POEMs

Patient-Oriented Evidence That Matters

Nirmatrelvir/Ritonavir Reduces Risk of Hospitalization in At-Risk Outpatients

Clinical Question

Does nirmatrelvir/ritonavir (Paxlovid) safely reduce the risk of hospitalization or death in unvaccinated at-risk outpatients with COVID-19?

Bottom Line

Nirmatrelvir/ritonavir significantly reduces the likelihood of hospitalization or death in unvaccinated adults with confirmed COVID-19 who are at risk of a more severe course of disease (number needed to treat [NNT] = 18). (Level of Evidence = 1b)

Synopsis

Nirmatrelvir is a protease inhibitor; its potency is increased by combining it with ritonavir. The researchers identified adults with confirmed COVID-19 and symptom onset within the past five days who were 60 years and older or had a comorbidity that increases the risk of hospitalization and death. Patients with a history of COVID-19 or who were vaccinated were excluded. A total of 2,246 participants were randomized to nirmatrelvir/ritonavir, 300 mg/100 mg, or matching placebo every 12 hours for five days. The mean age of patients was 46 years, two-thirds had symptoms for three days or less, and the primary outcome was the likelihood of hospitalization or death caused by COVID-19 within 28 days. The outcome was calculated for several modified intention-to-treat populations. In patients with five or fewer days of symptoms who were not expected to get a COVID-19–specific monoclonal antibody (n = 2,085), the primary outcome occurred significantly less often in the treatment group (0.8% vs. 6.3%; $P < .001$; NNT = 18). The secondary outcome of all-cause mortality was less likely in the treatment group (0.0% vs. 1.1%; $P = .001$; NNT = 91). When analysis was limited to those with symptom onset in the past three days (n = 1,379), results were similar (0.72% vs. 6.45%; $P < .001$; NNT = 17). Most patients were infected with the Delta variant, so the drug's efficacy in vaccinated people and those with the Omicron variant is not known. Dosage adjustment is needed for patients with moderate or worse renal impairment. Because nirmatrelvir/ritonavir is a cytochrome P450 3A inhibitor, a number of other drugs should be withheld or their dose adjusted during administration, most notably other protease inhibitors and HIV drugs, macrolides, calcium channel blockers, and statins. Nirmatrelvir/ritonavir was well tolerated with few adverse events.

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry

Allocation: Uncertain

Setting: Outpatient (any)

Reference: *Hammond J, Leister-Tebbe H, Gardner A, et al.; EPIC-HR Investigators. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19.* N Engl J Med. *Published online February 16, 2022. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2118542?articleTools=true*

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Ibuprofen, Ketorolac, and Diclofenac Are Equivalent for the Treatment of Acute, Nonradicular Low Back Pain

Clinical Question

How do ibuprofen, ketorolac, and diclofenac compare with one another for the treatment of acute, nonradicular low back pain in adults?

Bottom Line

This study found no differences among ibuprofen, ketorolac, and diclofenac in the primary outcome of overall clinical improvement at five days in adults presenting to the emergency department with acute, nonradicular low back pain. Some of the secondary outcomes favored ketorolac, leaving open the possibility that ketorolac is superior to ibuprofen and diclofenac. (Level of Evidence = 1b–)

Synopsis

Although nonsteroidal anti-inflammatory drugs (NSAIDs) are the recommended first-line treatment for acute low back pain, there is no clear evidence for recommending one oral NSAID over another. The investigators identified adults, 18 to 65 years of age, who presented to an emergency department with acute low back pain. Eligibility criteria included pain between the lower border of the scapulae and the upper gluteal folds without any radicular symptoms that lasted less than two weeks, or a history of direct trauma to the back within the past month. Patients (N = 198) randomly received (concealed allocation assignment) ibuprofen (600 mg every eight hours, as needed), ketorolac (10 mg every eight hours, as needed), or diclofenac (50 mg every eight hours, as needed). Study participants masked to treatment group self-rated overall symptoms, including pain and function, using a validated 24-item low back pain scoring tool. Complete follow-up occurred for 86% of patients at five days.

Using intention-to-treat analysis, no significant group differences occurred in the primary outcome of an improved pain and function score. Several secondary outcomes were assessed, some of which significantly favored ketorolac. The investigators, however, appropriately concluded that the study found no clear evidence to recommend one NSAID over the others.

Study design: Randomized controlled trial (double-blinded)

Funding source: Self-funded or unfunded

Allocation: Concealed

Setting: Emergency department

Reference: *Irizarry E, Restivo A, Salama M, et al. A randomized controlled trial of ibuprofen versus ketorolac versus diclofenac for acute, nonradicular low back pain.* Acad Emerg Med. *2021;28(11):1228-1235.*

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Dual Antiplatelet Therapy With Aspirin Plus Clopidogrel for 30 Days Is the Best Option After Minor Stroke or TIA

Clinical Question

What is the balance of benefits and harms for dual antiplatelet therapy compared with monotherapy for the secondary prevention of ischemic stroke?

