evidence-based guidelines from 1998 also recommend MDI/S for children aged >1 year with acute asthma exacerbations.[9] This guideline suggests using 4 to 8 puffs from a 90 µg albuterol MDI at 1- to 2-minute intervals every 20 minutes for 1 hour, then every 1 to 4 hours subsequently.

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CLINICAL COMMENTARY

Use MDIs with spacers in all but the youngest patients

Until recently, using a nebulizer for the wheezing child or infant seemed intuitively to be the most effective way to deliver bronchodilators. However, with recent data showing that MDIs with spacers are just as effective, I have been using MDIs with spacers for all but my youngest patients. Parents as well as physicians may need to be convinced that using less technology in this case is better for their child. In some cases, parental acceptance of therapy necessitates using a nebulizer.

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Do antipyretics prolong febrile illness?

EVIDENCE-BASED ANSWER

Antipyretics appear to have minor and variable effects on the course of febrile illness. Aspirin and acetaminophen do not prolong the course of rhinovirus illness, although they may prolong the period of viral shedding and worsen nasal congestion (strength of recommendation [SOR]: **A–**, based on small randomized controlled trials).

Acetaminophen did not affect symptoms, overall condition, or time to complete healing in children with varicella, although it increased the time to total scabbing of lesions (SOR: **A**, based on a small randomized controlled trial). Aspirin and acetaminophen may prolong influenza A illness (SOR: **C**, based on a poor-quality, retrospective observational study).

Acetaminophen may prolong the course of *Shigella sonnei* infection (SOR: **B–**, based on a small retrospective cohort study). It does not affect malaria cure rate, and there are insufficient data to assess clearance of *Plasmodium falciparum* (SOR: **C**, based on small randomized controlled trials with heterogeneous results).

EVIDENCE SUMMARY

Acetaminophen has a different mechanism of action from other antipyretics. It halts the production of prostaglandin in the brain but not in

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the periphery, solely lowering fever. Aspirin and other nonsteroidal anti-inflammatory agents inhibit both central and peripheral cyclooxygenase and may cause multiple effects in addition to temperature reduction. Clinical outcome studies of their antipyretic effects are inconclusive.[1]

A randomized controlled trial involving 60 volunteers given intranasal rhinovirus type 2 monitored the effect of aspirin, acetaminophen, ibuprofen, or placebo on virus shedding, immune response, and clinical status. There was no difference in duration of illness. There was a trend toward longer duration of virus shedding in the aspirin and acetaminophen groups, but serum neutralizing antibody response was suppressed ($P<.05$ vs placebo). Aspirin and acetaminophen worsened symptoms of turbinate edema and nasal obstruction ($P<.05$ vs placebo).[2]

In 2 double-blind trials, 45 adults infected with rhinovirus were given aspirin or placebo for 5 days, beginning on the day after viral exposure (as opposed to the typical use in response to symptoms). Aspirin treatment improved symptoms of conjunctivitis significantly, but did not change the duration of illness. Other symptoms (headache, sneezing, chills, malaise, nasal discharge) were not significantly different. Aspirin increased the amount of viral shedding by 36% in 1 trial and 17% in the other ($P<.01$), potentially increasing risk of spread.[3]

In a randomized controlled trial evaluating antipyretic effects on the duration or severity of childhood varicella, 31 children received placebo and 37 received acetaminophen for 4 days. There was no difference in itching, appetite, activity, or overall condition between the 2 groups. Children treated with acetaminophen took 1.1 days longer to total scabbing ($P<.05$), although the number of days until the appearance of the last new vesicle and the time to total healing were unchanged. The duration of viral shedding was not measured, but it is possible that the delay in healing of lesions would prolong viral shedding as well.[4]

A retrospective observational study of 54 volunteers demonstrated prolonged illness in subjects infected with influenza A that received antipyretic therapy. Patients who got antipyretics were sick 3.5 days longer than those who did not (8.8 ± 2.3 days vs 5.3 ± 3.0 days; $P<.001$). Only patients with temperatures >38.9°C on 2 readings 6 hours apart received antipyretics, indicating that the longer course correlated with greater severity of illness as well as with antipyretic use.

