In the obese adolescent, when should you start screening for hyperlipidemia?

Evidence-based answer

The answer is not completely clear. Hyperlipidemia in childhood does not always correlate to elevated cholesterol levels as an adult, and hyperlipidemia in adolescents with an elevated body mass index (BMI) does not directly correlate to hyperlipidemia in adulthood (SOR: C, disease-oriented outcomes). Current National Institutes of Health guidelines recommend universal screening for children between the ages of 9–11 and 17–21 years and in obese children (BMI >85th percentile) aged 12–16 years (SOR: C, expert opinion).

Evidence summary

An aggregate of 3 population-based prospective cohort trials examined the correlation between adolescent serum lipid levels and the development of dyslipidemia as an adult. Data were examined from 1,809 individuals, originally aged 12–18 years, from Australia, Finland, and the United States. Mean follow-up time was 20 years.

The accuracy of predicting dyslipidemia levels as an adult (with adult lipid levels as the gold standard) in adolescents with high-risk lipid levels (total cholesterol >240; low-density lipoprotein [LDL] >160 mg/dL; triglycerides >200 mg/dL) was not very sensitive or specific. Total cholesterol had a sensitivity of 68% and a specificity of 71%; the positive likelihood ratio (LR+) was 2.3 and the negative likelihood ratio (LR−) was 0.45. LDL had a sensitivity of 65% and a specificity of 75% (LR+ 2.6; LR− 0.47). Triglycerides had a sensitivity of 14% and a specificity of 96% (LR+ 4.7; LR− 0.89).

A subset study of data from 1,180 Finnish individuals examined the effectiveness of different screening strategies for identifying adolescents who will develop adult dyslipidemia. Universal screening of LDL levels was somewhat predictive of adult LDL levels (sensitivity 74%, specificity 66%; LR+ 2.2, LR− 0.39). There was no improvement in detecting dyslipidemia as an adult when screening adolescents who were overweight (sensitivity 79%, specificity 55%; LR+ 1.8, LR− 0.38).
A systematic review of 11 cohort trials (with nearly 240,000 patients) examined the correlation between childhood obesity and the risk of adult metabolic syndrome, including dyslipidemia.\(^2\) Initial BMI was measured at ages 2–18, and adult outcomes measured at ages 18–71. Data were not pooled because of heterogeneity between trials. No consistent correlation was found between childhood BMI and adult levels of total cholesterol, LDL, or high-density lipoprotein. Four trials (N=6,154) examined the correlation between pediatric BMI and adult total cholesterol. Two had weak to moderate correlations and 1 showed a negative correlation with BMI at 9 years old. The last trial showed no correlation. Three (N=3,708) of these trials evaluated LDL, and 1 trial showed a weak correlation between childhood BMI and adult LDL, but that correlation disappeared after adjusting for adult BMI. The other 2 trials did not show any correlation.

A longitudinal observational study of 678 children in Texas, ages 8–14, examined the efficacy of various screening programs in predicting dyslipidemia in pediatric patients.\(^3\) The screening programs included targeted screening based on BMI or family history of cardiovascular disease, or both. For elevated total cholesterol and LDL, the sensitivity of screening based on family history alone compared with screening based on BMI >85% alone was no different (total cholesterol 38% vs 34%; \(P>.05\); LDL 41% vs 38%; \(P>.05\)), but screening based on BMI was more specific (total cholesterol 65% vs 78%; \(P<.05\); LDL 65% vs 79%; \(P<.05\)). However, compared with screening based on BMI >85% and/or family history, screening based on family history alone had less sensitivity (total cholesterol 38% vs 54%; \(P<.05\); LDL 38% vs 54%; \(P<.05\)) but greater specificity (total cholesterol 65% vs 50%; \(P<.05\); LDL 65% vs. 51%; \(P<.05\)).

The National Heart, Lung, and Blood Institute guidelines recommend, in most cases, against targeted screening of individuals with a significant family history or obese individuals.\(^4\) They recommend universal screening for children aged 9–11 and 17–21 years (Grade B, “diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies”). Because of expected changes to the serum lipid profile, they recommend only targeted screening for individuals 12–16 years with obesity, a high-risk family history, known dyslipidemia, diabetes, hypertension, cigarette smoking, or moderate- to high-risk medical conditions (also Grade B).

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REFERENCES

GLOSSARY

<table>
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<th>ARR=absolute risk reduction</th>
<th>HR=hazard ratio</th>
<th>OR=odds ratio</th>
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<td>CDC=Centers for Disease Control and Prevention</td>
<td>LOE=level of evidence</td>
<td>RCT=randomized controlled trial</td>
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<tr>
<td>CI=confidence interval</td>
<td>MRI=magnetic resonance imaging</td>
<td>RR=relative risk</td>
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<tr>
<td>CT=computed tomography</td>
<td>NNH=number needed to harm</td>
<td>SOR=strength of recommendation</td>
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<tr>
<td>FDA=US Food and Drug Administration</td>
<td>NNT=number needed to treat</td>
<td>SSRI=selective serotonin reuptake inhibitor</td>
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A small connector

I have lived in the Seattle area for 25 years and every summer enjoy getting out on the trails around town, visiting local destinations such as Mount Si and Granite Peak, Snow and Gem Lakes, Klapatche and Spray Meadows, and Mount Rainier and North Cascades National Parks. But after so many years, I was beginning to think I had been everywhere and hiked every trail.

Then, last year, I discovered a short connector trail I had never noticed before, one that ran from the Pratt Lake trail complex to the Mount Defiance trail complex. It was not listed in any of the guidebooks. I had passed it 3 or 4 times in the past but somehow never really noticed it. I had lots of daylight and so with great delight, decided to explore.

