Denosumab for osteoporosis

Bottom line

Denosumab (Prolia®) provides an alternative treatment for patients with osteoporosis that progresses despite bisphosphonate therapy, and for patients who cannot tolerate bisphosphonate therapy. Denosumab appears to be cost-effective compared with bisphosphonate therapy.

Background

Denosumab is a monoclonal antibody that inhibits osteoclast recruitment, reversibly inhibiting bone resorption by a novel pathway not shared with bisphosphonates or estrogen. Denosumab was approved by the US Food and Drug Administration in June 2010.

Evidence summary

The FREEDOM study found fewer fractures with denosumab

The Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) study evaluated 7,868 ambulatory postmenopausal women between 60 and 90 years of age with bone mineral density (BMD) T scores between −2.5 and −4.0 at the lumbar spine or hip. Participants were randomized to receive subcutaneous injections of either denosumab (60 mg) or placebo every 6 months for 36 months.12

Hip fractures (RR=0.60; 95% CI, 0.37–0.97; P=.04), nonvertebral fractures (RR=0.80; 95% CI, 0.67–0.95; P=.01), vertebral fractures (RR=0.31; 95% CI, 0.20–0.47; P<.001), and multiple (≥2) vertebral fractures (RR=0.39; 95% CI, 0.24–0.63; P<.001) were significantly reduced in the denosumab group.2

The STAND study found greater BMD with denosumab

The Study of Transitioning from AlenDronate to Denosumab (STAND) study assessed 504 ambulatory postmenopausal women at least 55 years of age with a BMD T score between −2.0 and −4.0 at the lumbar spine or hip over 12 months.3 Women were randomized to receive subcutaneous injections of either denosumab (60 mg) or placebo every 6 months plus an oral placebo once weekly or a placebo injection every 6 months plus a weekly oral alendronate (70 mg) tablet. In contrast to the FREEDOM study, all participants had been treated with alendronate for at least 6 months.

CONTINUED
In participants transitioning from alendronate to denosumab, BMD increased 1.9% (95% CI, 1.6–2.2) at the total hip at 12 months, while patients maintained on alendronate therapy had a 1.1% (95% CI, 0.76–1.3) increase. This differential increase in BMD was statistically significant. At the lumbar spine, the denosumab group increased BMD by 3.0% (95% CI, 2.6–3.4) at 12 months, compared with 1.9% for the alendronate group (95% CI, 1.4–2.3; \( P < .001 \)). Significant increases in BMD at the femoral neck and the radius were also found in the denosumab group compared with the alendronate group. Greater increases in BMD were also observed at 6 months in the denosumab group versus the alendronate group. Greater increases in BMD were also observed at 6 months in the denosumab group compared with the alendronate group. The clinical effects of this increase in BMD was not assessed in this study.

Adverse events
Common adverse events reported with denosumab included back pain, extremity pain, hypercholesterolemia, musculoskeletal pain, and cystitis. The FREEDOM study reported a greater incidence of serious cellulitis in the denosumab group (12 subjects, 0.3%) compared with the placebo group (1 subject, <0.1%) (\( P = .002 \)); however, the overall incidence of any cellulitis was not significantly different. Other significant adverse events included falls resulting in a fracture (4.5% denosumab group vs 5.7% placebo group, \( P = .02 \)), eczema (3.0% denosumab group vs 1.7% placebo group, \( P < .001 \)), and flatulence (2.2% denosumab group vs 1.4% placebo group, \( P = .008 \)).

No significant differences were noted in adverse effects between groups in the STAND study.

Although neither the FREEDOM nor STAND studies reported osteonecrosis of the jaw (ONJ), this serious complication has been reported with denosumab in 30 patients with metastatic cancer. ONJ is usually associated with dental procedures such as tooth extraction or local infection with prolonged healing. Dental examinations are recommended prior to treatment with denosumab for patients who have ONJ risk factors, including previous bisphosphonate use, immunosuppression, or poor dental history. Oral hygiene should be encouraged for patients taking denosumab.

Clinical application
Denosumab is approved for the treatment of osteoporosis in postmenopausal women at high risk for fracture and for patients who have failed or are intolerant to other osteoporosis treatments. If a dose is missed, the missed dose should be administered as soon as possible, and regular injections should be resumed 6 months later.

Calcium and vitamin D supplementation is recommended
All patients are advised to take 1,000 mg calcium and at least 400 IU vitamin D daily. Incidental hypocalcemia must be corrected prior to the initiation of denosumab. Patients with severe renal impairment (CrCl <30 mL/min) or receiving dialysis are at greater risk of hypocalcemia. The manufacturer recommends that clinicians monitor patients’ serum calcium, phosphorus, and magnesium levels.

