
<td>71 (21.9)</td>
<td>43</td>
<td>5 (1.5)</td>
<td>268 (83.8)</td>
<td>52 (16.2)</td>
</tr>
<tr>
<td>Total</td>
<td>404 (100)</td>
<td>39</td>
<td>(9–81)</td>
<td>316 (78.2)</td>
<td>44</td>
<td>(11–87)</td>
<td>88 (21.8)</td>
<td>52</td>
<td>12 (9.9)</td>
<td>334 (82.7)</td>
<td>68 (16.8)</td>
</tr>
</tbody>
</table>

* Description of gallbladder after histopathologic examination, independent of additional complications. P < 0.001 for comparison of chronic and acute conditions in the Salmonella-positive group vs. the culture-negative group, and for comparison of chronic and acute conditions in the Salmonella-positive group vs. the non–Salmonella-positive group (Fisher exact test).
† History of enteric fever confirmed by blood culture or presence of S. typhi or S. paratyphi A.
Annals of Internal Medicine

Table—Continued

<table>
<thead>
<tr>
<th>Gallstones at Surgery, n (%)</th>
<th>Cholecystitis, n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>Multiple</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>15 (68.2)</td>
<td>14 (63.6)</td>
</tr>
<tr>
<td>15 (68.2)</td>
<td>14 (63.6)</td>
</tr>
<tr>
<td>18 (4.45)</td>
<td></td>
</tr>
</tbody>
</table>

Objective: To report the isolation of Mycobacterium kyorinense, a recently isolated novel mycobacterium (1), from a patient with impending respiratory failure.

Case Report: An 89-year-old man was admitted to our department for worsening dyspnea. He required long-term oxygen therapy for chronic obstructive pulmonary disease induced by tobacco smoking and had a history of pulmonary tuberculosis. He also had a history of bladder carcinoma, treated with cisplatin and radiation, and prostate carcinoma, treated with leuprorelin and bicalutamide. Vital signs on admission included a temperature of 36.9 °C, respiratory rate of 18 breaths/min, and blood pressure of 100/60 mm Hg. According to the laboratory examination on admission, pH was 7.489, PaCO2 was 34.7 mm Hg, PaO2 was 44.0 mm Hg, and HCO3− was 26.1 mmol/L (on room air), suggestive of respiratory failure. The erythrocyte sedimentation rate was 90 mm/h and the C-reactive protein level was 94 mg/L, suggestive of enhanced inflammation.

Compared with previous imaging (Figure, A and C), the patient’s chest radiograph on admission showed right lung infiltration (Figure, B), and his chest computed tomography scan showed precisely delineated consolidation, new infiltration accompanied by air bronchograms, thickness of the bronchial wall, and pleural effusion (Figure, D). The pleural fluid was exudative (protein level, 43 g/L; serum protein level, 70 g/L), pH was 8.0, adenosine deaminase level was 26.2 U/L, and leukocyte count was 1.15 × 106 cells/L (lymphocyte, 91%; neutrophil, 3%; eosinophil, 1%).

We initially suspected community-acquired pneumonia and started biapenem treatment. Sputum testing then showed acid-fast bacilli in 7 specimens, and Mycobacterium was repeatedly cultured. We detected antibodies against tuberculous glycolipid by using a standard test (Kyowa Medex, Tokyo, Japan), but both polymerase chain reaction and DNA–DNA hybridization assay revealed that the mycobacterium was neither M. tuberculosis nor 17 other frequently cultured nontuberculous mycobacterial species. The patient then developed a refractory and recurrent pneumothorax in his left lung. Neither thoracic drainage to expand the lung nor noninvasive positive pressure ventilation improved his respiratory condition, and he subsequently died of respiratory failure. Later, the isolated mycobacterium was identified as a novel species, M. kyorinense (1).

Discussion: We speculate that M. kyorinense was the cause of the radiographic findings and clinical deterioration we observed. Little is known about the organism or its clinical significance. It is genetically related to 2 other nontuberculous mycobacterial species, M. celatum and M. branderi (1), which are susceptible to ethambutol, clarithromycin, and levofloxacin and resistant to rifampicin (1, 2). Mycobacterium celatum and M. branderi cause disseminated disease in immunocompromised patients (2, 3) and can be pathogenic to immunocompetent hosts (4). Our patient had received cancer chemotherapy in the past, and we speculate that he had local immunodeficiency as a consequence of pulmonary tuberculosis and chronic obstructive pulmonary disease, resulting in bronchiectasis, potentially clinically significant M. kyorinense colonization, and ultimately infection. Mycobacterium celatum and M. branderi infection are characterized as causing lung cavitation. Our patient did not have lung cavitation, perhaps because of pneumothorax and severe emphysematous changes (Figure). These similarities to other clinically significant organisms and the dramatic clinical deterioration in our patient, as well as the repeated isolations of M. kyorinense in the sputum (5), lead us to conclude that M. kyorinense infection was the cause. Awareness of the organism is important, and information about its clinical and microbiological significance should be documented so that we can better judge the possible threat posed by this novel mycobacterium.

Conclusion: Mycobacterium kyorinense is a possible cause of clinically significant respiratory disease.
STRONGYLOIDES HYPERINFECTION: AN UNUSUAL CAUSE OF RESPIRATORY FAILURE

Background: Infection with Strongyloides stercoralis may present with symptoms of asthma or chronic obstructive pulmonary disease (COPD) (1). However, use of steroids in a wheezing patient with chronic strongyloides may trigger disseminated strongyloides infection (1, 2). In this case, steroid-induced immunosuppression triggered strongyloides hyperinfection in a chronically infected patient.

