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TOMORROW'S TRIAL

Do Antibiotics Improve Survival, Quality of Life, and Comfort in Patients with Advanced Dementia and Pneumonia?

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Abstract

Patients with advanced dementia and suspected pneumonia are at high risk of death. Antibiotics are commonly prescribed for these patients; however, there is little evidence that treatment meaningfully prolongs life, improves quality of life, or promotes comfort. At the same time, treatment with antibiotics in this population has potential side effects, contributes to antibiotic overuse, and may be burdensome for these frail patients who are near the end of life. This Tomorrow's Trial reviews the existing evidence, and the article proposes a trial to address the question, "Do Antibiotics Improve Survival, Quality of Life, and Comfort in Patients with Advanced Dementia and Pneumonia?"

Chana A. Sacks, M.D., M.P.H., Editor

The Problem

An 87-year-old woman with advanced dementia is transferred to the hospital from a nursing home with a temperature of 39.1°C, a productive cough, and a respiratory rate of 29 breaths per minute. At baseline, she is bedbound, nonverbal, and dependent for all activities of daily living. She no longer recognizes her daughter, who is her health care proxy.

A nasopharyngeal swab is negative for influenza, respiratory syncytial virus, and SARS-CoV-2, and an x-ray of her chest shows a consolidation in her left lower lung. Her care team is considering starting antibiotics for possible bacterial pneumonia. Her daughter shares that her mother still appears to have moments of joy. She feels her mother would want to continue living as long as she maintained her baseline quality of life (QoL) and was not suffering. Would antibiotics meaningfully improve survival and QoL and promote the comfort of this patient?

The Pros and Cons

Patients with advanced dementia and pneumonia are at high risk of death,[1] with some studies reporting up to 88% mortality at 6 months.[2,3] Antibiotics are commonly prescribed for these patients with the intent that they will improve survival (i.e., curative intent) and/or reduce symptom burden (i.e., palliative intent). There are no randomized clinical trials comparing survival, comfort, or QoL among patients with advanced dementia who do and do not receive antibiotics for suspected pneumonia.[2,4] The best current evidence comes from

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observational studies, which are limited by selection bias and uncontrolled confounding. For example, decisions on whether or not to prescribe antibiotics may be influenced by a clinician's assessment of a patient's prognosis.[4,5]

One observational study found that antibiotics given for lower respiratory infections in this population reduced the proportion of patients who died within 10 days (no antibiotics, 76%; with antibiotics, 39%; absolute risk reduction, 37 percentage points; adjusted hazard ratio, 0.51; 95% confidence interval [CI], 0.30 to 0.87), but not after 10 days, (adjusted hazard ratio, 1.5; 95% CI, 0.42 to 5.2).[3] These findings suggest treatment with antibiotics may delay death by up to about 10 days, while at the same time extending the dying process.[3]

Antibiotics also have the potential to cause discomfort related to the administration of parenteral medications, transfer to an acute care setting, occurrence of adverse effects (e.g., allergic reactions, renal failure, diarrhea), and infection with *Clostridiodes difficile*, which can be fatal.[6] In addition, there is a lot of misuse of antibiotics. One observational study of nursing home residents with advanced dementia reported that antibiotics were prescribed for 70.3% of suspected respiratory tract infections, yet only 33.7% of treated episodes met minimum clinical criteria for a possible bacterial infection based on clinical signs and symptoms.[7] Overuse of antibiotics contributes to antibiotic resistance, a major public health concern.[8]

For patients living in a nursing home with advanced dementia, antibiotics are often prescribed empirically in this setting based on clinical signs and symptoms without diagnostic imaging. However, the workup and treatment of suspected pneumonia are very common reasons these patients are transferred to the hospital. Hospital transfers are typically burdensome for patients with advanced dementia due to the receipt of invasive investigations and treatments; the disruption of being transferred to an unfamiliar, busy environment; and being cared for by clinicians who are strangers to them.[9]

What We Know

There is wide global and regional variation in antibiotic prescribing practices for patients with advanced dementia and pneumonia, perhaps due to different interpretations of the evidence. In one observational study, 23% of nursing home residents with dementia and pneumonia were managed without antibiotics in the Netherlands compared with 15% in Missouri. Higher illness severity was associated with greater use of antibiotics in Missouri but not in the Netherlands, where the decision to withhold antibiotics was driven explicitly by the intent to direct care toward palliation.[10] Within the United States, antibiotic use in this population varies across regions, and is influenced by institutional culture, physician practice patterns, patient preferences, and access to palliative care.[11]

A prospective study of 225 nursing home residents with advanced dementia and suspected pneumonia found that antibiotics improved survival compared with no treatment, but may be limited by selection bias.[2] Several observational studies have reported an association between antibiotic treatment and improved comfort among patients with advanced dementia and pneumonia,[2,12,13] although one observational study did not find such an association.[14]

What We Need

A randomized, double-blind, multicenter trial could help evaluate the efficacy of antibiotics in older adults with advanced dementia and suspected bacterial pneumonia to improve survival, QoL, and comfort. The primary outcome would be survival at 30 days, with secondary outcomes including survival at 6 months and up to 18 months, and patient- and caregiver-centered measures such as QoL (measured using validated tools such as the Quality of Life in Late-Stage Dementia scale[15]), symptom burden, health care utilization, and adverse events.

Eligible participants would include patients with a diagnosis of advanced dementia, defined by validated tools (e.g., the Global Deterioration Scale[16]), who are hospitalized with suspected or confirmed bacterial pneumonia using clinical and radiographical criteria. Participants would be randomly assigned 1:1 to receive either intravenous (IV) antibiotics or IV placebo infusion, with both groups receiving protocolized supportive management (e.g., analgesia, supplemental oxygen, IV fluids). IV infusion (vs. oral or intramuscular injection) was chosen as the mode of delivery as it is typically provided in the acute care setting and reflects a higher level of illness severity, motivating hospital-level care.

We believe it would be ethically defensible to randomly assign participants to either antibiotics or placebo infusion, given the uncertain benefits and risks of the two treatment options in this population. Given the patient's lack of decision-making capacity, informed consent must be obtained from their designated surrogate decision maker. The informed consent process should include a clear explanation of the uncertainties of the potential benefits and risks

of the treatment options, and the limitations of the evidence related to the efficacy of antibiotics to improve survival, QoL, and comfort.

Treating physicians would select the IV antibiotic for each participant based on clinical judgment prior to random assignment. Participants would then be randomly assigned to receive either the selected antibiotic or a matched IV placebo. Assuming a median survival of 6 months (standard deviation, ±4 months), a sample size of 502 participants (251 per group) would provide 80% power to detect a statistically significant difference in survival time of 1 month.[9] No established minimal clinically important difference exists for survival in this population, and we recognize that a few additional days of survival may be meaningful for some patients but not others. Studies suggest that most patients and caregivers prioritize QoL and comfort over marginal life prolongation.[17] However, 1 month may be viewed as important for those who value survival, while balancing prioritization of comfort and QoL.[17]

Globally, there is a need to improve care for millions living with advanced dementia. This trial would address key knowledge gaps and provide high-quality evidence to inform shared decision-making, ensuring that care balances survival with QoL and comfort, and aligns with patient-centered goals.

Disclosures

Author disclosures are available at evidence.nejm.org.

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