The trail was only a mile or so long, but it was relatively flat, weaving along the top of a ridge, through a beautiful bit of old-growth forest, high above a series of alpine lakes. The trail bed was soft with accumulated pine needles and the ground brilliant green with moss. The unexpected ramble was pure joy.

I thought of my delightful connector when I read of a new finding in human anatomy. Some Belgian anatomists reported finding a new lateral ligament in the knee.1 They call it the anterolateral ligament and it runs 4 cm from the anterolateral tibia to the lateral fibula. They found it in 40 of 41 knees they evaluated. Prior anatomists had mentioned it in passing, but had not really explored it.

I compared their anatomic knee drawing with the drawing in my old Clemente’s Anatomy. Where Clemente shows 1 lateral knee ligament, this research report shows 2. I got the same thrill I get when looking at a set of discordant maps. Someone had found a new way around.

It remains to be seen if other anatomists will concur. But how wonderful it is to find new connections in terrain we thought we knew so well.

Jon O. Neher, MD

REFERENCE
Diving for PURLs

**PURLs Criteria**

**Relevant:** Is the topic relevant to family medicine?

**Valid:** Are the findings scientifically valid?

**Change in practice:** Would this change practice?

**Medical care setting:** Is this implementable in clinic, etc?

**Implementable:** Can we implement this immediately?

**Clinically meaningful:** Are results clinically meaningful?

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**Keep kids with asthma out of the hospital—Add an inhaled anticholinergic**


This meta-analysis of 20 RCTs enrolled 2,697 patients and compared combined inhaled anticholinergics plus short-acting beta-agonists (SABA) with SABA alone in children presenting to an emergency department with an acute asthma exacerbation. The frequency of doses of anticholinergic (ipratropium bromide) varied among studies.

The primary outcome measure was hospital admission. Secondary outcomes included adverse effects such as nausea and tremor.

Addition of an anticholinergic to a SABA reduced the risk of hospital admission (RR 0.73; 95% CI, 0.63–0.85), with a NNT=16. Combined therapy was also associated with fewer reports of nausea (RR 0.60; 95% CI, 0.38–0.95) and tremor (RR 0.69; 95% CI, 0.51–0.93).

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**Bottom line:** Adding an inhaled anticholinergic to SABA when treating children with an acute asthma exacerbation decreases the need for hospitalization and leads to fewer medication adverse effects.

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**Botulinum toxin A may help improve sleep and reduce pain in patients with postherpetic neuralgia**


This randomized, double-blind, placebo-controlled trial of 30 patients compared botulinum toxin A (BTX-A) with placebo injection for pain reduction and sleep improvement in elderly patients (aged >70 years) with >3 months of moderate to severe postherpetic neuralgia (PHN).

The intervention group received a single set of 40 subcutaneous injections of BTX-A over the affected area; the control group received normal saline injections. A 10-point visual analog scale (VAS) pain score and sleep score measured on a validated 15-point scale were assessed for the following 24 weeks. The primary outcome was >50% reduction in VAS pain score within 4 weeks of injection.

Thirteen patients who received BTX-A achieved and maintained ≥50% VAS score reduction for a median of 16 weeks compared with none of the placebo patients (absolute risk reduction 0.87; 95% CI, 0.55–0.96; \( P < .001 \); NNT=2). Patients receiving BTX-A also had a significant improvement in quality-of-sleep score for 12 weeks (mean change 4.6; \( P < .001 \)), whereas the change was not significant in patients given placebo (mean change 0.5; \( P < .068 \)).

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**Bottom line:** BTX-A injection may improve pain and quality of sleep in elderly patients with moderate to severe PHN for >3 months. Barriers to implementation include procedural training for physicians and access and affordability of BTX-A.

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**Additional information can be found at:** www.fpin.org/purlsoverview
Do not use perioperative beta-blockers to prevent morbidity and mortality in noncardiac surgery


Guidelines currently recommend initiating beta-blockers for high-risk patients undergoing intermediate to high-risk surgery. These guidelines, unfortunately, were partly influenced by data from fraudulent studies. This meta-analysis of 9 RCTs compared initiation of beta-blockers in the perioperative period with placebo in patients undergoing noncardiac surgery. Published intention-to-treat RCTs with no language restriction published between 1966 and April 2013 were included.

The primary outcome was all-cause mortality at 30 days. Secondary outcomes were nonfatal myocardial infarction (MI), stroke, and hypotension. A total of 10,529 patients were included.

There were 162 deaths among the 5,264 patients in the beta-blocker arm compared with 129 deaths in the 5,265 randomized to placebo (RR 1.3; 95% CI, 1.0–1.6). Initiation of beta-blockers was found to reduce nonfatal MI (RR 0.73; 95% CI, 0.61–0.88) but increase stroke (RR 1.7; 95% CI, 1.0–3.0) and increase hypotension (RR 1.5; 95% CI, 1.4–1.7).

**Bottom line:** Initiation of beta-blockers perioperatively in patients undergoing noncardiac surgery was found to increase all-cause mortality and the risk of stroke and hypotension, but to decrease the risk of nonfatal MI.

AAA surveillance: Are we screening too often?


This meta-analysis of 18 RCTs and observational studies evaluated the growth and rupture rates of small (3.0–5.4 cm) abdominal aortic aneurysms (AAA) in >15,000 men and women followed 1–8 years using individual patient-level data and combined study estimates.

