Higher dose antibiotic shown safe in TB patients likely more effective in treating deadliest form of TB

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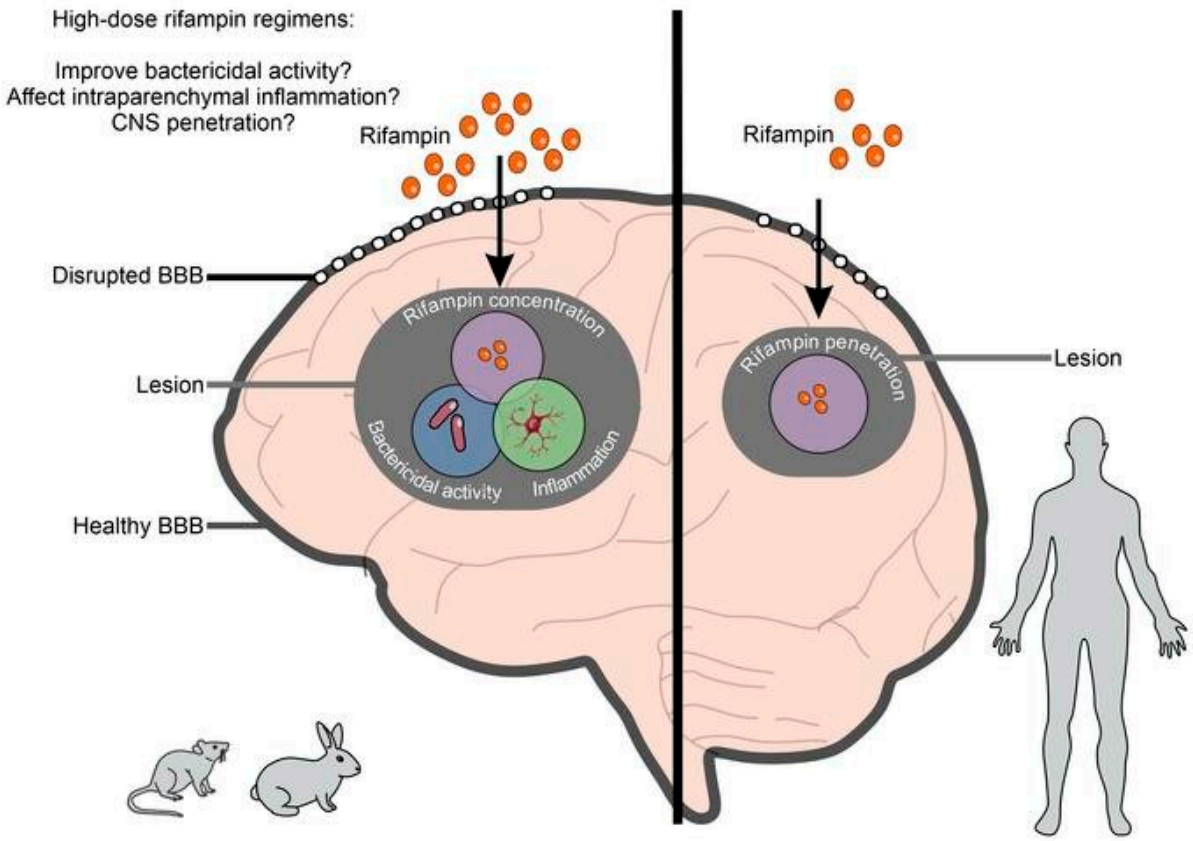

Credit: Johns Hopkins University School of Medicine

A Johns Hopkins Children's Center-led study in animals suggests that

high doses of a widely used antibiotic called rifampin may safely treat and reduce the duration of treatment for the deadliest form of tuberculosis that affects the brain, potentially improving survival rates for patients and decreasing the likelihood of lasting adverse effects of the disease. Additional studies in a small number of people also shed light on how rifampin moves through the body, including into the brain, and how rifampin levels could change during treatments, showing how the research could potentially translate to humans.

According to the World Health Organization, an estimated 10 million people worldwide developed disease by the bacterium that causes TB in 2020. It's also one of the leading infectious disease killers. Previous studies have shown the deadliest form of TB, TB meningitis, affects more than 100,000 people each year, damaging brain tissue and even proving fatal, especially among young children and those with HIV and AIDS due to a weakened immune system. Treatment generally requires lengthy courses of antibiotics and monitoring to assure compliance with therapy.

In a study published March 15 in *The Journal of Clinical Investigation*, Johns Hopkins Medicine investigators showed that higher doses of rifampin can treat TB meningitis more effectively by killing bacteria faster while not increasing brain inflammation.

