Enough with “watchful waiting,” says Pitt’s Hoberman. There’s no reason doctors can’t learn to make accurate diagnoses regarding ear infections so children can be treated for this painful condition.
UNCERTAINTY IS NOT AN OPTION
REMOVING DOUBT FROM EAR INFECTION
TREATMENT | BY CHUCK STARESINIC

Ear infection is the most frequently diagnosed illness in children. This should come as no surprise to parents, many of whom are familiar with the midnight wailing of an inconsolable child with ear pain. What is surprising is a longstanding question doctors have concerning how best to treat acute otitis media (AOM). Should they prescribe antibiotics or wait a few days and see whether symptoms resolve on their own?

One might think this question had been answered long ago and that antibiotics were recommended for AOM. It is the most-common course of action in this country. But doctors in some European countries follow a strategy of “watchful waiting” for nearly all cases of AOM, reserving antibiotics for those children who fail to improve within two or three days. The Canadian Paediatric Society recommends this strategy for all children older than 6 months of age. A 2004 clinical practice guideline from the American Academy of Pediatrics (AAP) is more cautious, saying watchful waiting is an option for children with mild symptoms and an uncertain diagnosis.

But that doesn’t sit well with everyone. Alejandro Hoberman (Fel ’92), for one, is no fan of this kind of uncertainty. He is chief of the Division of General Academic Pediatrics at Children’s Hospital of Pittsburgh of UPMC. In the 1980s, Hoberman completed medical school and a pediatrics residency in Buenos Aires before coming to Pitt for his fellowship.

“I came to Pittsburgh to work with Jack Paradise and Ellen Wald, who were the leaders in researching and writing about common pediatric problems. There is a history in this institution of landmark studies of conditions that affect millions of children,” says Hoberman, who is now the Jack L. Paradise Professor of Pediatric Research in the University of Pittsburgh School of Medicine. (Paradise is a Pitt emeritus professor of pediatrics, while Wald is now chair of pediatrics at the University of Wisconsin.) Hoberman points out that, back in the days when tonsillectomies were more frequently performed, Paradise showed that the operation was appropriate only when there were specific, limited indications. (These criteria were only recently endorsed by the Society of Otolaryngology–Head and Neck Surgery, years after the studies were completed.) Paradise later showed that surgical insertion of ear tubes in many children with persistent fluid in the middle ear did not benefit the children’s speech, language, or cognitive development.

In the spirit of these studies, Hoberman and colleagues set out to eliminate the uncertainty around AOM. They were not alone in being irritated by the phrase if diagnosis is uncertain in the AAP’s language.

“The uncertain diagnosis should not exist,” Hoberman says. “One should be able to clear the cerumen [ear wax] in order to be able to see the eardrum and make a diagnosis or not make a diagnosis.” With Nader Shaikh, assistant professor of pediatrics at Pitt, and other colleagues, Hoberman created a seven-minute video tutorial for The New England Journal of Medicine (NEJM), demonstrating removal of wax and detection of AOM’s telltale bulging eardrum.

From 2006 to 2009, Hoberman’s team conducted a double-blind, placebo-controlled trial of antibiotic treatment for AOM. Unlike the many disparate studies of inconsistent quality used in the meta-analysis that yielded a recommendation for watchful waiting, Hoberman’s trial had strict diagnostic criteria. The children, from 6 to 24 months of age, were randomly assigned to receive antibiotics or a placebo.

Before completing the study, the team consulted with outside experts. “We thought antibiotics would have a failure rate of about 15 percent,” says Hoberman, “because we had done previous studies with antibiotics. We asked, ‘What failure rate for placebo would make you really want to use antibiotics? How much would you like to see before making that recommendation?’ Everybody we consulted said twice as much. So a difference of 15 and 30 percent in failure rate would do it for everybody. We found 15 and 50.”

Hoberman’s landmark paper—with Paradise and Wald among the coauthors—appeared in the January 13, 2011, NEJM, alongside a very similar study from Finland, which reached the same conclusions.