In males, each 0.5-cm increase in baseline AAA diameter led to an increase in the average growth rate of 0.59 mm/year (95% CI, 0.51–0.66) and a doubling of the rupture rate (RR 1.9; 95% CI, 1.6–2.3). The estimated mean time to have a 10% chance of reaching 5.5 cm for men with a baseline 3.0 cm AAA was 7.4 years (95% CI, 6.7–8.1), with a baseline 4.0 cm AAA was 3.2 years (95% CI, 3.0–3.4), and with a baseline 5.0 cm AAA was 8 months (95% CI, 7.2–9.6).

The average time to reach a rupture risk of 1% for AAA diameters of 3.0 to 4.5 cm was ≥2 years and for a 5.0 cm AAA was approximately 1.4 years.

Women had a 4-fold greater rupture risk for all AAA sizes and reached a rupture risk of >1% in a much shorter time than men (for 5 cm AAA: 8 months for women vs 1.4 years in men).

**Bottom line:** Most AAAs between 3.0 and 5.4 cm do not reach the size threshold for surgical intervention or rupture over many years. We are concerned about unexplained differences in growth and rupture rates in the included studies.

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Are any office-based interventions proven to be effective to end bullying?

**Bottom line**

Outpatient family therapy has been shown to reduce bullying behavior. However, the 3 trials that investigated this intervention were all conducted by the same principal investigator in 1 region of rural Germany, and none described how bullying behavior was assessed (SOR: C, low-quality RCTs by a single research team).

**Background**

Bullying is a type of aggression that involves behavior intended to harm that is repeated over time and depends on an imbalance of power between the perpetrator and the victim. Bullying has been associated with poor psychosocial adjustment, anxiety, depression, psychosomatic symptoms, eating disorders, and substance use.¹,²

Only 3 RCTs have investigated office-based interventions to reduce bullying, all of which were studies of outpatient family therapy that were conducted by the same principal investigator in 1 region of Germany using similar study designs. None reported the means of assessing bullying behavior.

**Evidence summary**

A 2005 trial included 44 adolescent boys between the ages of 14 and 16 with bullying behavior of at least 6 months’ duration. The boys were randomized to 6 months of family therapy or placebo intervention. At the end of the intervention, 27% of boys in the intervention group (6 of 22) were still bullying compared with 91% of the controls (20 of 22, \( P < .05 \)) \(^{3} \) a significant difference persisted at 1 year of follow-up.²

A 2006 trial included 40 15-year-old girls who had shown direct physical and/or verbal bullying of at least 6 months’ duration who were randomized to 3 months of family therapy or placebo intervention. After 3 months there was a statistically significant reduction between the groups in the number of girls participating in bullying behavior (from 20 to 6 girls in the intervention group and from 20 to 18 girls in the control group, \( P = .05 \))². Again, the authors’ means of assessing bullying behavior were not reported.

In another 2006 trial, 36 boys aged 14 to 15 years who engaged in bullying by self-report were randomized to family therapy or placebo intervention. At the end of 12 weeks there was a statistically significant reduction in the number of boys participating in bullying behavior in the intervention arm compared with the control group (from 36 to 11 boys in the intervention and from 36 to 29 boys in the control group, \( P = .017 \)). Once again, no assessment tool for bullying was described.⁵

**REFERENCES**


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**RECENT PUBLICATIONS IN CLINICAL INQUIRIES**


For more information regarding the Clinical Inquiries writing series, please contact the Family Physicians Inquiries Network at 573-256-2066.
Which psychological interventions are effective in managing pediatric needle pain?

Bottom line
Distraction and hypnosis reduce the pain of needle procedures in children and adolescents. Distraction can be as simple as reading stories, watching videos, listening to music, or talking about something other than the procedure. Hypnosis reduces both pain and distress but may be less generalizable in a pediatric setting.

Background
Medical procedures, particularly involving needles, are among the most feared experiences of children. Vaccination schedules recommend 20 different immunizations before age 18, and children with chronic illness or those who are hospitalized may experience even more procedure-related needle pain. This pain is associated with emotional and psychological distress.

The evidence
Study details
A 2013 Cochrane reviewed 39 RCTs of multiple psychological interventions for pediatric needle pain. Studies with children and adolescents aged 2 to 19 years were included, and the most commonly performed needle procedures were venipuncture, immunizations, and injections. Primary outcomes focused on pain and distress such as heart rate, respiratory rate, blood pressure, oxygen saturation, cortisol levels, transcutaneous oxygen tension, and transcutaneous carbon dioxide tension.

Distraction
Nineteen RCTs with 1,759 participants examined the effect of distraction on self-reported pain. All studies included a control arm, which was predominately usual care. Distraction techniques included listening to music, watching cartoons, playing with a toy, nonprocedural talk, squeezing a rubber ball, using cards with questions on them, listening to stories via earphones, mother distraction, or a combination.

Distraction resulted in a significant reduction in self-reported pain (standardized mean difference [SMD] –0.61, P<.0001). Five studies with 447 participants found that distraction was marginally effective on observer-reported pain (SMD –0.87, P=.05). Regarding secondary outcomes, the effect of distraction on heart rate (SMD –0.70, P=.0003) and oxygen saturation (SMD 0.60, P=.002) were significant. The effects of distraction on self- and observer-reported distress were not found to be significant. Likewise, the effect of distraction on behavioral measures of both pain and distress were not significant.

Hypnosis
Hypnosis was found to have the largest effect across multiple outcome measures. The control arms were other active treatment and usual care. The significant effects of hypnosis were seen on self-reported pain (SMD –1.4, P=.003), self-reported distress (SMD –2.5, P=.0004), and behavioral measures of distress (SMD –1.2, P=.0003). The effects of hypnosis on observer-reported distress and behavioral measures of pain could not be evaluated because of a lack of studies evaluating these measures. The authors noted that the generalizability of hypnosis may be limited given the lack of health professionals trained in this modality.

