In children with fever, researchers distinguish bacterial from viral infections

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Using microarray technology, researchers can distinguish between viral and bacterial infections in children with fever by profiling the activity of genes in a blood sample. While more research is needed, the new technology could one day help to identify the cause of illness and ensure that children get the right treatment. Credit: Robert Boston, Washington University in St. Louis

In children with fever but no other symptoms of illness, it is difficult to know whether a child has a viral infection that will resolve on its own or

a potentially serious bacterial infection that requires antibiotics.

Now, researchers at Washington University School of Medicine in St. Louis report that they can distinguish between viral and bacterial infections in children with fever by profiling the activity of genes in a blood sample. In a small study, analyzing genes in white blood cells was more than 90 percent accurate, far better than the standard diagnostic test, which is only correct about 70 percent of the time.

The research is published July 15 in the *Proceedings of the National Academy of Sciences* Online Early Edition.

While more work is needed, the study's results support the notion that analyzing the activity of the body's genes in response to childhood infections could help to identify the cause of illness and ensure that children get the right treatment.

"It's a common problem that children develop a fever without any apparent cause," says senior author Gregory Storch, MD, the Ruth L. Siteman Professor of Pediatrics and chief of the Division of Pediatric Infectious Diseases at Washington University School of Medicine and St. Louis Children's Hospital. "Some of these kids have serious bacterial infections that can be life threatening, but the largest number have viral infections. The trouble is, from a practical standpoint, it's hard to know which is which."

As a precaution, many children who have a fever without an apparent cause are treated with antibiotics even though the drugs don't work against viruses and overprescribing them contributes to antibiotic resistance.

The new study involved 30 children ages two months to 3 years who had fevers above 100.4° F but no obvious signs of illness, like a cough or

diarrhea. Twenty-two of the children were known to have viral infections based on previous extensive genomic testing that is not yet practical to use in a clinic setting, and eight others children had bacterial infections.

But Storch and his colleagues at the university's Genome Institute and the Genome Technology Access Center wanted to know whether a test called a gene expression microarray could identify patterns of gene activity in white blood cells that could discriminate children with viral infections from those with bacterial infections. White blood cells are the immune system's first line of defense against foreign invaders, and the scientists theorized that they would respond differently to viruses than to bacteria.

The researchers also had access to results of a standard diagnostic test performed when the children initially were evaluated with fevers at St. Louis Children's Hospital. That test involves analyzing the number of white blood cells in a blood sample. Generally, the counts are elevated for bacterial infections and either low or normal for viral infections.

"We know there are many exceptions to that rule, and we certainly saw that in this study," Storch said. "A lot of patients with viral infections had elevated white-blood cell counts so doctors thought they had bacterial infections and prescribed antibiotics, which in fact were not necessary."

Using microarray technology, the researchers could easily distinguish bacterial infections from viral infections based on distinctive patterns of gene expression. "That's really important for clinicians because if they see a pattern of gene expression that indicates a viral infection, they could feel comfortable not prescribing antibiotics," Storch added.

As a comparison, the research team performed the microarray analysis

on blood samples from 35 children without fever, also ages 2 months to 3 years, who were having outpatient surgery. Earlier genomic testing showed that eight of those children had viruses, even though they didn't cause any symptoms.

"In the kids with a virus and a fever, many genes were very active, compared with kids who had viruses and no fever, whose genes were quiet," Storch explained. "The microarray basically tells us how a patient is reading the infection. The very active genes tell us that an infection is making a patient sick, while quiet genes tell us either there's no infection or maybe a bacterium or virus is there, but it's not causing fever or illness."

This distinction is important because when standard tests suggest a child has a virus, doctors don't know whether that virus is producing a child's illness or whether it's an innocent bystander. According to Storch, "the danger of attributing symptoms to a virus that is actually an innocent bystander is that the child might not receive needed antibiotics."

This points to the potential benefit of using tests that measure the response of genes to get more conclusive answers to illness. This would help to ensure that antibiotics are targeted to those children who really need them, he added.

Next, Storch hopes to refine the microarray technology, which simultaneously analyzes all 25,000 genes in the body. This makes the test too time consuming and expensive to use in a clinic setting. But he and his co-workers want to identify a smaller number of critical genes that could be used to distinguish between viral and bacterial infections and evaluate a second-generation test in children as part of a new study.

More information: Storch GA, Crosby SD, Yu J, Hu X. Gene expression profiles in febrile children with defined viral and bacterial

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infection. *Proceedings of the National Academy of Sciences*. Online July 15, 2013. www.pnas.org/cgi/doi/10.1073/pnas.1302968110

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