"Based on what is seen clinically and in previous research, most people with TB meningitis will die and, even if treated, may suffer lasting brain damage, since it is difficult to recognize the disease in early, more treatable stages," according to study first author, Camilo Ruiz-Bedoya, M.D., pediatric infectious diseases fellow at Johns Hopkins University School of Medicine.

Treatments for TB meningitis are long and can take up to 12 months. Shorter regimens can lead to better compliance, lower costs, and better

outcomes for patients, adds senior author Sanjay Jain, M.D., professor of pediatrics, and of radiology and radiological sciences at the school of medicine and a pediatric infectious diseases specialist at Johns Hopkins Children's Center.

The standard therapy for TB meningitis is a combination of antibiotics, including rifampin, a 50-year-old drug that has been a mainstay in the global fight against TB and other bacterial diseases. However, the currently recommended dose of rifampin (10-15 mg/kg/day) given orally does not lead to sufficient rifampin levels in the brain to target and kill the bacteria. This is because of the blood-brain barrier, which protects the brain and prevents the entry of infections, toxins, and drugs, including antibiotics. This limits the drug's effectiveness and can also lead to the development of antibiotic-resistant strains. Previous clinical studies revealed conflicting results on whether higher doses of rifampin were a more effective treatment for TB meningitis.

The team conducted studies in mice and rabbits with TB meningitis to evaluate a high-dose (35 mg/kg/day) rifampin-containing oral regimen. "Some animals were given the high-dose regimen, and others were given the standard regimen. We also used advanced positron emission tomography (PET) and computed tomography (CT) imaging to identify sites of brain infection as well as track the drug penetration and distribution," says study co-first author Filipa Mota, Ph.D., former pediatric infectious diseases fellow at the school of medicine.

The researchers found in both animal models of TB meningitis that the high-dose rifampin regimen killed TB bacteria found in brain tissue at a rate of 10 times higher as early as two weeks after the start of treatment. Giving a much higher dose of rifampin also achieved much higher rifampin levels in the brains and cerebrospinal fluid (or CSF) than the standard dose while not increasing brain inflammation. But rifampin levels dropped after two weeks of starting treatment.

"The way rifampin kills the bacterium is the more a patient gets, the faster the bug dies," says study co-first author Elizabeth Tucker, M.D., assistant professor of anesthesiology and critical care at the school of medicine and pediatric anesthesiology and critical care specialist at the Children's Center. "So giving rifampin in the first two weeks of treatment is important to kill the bugs fast, but it is also important to prevent further inflammation and subsequent brain damage."

The researchers also conducted imaging studies in 12 patients with TB, including one with TB meningitis, who were enrolled from January 2017 to February 2019 at Johns Hopkins Health System hospitals. Using PET imaging, the team looked at how rifampin moves through the body, including the brain, and how those levels change during treatments in 12 patients with pulmonary TB or TB meningitis.

In a retrospective analysis, the team reviewed medical records of four patients at the same hospitals treated between July 2011 to July 2021 with confirmed TB meningitis who underwent MRIs during their TB treatment. The goal was to see how the patients' blood-brain barrier was affected by TB and treatment. They found that the changes in the patients' blood-brain barrier changes were compartmentalized and changed over time, suggesting that rifampin levels varied in different brain areas and also significantly decreased with treatment over time.

"One interesting finding was that rifampin levels and markers of inflammation in the CSF, which acts as a cushion between the brain and the skull, were substantially different from those within the brain. This is important as the CSF analysis is commonly utilized in many trials to study what is happening in the brain, but we now know that studying CSF may not represent the full picture," Jain says.

Based on their findings, the team believes their animal models of TB meningitis could be used to evaluate and prioritize promising treatments

before their evaluation in clinical trials and could also be combined with imaging approaches to provide detailed information on how drugs penetrate into the brain and through the body.

The investigators noted the limitations of their study. For example, the team performed their research at different time points early in the treatment regimen, at up to six weeks. "While antibiotic treatment for TB meningitis is typically for 12 months, most deaths and neurological damage in TB meningitis occur early in the course of treatment, which highlights the need for early interventions for TB meningitis," Jain says.

If further research validates their findings, the research team believes the high-dose regimen could prevent deaths from TB meningitis.

More information: Camilo A. Ruiz-Bedoya et al, High-dose rifampin improves bactericidal activity without increased intracerebral inflammation in animal models of tuberculous meningitis, *Journal of Clinical Investigation* (2022). DOI: 10.1172/JCI155851

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