“Fifty percent is not an acceptable proportion of children who will continue to have an ear infection,” says Hoberman, who is on the committee tasked with rewriting the AAP’s clinical guideline for AOM.

The Pittsburgh team saw no change in either the placebo group or the antibiotic group for levels of antibiotic-resistant bacteria colonization in the back of the nose. However, diarrhea and diaper rash were more common among children who received the antibiotic.

“It’s amazing how many areas of the care of children have not been methodically addressed,” says Hoberman, who is also pursuing clinical studies in urinary tract infection and other common pediatric problems. “Being able to do that makes me want to wake up in the morning and come to work, filled with energy to take care of patients and ask families to consent to participate in the studies we do.”
For pregnant women, fetal genetic testing involves a complex and confusing set of calculations of potential risks. Noninvasive screening—typically an ultrasound and a simple blood test—is recommended for all pregnant women in the first trimester. But these tests cannot conclusively determine whether genetic anomalies are present—the detection rate is just 85 percent. Even worse, they have a false-positive rate of 5 percent, so one in 20 women who are screened will be advised to undergo an unnecessary follow-up procedure: either sampling amniotic fluid cells via a needle in the abdomen (amniocentesis) or sampling placental cells via either the same method or a catheter to the cervix (chorionic villus sampling, or CVS). Between one in 100 and one in 1,000 of these invasive procedures—currently the only diagnostic forms of prenatal genetic testing—will result in a miscarriage.

It’s a risky venture, says David Peters, a PhD and associate professor in the Division of Reproductive Genetics at the University of Pittsburgh and scientific director of Magee-Womens Research Institute’s Center for Fetal Medicine, who first became interested in reproductive genetics when his wife underwent an amnio. “If someone said you had a one in 200 chance of dying of a mammogram or prostate exam, you wouldn’t get it.”

In the United States, genetic abnormalities account for most deaths that occur around the time of birth. And yet only a few percent of pregnant women opt for invasive testing—typically women who are 35 or older, who have a family history of genetic abnormalities, or whose screening tests show an elevated probability for fetal genetic abnormalities.

Advising expectant parents based on probabilities is extremely difficult. Everyone interprets the odds differently. For some, a one-in-100 chance of an abnormality seems extremely high. For others, it seems minor.

Pitt’s Aleksandar Rajkovic, an MD/PhD associate professor and director of reproductive genetics, codirects research for the Center for Fetal Medicine with Peters. The pair hope to develop a new test that detects fetal genetic abnormalities with 95 percent accuracy, using only a blood sample drawn from the mother’s arm. They estimate that if they’re successful, the number of miscarriages associated with invasive prenatal testing could fall by 80 percent.

Researchers worldwide have been trying to develop such a test since 1997, when it was first discovered that during pregnancy a small amount of fetal DNA escapes the placenta and circulates in the maternal bloodstream. The challenge is that the maternal DNA veils some aberrations in the fetal DNA. In Hong Kong and Boston, researchers are using various methods to enhance, mark, or separate the fetal DNA circulating in maternal blood. The beauty of the Pitt method, says Peters, is that it doesn’t require any of these processes. The Pitt researchers have applied a new technology that processes vast quantities of DNA at high resolution, providing a clearer, more complete picture of the genetic makeup of the cells.

Peters and Rajkovic are conducting a National Institutes of Health–funded trial of a testing method that uses “next-generation shotgun sequencing.” This sequencing method allows them to analyze large quantities of DNA randomly gathered from maternal plasma, compare that to samples from genetically normal mothers and babies, and tag irregularities that originate in the fetus.

Peters and Rajkovic hope their test will be on the market within five years. “I think that this will lead to a new way of looking at pregnancy and genetic disorders and new ways in which to counsel couples on the uncertainties of undiagnosed disorders,” says Rajkovic.

