Study finds more effective treatment for pneumonia following influenza

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Scientists at St. Jude Children's Research Hospital have demonstrated a more effective treatment for bacterial pneumonia following influenza. They found that the antibiotics clindamycin and azithromycin, which kill bacteria by inhibiting their protein synthesis, are more effective than a standard first-line treatment with the "beta-lactam" antibiotic ampicillin, which causes the bacteria to lyse, or burst.

The finding is important because pneumonia, rather than the influenza itself, is a principal cause of death from influenza in children and the elderly. During pandemics—such as the one that may arise from avian influenza—up to 95 percent of influenza deaths are due to pneumonia. A bioterrorism attack using the influenza virus would likely result in the same high percentage of pneumonia deaths, according to the researchers.

The group, led by Jonathan McCullers, M.D., associate member of the St. Jude Infectious Diseases department, expect the new findings, currently demonstrated in mice, to be incorporated into standard clinical practice guidelines during the next few years.

McCullers and his colleagues published their findings in the advanced, online issue of the *Journal of Infectious Diseases*. The researchers based the new treatment on growing evidence that beta-lactams are relatively ineffective against secondary pneumonia because the drugs exacerbate inflammation caused by influenza.

"With severe secondary pneumonia, it has seemed that physicians do

almost everything they can, and it doesn't work," McCullers said. "People still die despite treatment with antibiotics that can kill the bacteria. Our research is showing that the intense inflammatory response that is already there from the virus is amplified by the bacterial infection. And, treatment with beta-lactams releases bacterial components into the bloodstream that the immune system recognizes, triggering an inflammatory burst that can be deadly.

"Traditional first-line therapy has been based on the belief that the bacteria are bad, so we have to get rid of them as quickly as possible," McCullers said. "But what we are finding is that maybe it is the inflammation we need to worry about first, and the bacteria second. Protein synthesis inhibitors shut down the bacterial protein-making factory, and they can avoid the inflammatory burst by killing them over days instead of quickly lysing them."

In their experiments, the St. Jude researchers infected mice with a mild form of influenza that restricted itself to the lungs. After a week, the scientists infected the mice with pneumonia bacteria. This sequence mimics how humans with influenza would contract secondary pneumonia.

The researchers treated groups of the doubly infected mice with ampicillin, clindamycin, combined clindamycin and ampicillin, or azithromycin. They found that 56 percent of the mice survived with ampicillin treatment, 82 percent survived with clindamycin, 80 percent with clindamycin and ampicillin, and 92 percent with azithromycin. Significantly, while clindamycin and azithromycin both inhibit protein synthesis, azithromycin also has anti-inflammatory properties.

Ampicillin aggravated inflammation compared to clindamycin, the researchers confirmed in test tube studies. The investigators also found evidence of increased inflammation in lung cells of ampicillin-treated

animals.

According to McCullers, lung tissue studies of ampicillin-treated animals also revealed the antibiotic's deleterious effects.

"We saw in those animals that, even though we were clearing their lungs of bacteria, the lungs looked just like those of animals in which the bacteria were continuing to multiply," McCullers said. "The damage process was continuing."

McCullers said he would like the new findings to influence treatment guidelines immediately for pneumonia secondary to influenza.

"The current guidelines still adhere to the theory that beta-lactams are the only drugs of choice, because it is necessary to kill the bacteria as fast as possible," he said. "However, our findings represent the first data showing that inflammation is important, and that alternative therapies such as protein synthesis inhibitors should be considered and incorporated into revised guidelines."

More broadly, McCullers said, the new findings support a growing body of evidence that treating severe pneumonia in general should take into account the inflammatory response and not just the rapid demise of bacteria.

Source: St. Jude Children's Research Hospital