Other interventions
The RCTs evaluated found no evidence supporting the effectiveness of preparation and information, cognitive behavioral therapy, parent coaching with distraction, suggestion, or virtual reality for reducing children’s pain and distress. No conclusions were made about the benefit of memory alteration, parent positioning with distraction, blowing out air, or distraction with suggestion due to a lack of RCTs.

Evidence was lacking to identify which techniques might be most effective for children by age or procedure.

REFERENCE

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How soon after term premature rupture of membranes (PROM) should oxytocin be started?

Evidence-Based Answer

In patients presenting at term with PROM who are not in labor, immediate induction with oxytocin is associated with a lower incidence of endometritis and chorioamnionitis, fewer admissions to the neonatal intensive care unit (NICU), and no increase in the rate of cesarean or operative vaginal births when compared with expectant management (SOR: A, meta-analysis).

A Cochrane systematic review evaluated 12 randomized or quasirandomized trials involving 6,814 women with PROM at term to compare outcomes of expectant management (defined as no planned intervention within 24 hours) versus immediate intervention.¹ Seven of the 12 trials used oxytocin for induction.

Induction significantly reduced the rates of chorioamnionitis (9 trials, N=6,611; risk ratio [RR] 0.74; 95% CI, 0.56–0.97) and endometritis (4 trials, N=445; RR 0.30; 95% CI, 0.12–0.74). Induction was associated with fewer NICU admissions (5 trials, N=5,679; RR 0.72; 95% CI, 0.57–0.92), although no difference was seen in the rate of neonatal infection (9 trials, N=6,406; RR 0.83; 95% CI, 0.61–1.1). No difference was noted between the induction and expectant groups in operative delivery rates (12 trials reporting cesarean sections, N=6,814; RR 0.94; 95% CI, 0.82–1.1; 7 trials reporting operative vaginal delivery, N=5,511; RR 0.98; 95% CI, 0.84–1.2). More women who were induced viewed their care more positively than those managed expectantly (1 trial, N=5,031; RR of “nothing liked” about the process 0.45; 95% CI, 0.37–0.54).¹

An economic analysis was performed in a large RCT published in 1997, which involved 5,041 women with PROM.² Costs were calculated for study patients in the United Kingdom, Canada, and Australia. The median cost per patient for immediate induction of labor with oxytocin was significantly less than expectant management (and induction with oxytocin if complications developed). In Canada the cost was $114 less (P=0.004); in the United Kingdom it was £113 less (P=.0001); and in Australia it was $30 less (P=.0342). The savings came from several sources: fewer newborns from the induction group were admitted to the NICU or special care nursery, and these newborns spent less time in the special care nursery. In addition, the mothers in the induction group spent significantly less time on the antenatal ward.

The American College of Obstetrics and Gynecology 2007 Practice Bulletin states that women with PROM at term should be induced at the time of presentation, to decrease the risk of chorioamnionitis (Level A recommendation, based on good and consistent scientific evidence).³

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How do you prevent MRSA colonization among close contacts of patients with abscess or cellulitis in the community?

Evidence-Based Answer

Basic hygienic practices, such as hand washing and keeping wounds covered, should be used to prevent the spread of methicillin-resistant Staphylococcus aureus (MRSA) among close contacts of patients with an abscess or cellulitis (SOR: C, expert opinion).

Guidelines for community-associated MRSA (CA-MRSA) prevention were developed from a comprehensive literature review, a Working Group meeting of Canadian and US experts, and extensive discussions within an expert panel writing group.¹

The English language medical literature was reviewed from 1980 to March 2006. This group concluded that the prevention of CA-MRSA requires the consistent use of good hygienic practices such as hand washing, not sharing possibly contaminated personal articles, and covering draining wounds. In addition, they recommended that the household environment be regularly cleaned with a standard household detergent. Clothes from individuals with MRSA-positive skin lesions can be included in the regular household laundry. Cutlery and dishes may be washed in the usual manner with other household utensils using soap and hot water, or a dishwasher (Grade AIII; strong recommendations based on evidence from opinions of expert authorities).¹
In 2010 an Expert Panel of the Infectious Diseases Society of America reviewed and analyzed data published since 1961 on the treatment of MRSA, and developed clinical practice guidelines. The panel systematically weighed the quality of the evidence and the grade of recommendation. These experts made the same recommendations regarding personal hygiene and wound care (Grade AIII).

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Evidence-Based Answer

The addition of matrix destruction with phenol appears more effective than surgical intervention alone in reducing the recurrence of ingrown toenails (SOR: B, systematic review of heterogeneous RCTs). No difference was noted in healing time, infection rate, hemorrhage, or postoperative pain when comparing surgical procedures with and without phenol (SOR: B, systematic review of RCTs).

A 2012 Cochrane review of 24 RCTs (N=2,826) examined a variety of interventions for ingrown toenails. Of these, 4 RCTs (N=778) compared recurrence rates for surgical intervention alone with surgery plus phenol chemical ablation over 6 to 30 months. A significant reduction of recurrence was found with the use of phenol in all 4 studies (risk ratio [RR] 0.25; 95% CI, 0.09–0.69; RR 0.12; 95% CI, 0.06–0.27; RR 0.09; 95% CI, 0.05–0.17; and RR 0.26; 95% CI, 0.12–0.53). Insufficient data precluded pooling data from all 4 trials, and the authors were unable to conclude whether the reduction in recurrence was due to the addition of the phenol ablation because surgical interventions varied (nail avulsion, nail edge excision, excision matricectomy).