But their vision of the future is much grander. Ideally, they’d like to map the fetal genome with such high resolution that they can begin to look for subtle genetic abnormalities, such as single-gene disorders. (Currently, the technology is limited to detecting additional whole chromosomes.) This higher specificity would give obstetricians new opportunities to treat congenital conditions before birth. The same methods might eventually be applied to the detection of the aberrations that cause certain cancers.
As a medical student working in pharmacologist Louis Ignarro’s lab at Tulane University in the mid-1980s, Jeffrey Isenberg saw something that changed his life. He watched as his colleagues pumped bubbles of nitric oxide gas—a common combustion byproduct, but also an important cellular-signaling chemical—into contracted mammalian arteries. The vessels instantly relaxed. “That was an epiphany for me,” says Isenberg, now an MD visiting associate professor in the Division of Pulmonary, Allergy, and Critical Care Medicine at the University of Pittsburgh. “I figured anyone who can control nitric oxide signaling could really change things for the better, healthwise.”

(In 1998, Ignarro, with Robert Furchgott and Ferid Murad, won the Nobel Prize in Medicine or Physiology for their nitric oxide work.)

Today, nitric oxide is used in many clinical settings. For example, nitric oxide gas is used to treat neonates with primary pulmonary hypertension. Drugs that release nitric oxide are used as medications for adult hypertension and heart failure. And nitroglycerin, prescribed for coronary artery disease and chest pain since the 1880s, is converted in the body into nitric oxide.

Pitt has made a name for itself in nitric oxide research. Its faculty members have studied pathways that increase nitric oxide levels as a means of treating heart and lung problems and for reducing stress responses during surgery and inflammation in diabetes. Now Isenberg and others have found a way to boost the efficacy of the gas and are hoping to apply that knowledge to treat a number of conditions. Isenberg may have found a way to improve cancer therapies.

After working for several years in academic and clinical practice, Isenberg in 2003 joined the National Cancer Institute, where he began pursuing his interest in nitric oxide under the wing of David Roberts. In 2005, Isenberg found cells extracted from mice that cannot produce a protein called thrombospondin-1 (TSP-1) have exaggerated responses to nitric oxide, which suggested that TSP-1 inhibits cellular responses to the gas. And in 2006, Isenberg and Roberts identified a cell-surface receptor called CD47 that mediates TSP-1-induced nitric-oxide inhibition; by turning off TSP-1 activity or blocking CD47, Isenberg and Roberts showed, it was possible to turn up nitric oxide signaling.

The team found that blocking CD47 activity relieves ischemia—when blood flow is too slow to meet a tissue’s needs—which is a hallmark of heart disease and diabetes and a common complication from transplantation and other surgeries. Nitric oxide could benefit patients who get vascular stents, he says: “Maybe you could reestablish flow and then get all new microvascular outgrowth” by introducing a stent that slowly releases a CD47 blocker.

The gas could also have implications for treating or preventing Alzheimer’s disease. Research by others has shown that the amyloid beta plaques that are believed to degrade nerve cells in Alzheimer’s patients prevent nitric oxide signaling. Blocking TSP-1 or its receptor might heighten the “pro-survival signal from nitric oxide, which could be good for neural health,” Isenberg says.

Targeting CD47, however, seems to play a much larger role in cell and tissue response to injury. In papers published in 2008 and 2009—the latter of which was recognized by the National Cancer Institute as one of 2010’s top science advances—Isenberg showed that when CD47 activity is blocked in mice with cancer, their healthy cells became more resistant to radiation therapy; the cancer cells in the mice, however, remain vulnerable. Isenberg suspects that blocking CD47 both protects the healthy cells and makes it easier to identify and kill cancer cells. By targeting the receptor, “you could treat cancers more effectively with lower doses of radiation,” he says.

The next step is to bring the new therapeutics to patients. Isenberg believes that the best bet is to find small molecules that can block CD47, the receptor for TSP-1, because “it seems to be necessary in all conditions for the inhibitory signal,” he explains. He and his colleagues are now developing a screening platform to find possible candidates. “It’s turning out to be a rather fascinating story. I think we’re just scratching the surface.”

COOKING WITH GAS

N.O. STUDIES TAKE AN UNEXPECTED TURN

BY MELINDA WENNER MOYER

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