Case Report: A 71-year-old woman presented with a 3-day history of shortness of breath associated with nonproductive cough and fever (temperature, 101.2°F).

Her medical history included stroke with subsequent aphasia, dysphagia, and dementia. She had a history of recurrent small-bowel obstructions secondary to adhesions resulting from a hysterectomy. She is a native of South America and now lives in a long-term care facility in the midwestern United States.

Physical examination showed tachypnea, bibasilar crepitations, and diffuse end expiratory wheezes. Chest radiography showed patchy infiltrates in the left lower lung field with slight hyperaeration suggestive of COPD. She was treated empirically for pneumonia with intravenous ceftriaxone and azithromycin. She also received methylprednisone, 80 mg intravenously every 8 hours, for presumed exacerbation of COPD. The patient’s condition deteriorated clinically over the next 3 days, with increasing leukocytosis and diffuse wheezing. Because of progressive respiratory failure, she required endotracheal intubation and mechanical ventilation. Her chest radiographs revealed progressive bilateral diffuse granular infiltrates (Figure 1). Bronchoscopy showed thick, slightly yellow mucus in both lungs. Bronchial washings showed inflammatory changes and larvae of S. stercoralis (Figure 2). A stool sample tested negative for Strongyloides larvae. Blood culture tests were persistently negative throughout hospitalization. Histoplasma antigen was negative. Bronchoalveolar cultures were negative for acid-fast bacilli, Pneumocystis carinii, or viruses. Fungal culture tests were positive for light growth of non-Candida yeast. The patient was treated with ivermectin and albendazole until her sputum was negative for Strongylodes larvae. However, the patient’s respiratory failure did not resolve, and she required continued ventilator support.

Discussion: Strongyloides stercoralis is a parasitic nematode that exists in 3 forms: adult nematode, filariform larvae, and rhabditiform larvae. The filariform larvae are the infective forms that start the parasitic phase of the life cycle by penetrating the human skin. The larvae then migrate with the blood to the lungs, where they are trapped in the pulmonary microcirculation and mature in the pul-

---

Potential Financial Conflicts of Interest: None disclosed.

References
monary parenchyma into rhabditiform larvae. Patients in this phase seem to have chronic bronchitis or bronchospastic syndromes. The rhabditiform larvae are also in the airways, where coughing propels them to the pharynx. Swallowing carries the larvae to the small intestine, where they mature into adult male and female nematodes. Female nematodes produce eggs that hatch into rhabditiform larvae. The rhabditiform larvae are either excreted in the stool to restart the life cycle or they become filariform larvae and automatically infect their human host by penetrating the intestine and migrating to the lungs (1, 3). Strongyloides infection is endemic in Asia, Southeast Asia, Africa, Central and South America, and the southeastern United States (1, 3). Because infected patients may be asymptomatic, diagnosis requires a high index of suspicion in patients with history of travel to endemic areas. Strongyloides infection may manifest as nonspecific cutaneous, gastrointestinal, or respiratory symptoms. This includes skin rash, diarrhea, abdominal pain, indigestion, pruritus ani, or asthma symptoms.

Strongyloides hyperinfection occurs when impaired immunity allows many Strongyloides filariform larvae to accumulate in the lungs (1, 2). Precipitating causes of impaired cell-mediated immunity include immunosuppressive therapy, transplantation, hematologic malignant conditions, and human T-cell lymphotropic virus-1 infection (4). Strongyloides hyperinfection usually presents with symptoms of new-onset asthma or COPD exacerbation that do not respond or even worsen with steroid treatment (1). It is associated with a wide array of nonspecific chest radiographic findings, including diffuse or segmental alveolar, interstitial, or nodular infiltrates (1). Eosinophilia is common (2, 3). Gram-negative or polymicrobial sepsis often occurs after gut penetration during the life cycle of S. stercoralis (2). In addition, Strongyloides larvae may disseminate to the central nervous system, liver, or heart, which are not involved in the Strongyloides life cycle. Strongyloides hyperinfection can be treated with albendazole, ivermectin, or both if the patient is immunosuppressed, until sputum is negative for Strongyloides larvae (3). The mortality rate is 61% to 85% unless diagnosed early and treated appropriately (1–3).

**Potential Financial Conflicts of Interest:** None disclosed.

**References**


**Corrections**

**Correction: Delayed Splenic Rupture**

In a recent letter (1), the patient’s hemoglobin level is reported in g/L (instead of g/dL). However, the numbers given are incompatible with the units and should be multiplied by 100. Thus, the hemoglobin level of 1.10 g/L should really be 110 g/L (or 11 g/dL), which is a reasonable value. This error carries through with all the hemoglobin values in the letter.

**Reference**


**Correction: Reliability of Compendia Methods for Off-Label Oncology Indications**

In the recent review by Abernethy and colleagues (1), there is a correction for Table 1. The table indicates that the 2008 update information for American Hospital Formulary Service Drug Information came from an institutional subscription viewed on 7 July 2008. In fact, the authors viewed American Hospital Formulary Service Drug Information Essentials on 22 May 2008 and had direct communication with the publisher for supplemental data on 7 July 2008.

**Reference**