However, in an RCT of 117 patients, when partial nail avulsion (PNA) with matrix excision (n=59) was compared with PNA plus phenol ablation (n=58), PNA plus phenol ablation was significantly more effective in preventing recurrence (RR 0.34; 95% CI, 0.17–0.69). Two RCTs (N=316) from the Cochrane review reported no significant difference in healing time when partial avulsion with phenol was compared with wedge excision, and when wedge excision was compared with and without phenol (2 weeks in both groups). Four RCTs (N=390) found that phenol combined with surgery (ie, Zadik, PNA with matrix excision, nail edge excision, total nail avulsion, wedge excision) did not significantly increase the postoperative infection rate compared with surgery alone (RR 1.5; 95% CI, 0.53–4.3). Two RCTs (N=101) showed no significant difference in postoperative hemorrhage when partial nail avulsion and phenol were compared with wedge resection and matrix excision (RR 1.2; 95% CI, 0.08–18) or when partial nail avulsion and phenol were compared with partial nail avulsion and matrix excision (RR 0.38; 95% CI, 0.08–1.7). Two RCTs (N=161) found no significant difference in postoperative pain when partial nail avulsion and phenol was compared with partial nail avulsion and matrix excision (scale 0–10, with 0 being not present or very satisfactory and 10 being heavy presence or very unsatisfactory; mean difference [MD] 0.40; 95% CI, –0.41 to 1.2), and when partial nail avulsion with phenol was compared with wedge excision and matricectomy (MD –3.9; 95% CI, –14 to 6.5).

A retrospective cohort trial (N=72) was conducted via telephone interviews of patients who underwent partial nail avulsion with partial matricectomy. Phenol matricectomy (PM, N=33) and surgical matricectomy (SM, N=39) were compared for differences in outcomes. PM had less postoperative pain based on an analog scale of 0–10 (mean difference 1.9; 99% CI, 0.57–3.3) and a shorter time to recovery (0.5 weeks PM vs 1.5 weeks SM; P=.007). Recurrence rates of ingrown nails were higher in the PM group compared with the SM group (32% vs 6.9%; P=.006).

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What is the best treatment for gastroesophageal reflux in an infant?

Evidence-Based Answer

Thickened feedings may be useful, but position changes and proton pump inhibitors (PPIs) do not appear to be helpful. Metoclopramide may be beneficial, but adverse effects may outweigh those benefits (SOR: B, systematic reviews of inconsistent RCTs).

A Cochrane review of 20 RCTs (N=771) examined the effects of positioning, thickened feedings, and metoclopramide on gastroesophageal reflux in children younger than 2 years. Five RCTs (N=158) evaluated elevating the head of infants and did not show any change in esophageal pH measurements (results not pooled due to heterogeneity).

Compared with unthickened feeds, thickened feeds demonstrated reduced regurgitation scores (2 trials, N=48; standardized mean difference [SMD] –0.94; 95% CI, –1.4 to –0.52) and reduced frequency of emesis (3 trials, N=88; SMD –0.91; 95% CI, –1.2 to –0.61). No reduction in reflux index score (% of time pH is <4) was found (2 trials, N=61; weighted mean difference [WMD] 0.48; 95% CI, –3.3 to 4.2). Rice cereal and carob bean gum were used as thickeners.

Compared with placebo, metoclopramide (0.1–0.3 mg/kg TID orally for at least 1 week) resulted in fewer daily symptoms (2 trials, N=101; SMD –0.72; 95% CI, –0.98 to –0.45) and a lower reflux index (2 trials, N=99; SMD –0.43; 95% CI, –0.72 to –0.14). More adverse effects were noted with metoclopramide, but the difference did not reach statistical significance (4 trials, N=120; risk difference 0.26; 95% CI, –0.02 to 0.53). Irritability was the most common adverse effect. Drowsiness and extrapyramidal symptoms were also reported.

A 2006 systematic review that included 5 RCTs (N=343) of infants with reflux evaluated metoclopramide versus no treatment or placebo. Various outcomes were measured including pH probe parameters, gastric emptying, weight gain, and symptom scores. Due to the small sample size and heterogeneity between studies, no conclusions could be drawn about efficacy or toxicity.

In a 2011 systematic review of 5 RCTs (N=170) for infants with reflux, 4 studies found that PPIs were not effective in reducing reflux symptoms. One trial (N=15) reported PPIs decreased reflux symptoms compared with hydrolyzed formula, but the methodological quality was poor and follow-up was lacking. The authors concluded that PPIs in infants were not effective. Because of the heterogeneity of the studies a meta-analysis could not be performed.

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What are the fetal risks of Coxsackie virus infection in a pregnant woman?

Evidence-Based Answer

Gestational exposure to Coxsackie B virus (CBV) may be associated with spontaneous abortion and fetal morbidity and mortality (SOR: C, case-control trials).

CBV may be transmitted to the fetus during pregnancy through placental infection or during delivery.

A case-control trial of 124 pregnant women in Sweden examined the prevalence of CBV-IgM antibodies in pregnant women with and without miscarriages. The study tested maternal blood samples from women in the same county matched to age and time of year and found CBV-IgM antibodies in 33% (16 of 48) of women who had a spontaneous abortion, compared with only 8% (3 of 37) of the gestational age–matched controls (P<.025).

A case-control trial of 22 patients examined placental tissue from 7 newborn infants with severe respiratory failure compared with 10 controls and 5 placentas with known viral diseases (Cytomegalovirus, herpes, and parvovirus). Using PCR and RNA probes, CBV was identified in 86% (6 of 7) of the severe respiratory failure study group, and none of the 15 in the known viral and control cases (no P value provided). All of the CBV-positive infants who survived had developmental delay.