In the same study, antipyretics were associated with a trend towards prolonged duration of illness in a group of 21 patients infected with *S sonnei* (4.6 ± 2.1 days with antipyretics vs 1.9 ± 1.6 days without; P=not significant).[5]

A Cochrane review examined 3 trials of acetaminophen vs placebo for fever in 128 adults and children with *P falciparum* malaria. Although fever clearance varied between the trials, the malaria cure rate was similar in all, and the review concluded that data were insufficient to evaluate an effect on parasitemia.[6]

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What are Clinical Inquiries?

Clinical Inquiries answer real questions that family physicians submit to the Family Practice Inquiries Network (FPIN), a national, not-for-profit consortium of family practice departments, residency programs, academic health sciences libraries, primary care practice-based research networks, and other specialists.

Questions chosen are those family physicians vote as most important through a web-based voting system.

Answers are developed by a specific method:

- FPIN medical librarians conduct systematic and standardized literature searches in collaboration with an FPIN clinician or clinicians.
- FPIN clinician authors select the research articles to include, critically appraise the research evidence, review the authoritative sources, and write the answers.
- Each Clinical Inquiry is reviewed by 4 or more peers and editors before publication in JFP.
- FPIN medical librarians co-author each of the Clinical Inquiries that have required a systematic search.
- Finally, a practicing family physician writes an accompanying commentary.

RECOMMENDATIONS FROM OTHERS

We found no recommendations regarding the use of antipyretics and their effect on the duration of febrile illness.

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CLINICAL COMMENTARY

The risk-benefit ratio of antipyretics may not be as favorable as you think

The doctor's recommendation, "Take two aspirin and call me in the morning," is an enduring stereotype, not an evidence-based therapy for a fever. This review reevaluates the simplistic notion that antipyretics are uniformly beneficial and safe in febrile illnesses.

Surprisingly, there appear to be some negative impacts from using antipyretics for common disease states without much clear benefit. It can be argued that the studies are small and purported negative consequences modest. Still, enough evidence exists to warrant more research and to cause clinicians to consider that the risk-to-benefit ratio of these medications may not be as favorable as once thought.

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Is folate supplementation indicated for patients with CAD?

EVIDENCE-BASED ANSWER

There is insufficient evidence to advocate the routine use of folate supplementation for the treatment of coronary artery disease (CAD). High levels of serum homocysteine have been associated in several studies with an increased risk for CAD (strength of recommendation [SOR]: **B**, associated in case-control studies). Folate supplementation decreases the level of serum homocysteine (SOR: **A**, meta-analysis of randomized controlled trials). This indirect evidence suggests that folate supplementation may be of benefit in slowing the progress of arteriosclerosis.

Two randomized controlled trials measuring the clinical benefits of folate supplementation for patients with CAD have been completed, with differing results. One study showed no benefit of 0.5 mg/d of folate for patients with stable CAD already on statin therapy. The other study found that patients given 1 mg/d of folate with vitamins B_6 and B_{12} had a decreased restenosis rate after percutaneous coronary intervention (PCI) (SOR: **B**, conflicting randomized controlled trials).

It is possible that larger doses of folate are needed to be of clinical benefit, or that the addition of vitamins B_6 and B_{12} are needed for synergy. Several randomized control trials are underway to further assess folate's affect on CAD.

EVIDENCE SUMMARY

Hyperhomocysteinemia is defined as a fasting plasma homocysteine level 15 µmol/L, although levels >10 µmol/L appear to have detrimental effects on risk profiles for CAD and arteriosclerosis.[1] In 22 of 27 retrospective case-control studies, patients with CAD had significantly higher plasma homocysteine levels than control subjects (odds ratio [OR]=1.2–10.9, after adjustment for other CAD risk factors).[2,3] However, only 4 of 7

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