LabWire
Laboratory News and Analysis for Clinicians November 2013

Laboratory Evaluation of the Pediatric Patient With an Acute Respiratory Illness

Respiratory infections are some of the most common causes for which children are hospitalized. Laboratory test methods for respiratory infections are changing from traditional culture and antigen tests to molecular tests. Traditional tests looked for the entire microorganism or its cytopathic effects in culture or for pathogen-specific proteins, and they required that the pathogen grow, which took time. Molecular methods (generally the polymerase chain reaction method, PCR) target pathogen-specific sequences of nucleic acid and do not require the pathogen to grow. They can detect the pathogen directly and immediately in the specimen. They are faster and more sensitive than traditional methods. Their final results are available the same day the specimen is collected. Instead of waiting for days for all the tests to be completed, the physician can have definitive and final results within the timeframe in which the physician is first assessing the patient and designing a care plan.

The pediatricians with the Bronson Children's Hospital have designed a clear algorithm for acute respiratory illnesses that guides the user on which laboratory tests to order and what to do if each test is positive or negative. All respiratory diagnostic tests are done on a nasopharyngeal swab collected early in the encounter (blood cultures are also indicated in some patients).

The algorithm separates into three tracks based on the child's clinical presentation, the season of the year, and other information about the patient *(see below)*.

The Algorithm's Three Tracks

- If the physician highly suspects influenza, the algorithm leads to an influenza-only PCR test.
- If the physician highly suspects pertussis, the algorithm leads to a pertussis-only PCR test.
- If it is not clear what disease the patient has by the presentation, the algorithm leads to a respiratory disease PCR panel that currently includes 11 respiratory pathogens (including influenza and pertussis).

Note that the panel is one test (it cannot be separated into components), it includes subtypes of some of the viruses (21 total targets), and it will show co-infections with more than one pathogen at the same time. Sometimes the clinical presentation of disease in some children is unclear because they have more than one infection at the same time.

We encourage you to use this new algorithm. Direct any questions or suggestions to Aaron Lane-Davies, MD, or Jeffery Pearson, MD. We will update the algorithm as new tests become available.

— Richard Van Enk, PhD

Richard Van Enk, PhD

Testing for Respiratory Diseases in Pediatric Patients: Rationale, FAQ and References

The Fundamental Question:

How will a particular test result change or impact the care of the individual patient?

Common Reasons to Obtain Diagnostic Lab Studies:

- Will impact decision to start antibiotics
- Will impact decision to perform or not perform additional testing (particularly invasive testing)
- There is overlap between infectious and non-infectious diseases on the differential diagnosis.
- Public health concerns

Respiratory Infectious Disease Panel Pathogens:

- Influenza A (2009 H1N1, H3, H1) & B
- RSV
- Parainfluenza Virus[1,2,3,4]
- Adenovirus
- Coronaviruses HKU1, NL63, 229E and OC43
- Human metapneumovirus
- Rhinovirus/Enterovirus
- Bordetella pertussis
- Chlamydophila pneumoniae
- Mycoplasma pneumoniae

Case Definition of Pertussis[1]:

- Cough lasting at least two weeks (and no other apparent cause) with one or more:
  - Paroxysms of coughing
  - Inspiratory "whoop"
  - Post-tussive vomiting

Supportive Care for Viral Respiratory Illnesses

- Explain the expected course of illness to caregivers (illness typically peaks around day four with gradual resolution of symptoms over the next one to two weeks).

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Testing for Respiratory Diseases in Pediatric Patients *(continued)*

- Importance of adequate hydration (small, frequent feeds)
- Nasal suctioning for infants (particularly before feeds)

Cost of Tests

The costs in the algorithm (at right) are list costs and are provided for comparison purposes only. The actual cost to the patient or insurance company are influenced by a variety of factors.

For questions regarding details of particular tests, please contact Dr. Jeffery Pearson at (269) 341-8997. For questions or comments regarding clinical decision making, please contact Dr. Aaron Lane-Davies at (269) 341-8986.

References

1. Michigan Department of Community Health
2. Utility of blood culture in uncomplicated pneumonia in children. Clin Med Insights Pediatr. 2013 Jan 24;7:1-5. Mendoza-Paredes A, et al.
3. The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Aug 2011. John S. Bradley et al.
4. Procalcitonin in children admitted to hospital with community acquired pneumonia. Arch Dis Child. 2001 Apr;84(4):332-6. Moulin F et al.