A blinded case-control trial examined the placentas of 60 neonates with complications (idiopathic fetal or neonatal death, severe respiratory distress, or CNS symptoms) and 17 neonate controls. An infectious
agent was identified in 76% (46 of 60) of the neonates with a complication versus none of the 17 placenta controls (no P value provided). Coxsackie virus was the most common infectious agent, found in 48% (22 of 46) of identified infections. Autopsy of 6 affected neonates showed Coxsackie virus in the spleen, heart, CNS, and lungs.

A case-control trial evaluated the presence of CBV in 180 patients with a miscarriage or an elective termination. CBV-IgM antibodies were present in significantly more women who miscarried before the 13th week compared with the elective termination control group (42% vs 18%; P<.001).

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the US Army at large, or the US Department of Defense.


How common is symptomatic hyponatremia in endurance athletes?

Evidence-Based Answer
Symptomatic exercise-associated hyponatremia (EAH) as seen in 0% to 1.1% of endurance athletes, typically manifesting as neurologic symptoms ranging from dizziness, headache, and lethargy to seizures and death (SOR C, cohort studies).

A nonconsecutive retrospective cohort trial of 2,135 competitive endurance athletes measured weight change and post-race serum sodium levels to evaluate proposed biological causes of EAH. Six percent (133/2,135) of participants had a post-race serum sodium concentration between 129 and 135 mEq/L and 1.5% had a concentration of less than 129 mEq/L. Symptoms consistent with exercise-associated hyponatremic encephalopathy (EAHE) such as dizziness, headaches, and lethargy were seen in 1.1% (24/2,135) of all athletes and in 18% (24/133) of those with EAH.

Overhydration is seen as a major risk factor, as athletes who gained more than 4% of their body weight during the events had a 45% probability of developing EAHE.1

In a prospective cohort trial of 200 male ultra-endurance athletes, including cyclists, mountain bikers, runners, and swimmers, the investigators evaluated the prevalence of EAH. All athletes ingested solid and fluid nutrition ad libitum and were evaluated for symptoms periodically throughout the events.

Twelve finishers (6%) developed EAH. The 26.4-km swim had the highest prevalence of EAH with 13% (2/15) athletes, followed by 11% (3/28) of cyclists in a 600-km cycling race, 8% (2/25) of runners in a 350-km mountain ultramarathon, 5% (5/95) of runners in a 100-km race, and 0% (0/37) of mountain bikers in a 120-km race. None of the 12 athletes who developed EAH showed clinical symptoms related to their hyponatremia.

A prospective cohort trial of 488 runners at the 2002 Boston Marathon was conducted to estimate the prevalence and investigate possible risk factors for development of EAH. Runners were given questionnaires before the race to evaluate demographics and training habits and a post-race questionnaire on the fluid consumption and urination during the event. Weight was taken before and after the event and serum sodium concentration was taken at the finish line.

The study showed 13% of runners developed EAH and 3 (0.6%) reached critical hyponatremia with serum sodium concentrations <120 mEq/L, but none of the runners showed symptoms related to EAH.

In a more recent marathon in Zurich, 167 runners were investigated in a cool-weather event with a 5-hour time limit to further investigate mechanisms for the development of EAH. Pre- and post-race weight and serum sodium concentrations were measured in addition to obtaining answers to a post-race questionnaire on hydration during the event.

Only 3% of participants (N=167), 4 women and 1 man, developed EAH, and no marathoners were symptomatic.

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What dietary changes and supplements effectively lower LDL cholesterol?

Evidence-Based Answer
A low-fat diet reduces low-density lipoprotein cholesterol (LDL-C), especially when the diet is rich in unsaturated fats (SOR: A, meta-analysis). Supplementing with 2 g phytosterols or phytostanols daily, 67 g of nuts daily, and probiotics daily reduces LDL-C (SOR: B, lower quality meta-analyses).

A 2012 Cochrane review of 48 RCTs involving nearly 81,000 adult participants evaluated the effect of low-fat and modified diets on a variety of measures. Reduced-fat diets (<30% total daily calories from fat) resulted in a significant reduction in LDL-C (14 trials, N=6,971; mean difference [MD] –3.9 mg/dL; 95% CI, –5.4 to –1.9) compared with control or usual diet. Reduced and modified-fat diets (<30% total daily calories from fat with higher levels of mono- and polyunsaturated fats) also resulted in reduced LDL-C (4 trials, N=627; MD –8.1 mg/dL; 95% CI, –14 to –3.1) compared with control or usual diet.

A 2009 meta-analysis of 19 RCTs involving 1,273 participants examined the efficacy of plant sterols and stanols on lipids. Patients consumed plant sterols, plant stanols, or plant stanol esters delivered in spreads, bread, yogurt, etc, with a mean dose of 2.1 g/d. The duration of the trials ranged from 3 weeks to 1 year. Compared with usual diet in patients with or without hypercholesterolemia, plant sterols and stanols significantly reduced LDL-C (MD –14 mg/dL; 95% CI, –18 to –8.5).

A 2010 pooled analysis of 25 trials (16 crossover and 2 parallel-design controlled trials and 7 consecutive uncontrolled trials) with 583 patients assessed the effect of nut consumption on blood lipids in patients not taking lipid-lowering medication. Patients consumed nuts daily, and reduced LDL-C (4 trials, N=627; MD –8.1 mg/dL; 95% CI, –14 to –3.1) compared with control or usual diet.