Bottom Line

For patients with minor stroke or transient ischemic attack (TIA), dual antiplatelet therapy with aspirin plus clopidogrel (Plavix) for up to 30 days reduces the likelihood of subsequent stroke (number needed to treat = 50) more than aspirin monotherapy, with a small increase in the risk of major hemorrhage (number needed to harm = 500). A longer duration of therapy increases the risk of harm without increasing the likelihood of benefit. (Level of Evidence = 1a)

Synopsis

The authors identified randomized trials that compared dual antiplatelet therapy with monotherapy, started within three days of the index stroke or TIA. In some cases, the researchers were able to get data for the subset of patients who were randomized within three days from studies in which longer intervals were allowed between stroke and randomization. The search was comprehensive, and the analysis was methodologically sound. The final analysis included 17 studies with a total of 27,358 patients. The mean age of participants was 65 years, approximately two-thirds were men, and most studies targeted patients with minor ischemic stroke or TIA. The studies were assessed to be at low risk of bias. Monotherapy was aspirin in 15 studies and clopidogrel in two studies. The most common dual antiplatelet therapy regimen was aspirin plus clopidogrel. The largest study (THALES) compared aspirin alone with aspirin plus ticagrelor (Brilinta); because of the size of the study, the authors performed sensitivity analyses with and without this trial. Using dual antiplatelet therapy instead of monotherapy for 30 days or less resulted in 20 fewer strokes (number needed to treat = 50) and two more major hemorrhages (number needed to harm = 500) per 1,000 patients. The likelihood of major hemorrhage was the same when the THALES trial was excluded, although there was no longer a significant difference in the risk of hemorrhage between the aspirin and dual antiplatelet therapy groups. The authors stratified the analysis by treatment of more than 30 days or 30 days or less. Although the benefit was similar for a treatment duration of up to 30 days, the risk of hemorrhage was greater with a longer duration of therapy.

Study design: Meta-analysis (randomized controlled trials)

Funding source: Self-funded or unfunded

Setting: Outpatient (any)

Reference: *Trifan G, Gorelick PB, Testai FD. Efficacy and safety of using dual versus monotherapy antiplatelet agents in secondary stroke prevention: systematic review and meta-analysis of randomized controlled clinical trials.* Circulation. *2021;143(25): 2441-2453.*

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Amoxicillin for Children With CAP: Low-Dose for Three Days Is Noninferior to High-Dose for Seven Days

Clinical Question

What is the optimal dosage of amoxicillin for managing community-acquired pneumonia (CAP) in children?

Bottom Line

In children with CAP who are discharged from an emergency department or inpatient setting within 48 hours, a lower dose of oral amoxicillin is noninferior to a higher dose, and three days of treatment is noninferior to seven days in reducing the need for antibiotic re-treatment. (Level of Evidence = 1b)

Synopsis

Although amoxicillin is widely recommended and used for the treatment of CAP in children, the optimal dose and treatment duration are uncertain. The investigators identified children six months and older with clinically diagnosed CAP (based on standard international guidelines) who were being discharged from the emergency department or inpatient ward within 48 hours of admission. Patients randomly received (concealed allocation assignment) one of four amoxicillin regimens: 35 to 50 mg per kg per day for three days; 35 to 50 mg per kg per day for seven days; 70 to 90 mg per kg per day for three days; or 70 to 90 mg per kg per day for seven days. Masking occurred by using matched active or placebo suspension for days 4 through 7. Individuals masked to treatment group assignment assessed the primary outcome of clinically indicated antibiotic re-treatment for respiratory tract infection within 28 days of randomization. The noninferiority margin was predetermined to be a conservative 8% difference in outcome rates. Complete follow-up data were available for 97% of participants at 28 days.

Using intention-to-treat analysis, the primary outcome occurred in 12.6% of children in the lower-dose groups vs. 12.4% in the higher-dose groups, and in 12.5% in the three-day treatment groups vs. 12.5% in the seven-day treatment groups. Both groups demonstrated noninferiority between dose and duration. In the subgroup of children with severe CAP, all groups demonstrated noninferiority.

This POEM aligns with Choosing Wisely Canada recommendations. The Choosing Wisely Canada Cold Standard toolkit provides tools for reducing unnecessary antibiotics.

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Concealed

Setting: Emergency department

Reference: *Bielicki JA, Stöhr W, Barratt S, et al.; PERUKI, GAPRUKI, and the CAP-IT Trial Group. Effect of amoxicillin dose and treatment duration on the need for antibiotic re-treatment in children with community-acquired pneumonia: The CAP-IT randomized clinical trial [published correction appears in* JAMA. *2021;326(21):2208].* JAMA. *2021;326(17): 1713-1724.*

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Editor's Note: Dr. Ebell is deputy editor for evidence-based medicine for *AFP* and cofounder and editor-in-chief of Essential Evidence Plus, published by Wiley-Blackwell. ■