— Aaron Lane-Davies, MD

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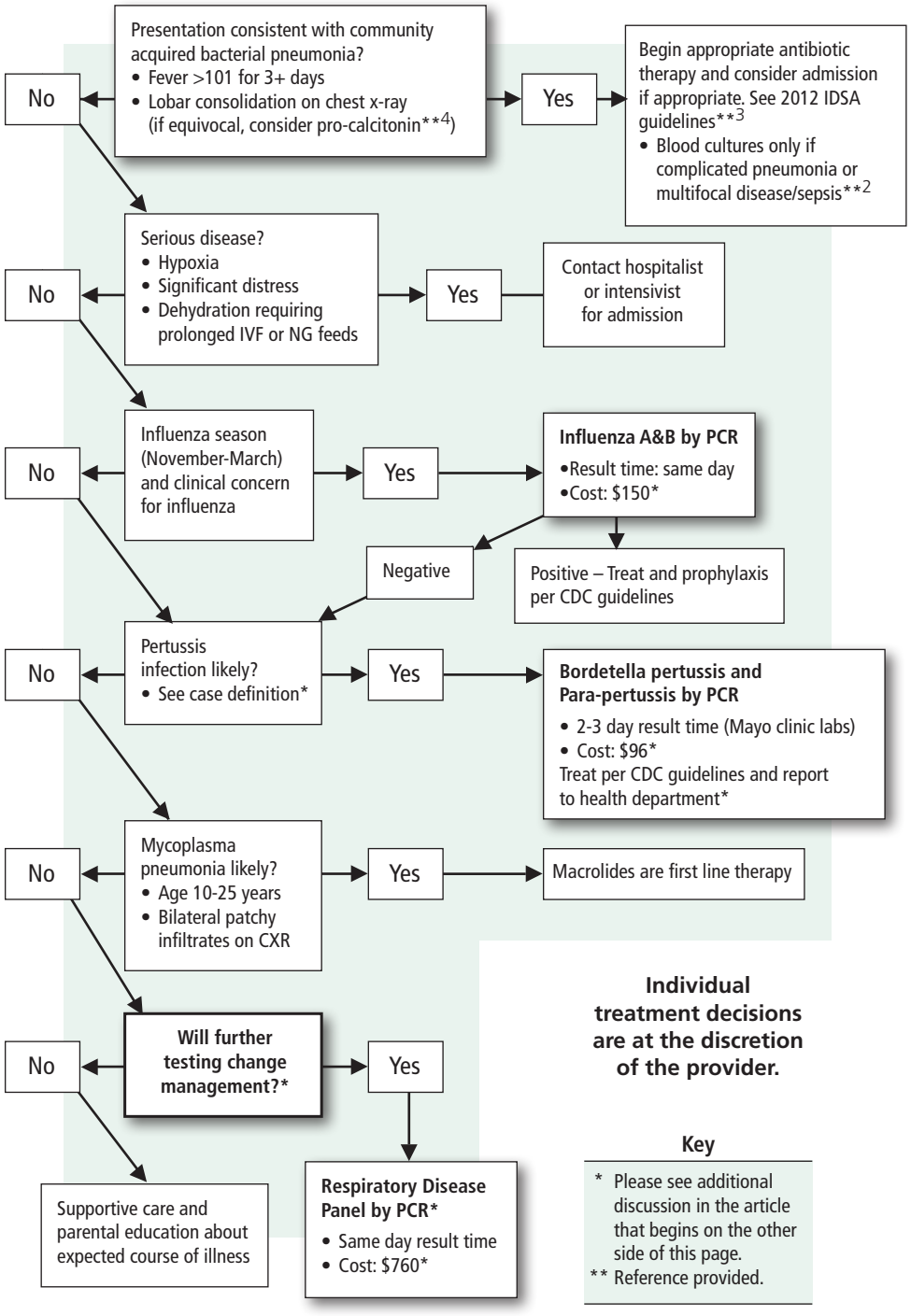
If the patient is less than four weeks old with fever, see the newborn sepsis map.



Individual treatment decisions are at the discretion of the provider.

Key

* Please see additional discussion in the article that begins on the other side of this page.

** Reference provided.

Aaron Lane-Davies, MD

This algorithm was created by Aaron Lane-Davies, MD, of Bronson Pediatric Referral Service.