A 2011meta-analysis of 13 RCTs with 485 patients measured the effect of a daily dose of probiotic capsules or yogurt on serum lipids. None of the participants were taking cholesterol-reducing drugs. Mean baseline LDL-C ranged from 100 to 172 mg/dL. Probiotics reduced LDL (MD –4.9 mg/dL; 95% CI, –7.9 to –1.9) compared with the control group. Only 1 RCT showed a significant difference between intervention and control groups and 10 RCTs showed only a trend toward benefit with intervention.

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Should the male partner of someone with HPV changes on cervical biopsy have androscopy?

Evidence-Based Answer
Based on limited evidence, male partners of women with human papillomavirus (HPV) infection should probably not be referred for androscopy (SOR: C, disease-oriented outcomes in cohort studies).

A prospective cohort trial examined the HPV prevalence among 30 couples in which the women had any grade of cervical intraepithelial neoplasia (CIN) and 60 couples without CIN. Women with CIN lesions had more HPV infections than women without CIN lesions (76% vs 15%; P<.01), but no difference was noted in the male partners between the 2 groups (23% vs 11%; P=.26). There were no differences in positive findings on male androscopy between the 2 groups (17% vs 15%; P=.92). Both partners were HPV positive in 23 (of 90) couples; of these, only 13% (3 of 23) of couples were positive for the same HPV type.

To study the prognostic significance of penile acetowhite staining, a large cohort of 3,210 male partners of women with either HPV infection and/or preneoplastic lesions of the lower genital tract were examined by gross examination and then androscopy with acetowhite staining. Of those men, 39% had gross HPV lesions and 3.6% had lesions identified by acetowhite staining. Only 43% of the acetowhite stained lesions were positive for HPV by cytology or biopsy and only 37% were HPV positive by DNA testing. Only 30 samples were positive by both biopsy/cytology and DNA typing.
A case-control trial of 60 married couples, half with a diagnosis of cervical cancer and half with no cervical cancer—designed to compare urine HPV testing versus genital scraping/biopsies—also reported the prevalence and concordance of HPV infection in these couples.\(^3\) Positive results for high-risk HPV (types 16 and 18) were found in 70% of women with cervical cancer and 30% of their partners, and in 17% of healthy women and 10% of their partners (\(P \leq 0.001\) comparing female cases vs female controls). No statistically significant difference was noted when comparing male cases with male controls. Additionally, this study found type-specific concordance (HPV 16) in 9 of 21 dually HPV-positive couples in the group with female cervical cancer and 1 of 5 dually HPV-positive couples in the control group (43% vs 20%; \(P\) not significant).

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How accurate is D-dimer for predicting recurrence of VTE in a patient with a history or current treatment of VTE?

**Evidence-Based Answer**

A persistently elevated D-dimer is associated with an approximate doubling of the odds of recurrent venous thromboembolism (VTE) (SOR: B, meta-analysis of and individual cohort studies). It is unclear how this information is best used clinically.

A meta-analysis of 4 cohort trials (\(N=1,539\)) evaluated the use of D-dimer as a prognostic test for recurrence of idiopathic VTE 1 month after discontinuation of oral anticoagulant therapy.\(^1\) The risk of VTE recurrence was greater in patients with persistently elevated D-dimer: 16% compared with 7.2% of patients with normal D-dimer (OR 2.4; 95% CI, 1.7–3.4). Variability between the 4 studies in D-dimer cutoff points and length of follow-up may have been potential weaknesses of this review.

A prospective cohort trial evaluated the value of D-dimer, measured at hospital discharge, for predicting recurrent VTE in patients with provoked (coagulopathies, cancer, immobilization, trauma, pregnancy, and surgery) and unprovoked acute pulmonary embolism (PE).\(^2\) The primary outcome measure was recurrent, symptomatic VTE. All patients (\(N=204\)) had a 3-month minimum treatment with vitamin K antagonists. D-dimer was tested at discharge; follow-up occurred at 3, 6, and 12 months and then every 12 months thereafter. Additionally, patients were assessed for PE by clinical history and physical examination, 12-lead electrocardiography, arterial blood gas analysis, chest x-ray examination, and lower-limb venous ultrasonography and confirmed by chest CT.

More patients with persistently elevated D-dimer experienced VTE recurrence: 21% compared with 6% for patients with decreasing D-dimer values (\(P=.001\)). This gave the D-dimer test a sensitivity of 64% and specificity of 71% (positive likelihood ratio of 2.2, negative likelihood ratio of 0.51) for all subjects and 67% and 71%, respectively, for those with unprovoked PE.\(^2\)

An observational, prospective multicenter study (\(N=355\)) examined the value of serial D-dimer testing, beginning after at least 6 months of anticoagulation therapy, for predicting recurrence in subjects with idiopathic VTE.\(^3\) At the end of anticoagulation treatment, patients with elevated D-dimer values (\(n=19\)) continued treatment and were reevaluated at 6 months. Patients with normal D-dimer values (\(n=336\)) stopped treatment and were retested 1 month later.

At 1 month, some patients (\(n=85\)) had abnormal D-dimer values and restarted anticoagulation and were seen in 3 to 6 months. Patients with a normal D-dimer value did not restart treatment, but were retested bimonthly for a year. For patients whose D-dimer value became abnormal (and remained abnormal) at 3 months, the risk of VTE recurrence was higher than in patients with persistently normal D-dimer values (22% vs 4.6%; \(P=.003\)).\(^3\)

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How does the ratio of risk to benefit change with increasing doses of ibuprofen?

Bottom line
Ibuprofen has greater analgesic efficacy with individual doses of 400 mg compared with 200 mg (SOR: A, systematic review of RCTs), but not at doses of more than 400 mg (SOR: B, single RCT). Higher cumulative daily doses of ibuprofen (>1,200–1,800 mg/d) are associated with an increased risk of cardiovascular (CV) events and more gastrointestinal (GI) complications (SOR: C, systematic review of case series).