The Futility of Measuring Folate Levels

Macrocytic anemia

Every physician is familiar with how to work up anemia by classifying it as microcytic, normocytic or macrocytic. Red blood cell macrocytosis has many potential causes including liver disease, hypothyroidism, alcohol abuse and certain drugs. Megaloblastic anemia can be caused by dietary deficiency in folate or cobalamin and frequently enters into the differential diagnosis for macrocytic anemia. But due to widespread folate supplementation of our food supply, folate deficiency is nearly non-existent. Anemias with megaloblastic change are much more likely to be due to drugs that interfere with DNA synthesis like methotrexate and hydroxyurea. Myelodysplasia may also mimic megaloblastic anemia. Cobalamin is a different matter. Deficiencies are uncommon, but they can be associated with neurologic manifestations in the elderly. Methylmalonic acid is a better test than serum cobalamin in this setting.

Folate supplementation

Folate cannot be synthesized by human enzymes and must be obtained through the diet. In 1998 the Food and Drug Administration mandated that certain grain products be supplemented with folate because it had been demonstrated that folate deficiency increased the risk of neural tube defects. Consequently dietary folate deficiency has steadily dropped to the point now where it is nearly non-existent in the United States. In the Bronson Laboratories, of nearly 3,000 tests for RBC folate only 9 (0.3%) were deficient.

Red blood cell folate vs. serum folate

Historically, when folate deficiency was more common, the RBC folate test was considered to better represent long term folate and serum folate was considered more of a short term measure as it could be affected by recent dietary intake. In practice, however, the differences between the two tests do not appear to be significant. The Mayo Clinic compared 1,082 patients with simultaneous serum and RBC folates. Only one patient was found to be deficient by both methods; eight were found to be deficient by serum folate alone and four by RBC folate alone. Of the latter four, they could not reproduce the results on repeat testing, probably because of variability caused by the red cell extraction process. Their conclusion was that folate deficiency was almost non-existent and with a prevalence of a tiny fraction of a percent that current assays are not robust enough to reliably diagnose it. Mayo also calculated the RBC folate had ten times greater cost to the laboratory because it required manual labor to hemolyze the RBCs.

Unavailability of reagents

The reagents necessary to run a RBC folate have become increasingly difficult to acquire. They have been on back order and Mayo Laboratories will not run the test because they consider it obsolete. We have been sending it all the way to ARUP Laboratories in Utah and they recently announced they too did not have reagent to run the test. For these reasons the RBC folate test will be removed from the Bronson Laboratories test menu. Serum folate will stay available and be performed on site.

Conclusions

- With dietary supplementation folate deficiency is vanishingly rare in the U.S.
- The prevalence of folate deficiency is so low that neither RBC folate nor serum folate have enough discriminatory power to reliably diagnose it.
- RBC folate costs much more to run because it requires a manual hemolysis step.
- The Bronson Labs and the Mayo Clinic Reference Lab consider RBC folate to be an obsolete test and will no longer run them.
- The serum folate test will still be offered on site, but should be ordered rarely and only when indicated by the clinical history.

Jeff Pearson, MD

— Jeff Pearson, MD

References

Saenger AK. Red Cell Folate Testing: Unwarranted and Overutilized in the Era of Folic Acid Supplementation. Mayo Clinic Hot Topics. Accessed online October 18, 2013. http://www.mayomedicallaboratories.com/articles/hottopics/2010-11a-rbc-folate.html

Shojania and von Kuster BMC Research Notes 2010, 3:22 Ordering folate assays is no longer justified for investigation of anemias, in folic acid fortified countries. Accessed online October 18, 2013. http://www.biomedcentral.com/1756-0500/3/22.

New Molecular Influenza Test

Beginning November 3, 2013, the Bronson Laboratories will be offering the CepheidXpert Flu Assay that detects influenza A, influenza B and 2009 H1N1 influenza viral RNA by reverse transcription polymerase chain reaction (RT-PCR). The test is extremely sensitive and specific and no backup testing is needed unlike some antigen detection tests. The required specimen is a nasopharyngeal swab placed in Viral Transport Media. Results should be available the same day. The charge is $150.

LabWire is published by Bronson Laboratory Services. If you have a topic you would like addressed in this publication, call (269) 341-8997 or send your request to Jeff Pearson, MD (pearsonj@bronsonhg.org).