Evidence summary
A meta-analysis and systematic review of 50 RCTs (N=3,745) compared at least 2 doses of aspirin, ibuprofen, and acetaminophen for the treatment of acute pain. Twenty trials of ibuprofen (N=2,145) compared single doses ranging from 50 to 900 mg. Of these, 16 trials demonstrated a trend toward greater analgesic benefit with a higher dose versus a lower dose. A pooled analysis of 13 trials (N=994) specifically comparing single doses of 200 mg with 400 mg found 68% of patients achieved at least 50% pain relief with the higher dose (relative benefit 1.2; 95% CI, 1.1–1.3; NNT=10).

In this meta-analysis, only 3 trials (N=790) were found that compared ibuprofen 400 mg with 800 mg. One RCT (n=200), which evaluated the analgesic efficacy of single doses of ibuprofen ranging from 400 to 800 mg after surgical molar removal, is discussed here based on its superior study design and large sample size. Pain intensity was recorded on a 4-point scale for 6 hours after extraction. Efficacy was reported as the overall pain intensity difference from baseline as a percent of total possible pain relief (%SPID). There were no differences found in summary %SPID scores, although all doses were significantly more effective than placebo (30% for placebo vs 72%, 78%, and 76% for ibuprofen 400, 600, and 800 mg, respectively; P<.05 for each intervention vs placebo).

A systematic review of observational trials investigated risk of CV events with NSAIDs. The analysis included 21 case-control trials (N=5,700 cases; 37,000 controls) and 17 cohort trials (N=26,000 person-years of exposure) of patients using ibuprofen. Eleven of these trials reported dose-effect relationships. Low-dose ibuprofen (defined as ≤1,200 mg/d in 8 trials, ≤1,600 mg/d in 1 trial; and <1,800 mg/d in 2 trials) did not increase the risk of CV events compared with placebo (RR 1.1; 95% CI, 0.96–1.2), whereas high-dose ibuprofen demonstrated an increased risk (RR 1.8; 95% CI, 1.4–2.3).

A systematic review and meta-analysis of 28 observational trials examined the risk of upper GI complications associated with various NSAIDs. Seven observational trials (N=130,000) evaluated dose-related increase of GI complications with ibuprofen. The trials’ definitions of low-medium dose of ibuprofen ranged from less than 200 mg/d to 2,400 mg/d, with 1,200 to 1,800 mg/d being most common. Compared with nonusers, users of low- to medium-doses of ibuprofen had an increased risk of GI complications (RR 2.2; 95%, CI, 1.7–2.8) as did the users of high-dose ibuprofen (RR 4.2; 95% CI, 1.8–10).

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REFERENCES
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1. Which statement regarding reflux disease in infants is true?
   - a. Thickened feeds reduce regurgitation scores
   - b. Thickened feeds have no effect on emesis
   - c. Proton pump inhibitors reduce reflux symptoms
   - d. Position changes improve esophageal pH

2. Which of the following statements about D-dimer value in predicting recurrence of venous thromboembolism (VTE) is most accurate?
   - a. A normal D-dimer identifies patients at a somewhat higher risk of VTE recurrence
   - b. A normal D-dimer identifies patients at a somewhat lower risk of VTE recurrence
   - c. A patient with a persistently elevated D-dimer has the same chance of recurrent VTE as a patient with a normal D-dimer
   - d. A patient with a persistently normal D-dimer has a higher risk of recurrent VTE than a patient with an elevated D-dimer

3. Which of the following statements is true about diet and supplements for lowering low-density lipoprotein cholesterol (LDL-C)?
   - a. Consumption of nuts significantly increases LDL-C in patients
   - b. A low-fat diet rich in unsaturated fats significantly lowers LDL-C
   - c. Probiotics have not been shown to significantly lower LDL-C in any patients
   - d. There is no significant reduction of LDL-C with consumption of phytosterols/stanols

4. Which of the following psychological interventions has been proven to be effective in managing needle-related pain and distress in children and adolescents?
   - a. Parent coaching
   - b. Hypnosis
   - c. Cognitive behavioral therapy
   - d. Preparation and information

5. What is the incidence of symptomatic exercise-associated hyponatremia among endurance athletes?
   - a. Hyponatremia does not occur in endurance sports
   - b. <2%
   - c. 3%–6%
   - d. 10%–12%

6. Which of the following is NOT recommended to decrease the spread of MRSA to household contacts of a patient with a draining abscess?
   - a. Frequent hand washing
   - b. Washing the patient’s clothes separately from others in the household
   - c. Keep the abscess covered
   - d. Washing the patient’s dishes with others in the dishwasher

7. What additional evaluation does an otherwise healthy and asymptomatic man need if his female sexual partner is diagnosed with human papillomavirus (HPV) and/or cervical intraepithelial neoplasia?
   - a. Androscopy examination with aceto white staining
   - b. Foreskin scrapings for HPV testing
   - c. Random penile biopsy for HPV testing
   - d. No specialized testing is necessary

8. Which of the following statements is CORRECT regarding findings from a study on the risks and benefits of ibuprofen?
   - a. There was no difference in pain reduction between ibuprofen 200 and 400 mg
   - b. Doses of ibuprofen ranging from 400 to 800 mg were found to have similar analgesic effects
   - c. Both low-dose and high-dose ibuprofen had increased risk of cardiovascular events compared with placebo
   - d. High doses of ibuprofen have an increased risk of gastrointestinal complications but low doses do not

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