Denosumab associated with overall cost savings
Researchers used adherence and cost data from Swedish claims reports and efficacy data from other sources, including the FREEDOM and STRAND studies, to determine relative cost-effectiveness of denosumab for osteoporosis. Although denosumab cost more compared with alternatives (425 €/year for denosumab vs 20 €/year for generic alendronate, 338 €/year for risedronate, and 415 €/year for strontium ranelate), the use of denosumab significantly increased adherence, resulting in lower cost per quality-adjusted life year and cost savings related to lower morbidity.

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REFERENCES
Dear EBP Readers,

Nowadays, men and women enter medical school in roughly equal numbers. But back when I was there, we had about 100 men and 20 women in my entering class. Probably 15 of those women were single at matriculation, and they had 4 long years to get to know their 90+ single male classmates really, really well. Not surprisingly, nearly all of the single women had married a classmate by graduation.

If we had discussed the “problem of multiple comparisons” with those 15 young women, we might have heard some interesting stories about trying to maintain personal and professional boundaries with large cohorts of wannabe suitors and the rigors of sorting through a bewildering array of options for partners. We might have heard that Jim was kinder than Harvey, Harvey was better looking than Bud, Bud was more interested in kids than Allen, and Allen—who was going into orthopedic surgery—was going to be richer than all of the others put together. Such delicious strife!

Having to make lots of comparisons is truly difficult, both in life and in research. In the academic realm the “problem of multiple comparisons” arises when you want to compare 2 groups (usually after an intervention) and you want to compare them in lots of different ways. The more things you compare, however, the more likely you will find what appear to be significant differences between the groups when, in fact, there are none.

The most rigorous fix is to state in advance the most important difference you are looking for (the primary outcome). The results of all other comparisons (secondary outcomes) should then be considered provisional. Even so, secondary outcomes should probably only be considered worthy of serious attention for P≤.01. To spark our enthusiasm, secondary outcomes have to be pretty darn amazing.

But this is exactly what you would expect. Once a young lady has set her sights on Jim, then poor Harvey, Bud, and Allen are going to have to generate some real fireworks in order to get any attention at all.

Regards,

Jon O. Neher, MD

Evidence-Based Practice / Vol. 14, No. 1
Diving for PURLs

How do we pick PURLs?
We scour sources that cover 500 journals daily for useful research evidence, and meet weekly to critically appraise and discuss studies that meet our criteria.
Here are our 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?

Probiotics decrease colic

This randomized controlled trial (RCT) enrolled 50 exclusively breastfed infants in Italy whose parents reported ≥3 hours of crying for ≥3 days during the week prior to entry. The infants were randomized to receive 5 drops of the probiotic Lactobacillus reuteri or an identical placebo, and they were followed for 21 days. The primary outcome measure was parent-reported crying times. Crying time was reduced in the probiotic group from 370 to 35 min/d; in the placebo group it was reduced from 300 to 90 min/d (P=.022) after 21 days. A total of 96% of infants in the probiotic group had a 50% reduction in crying time, compared with 71% in the placebo group; the number needed to treat to reduce crying time by 50% was 4 (P=.036).

Bottom line: L reuteri (Baby Gaia) reduces crying time in breastfed babies with symptoms of colic. While all infants cry less as they get older, the clinical significance of the results after 21 days was dramatic: 35 min of crying in the intervention group versus 90 min in the control group. We would like to see this RCT replicated, but in the meantime we see no harm in recommending this infant formula additive to parents.

Additional information can be found at: www.fpin.org/page/purlsoverview

Sibutramine increases cardiovascular events in high-risk patients

This randomized controlled trial of approximately 10,000 patients investigated the risk of the weight-loss drug, sibutramine (Meridia), on cardiovascular (CV) events in patients ≥55 years at risk for CV disease—either known CV disease or diabetes mellitus plus another CV risk factor, such as smoking or hypertension.

During a 6-week run-in period, all patients received sibutramine, and those with an elevated blood pressure or pulse during this phase were excluded. Remaining patients were randomized to sibutramine (10 or 15 mg, depending on adequacy of weight loss) or placebo, with mean duration of treatment 3.4 years.

CV event (fatal or nonfatal myocardial infarction or stroke) occurred in 11.4% of the sibutramine group and 10% of the placebo group (P=.02; the hazards ratio was 1.16 (95% confidence interval [CI], 1.03–1.31), and the number needed to harm for a CV event was 71. All-cause mortality was not significantly different.

Bottom line: Sibutramine was previously known to elevate blood pressure and heart rate, and a recommendation to avoid it in patients with CV risk factors already existed. This study confirms that recommendation.

Of note, sibutramine was withdrawn from the US market after this study was published, due to concerns about the CV effects.

Article Reviewer: Debra Stulberg, MD
Summary Author: Umang Sharma, MD

Relevant: Yes | Medical care setting: Yes
Valid: Yes | Implementable: Yes
Change in practice: No | Clinically meaningful: Yes

Additional information can be found at: www.fpin.org/page/purlsoverview
**Endometrial thickness confirmed as useful to rule out endometrial cancer**


This meta-analysis reanalyzed the performance of ultrasound in the diagnostic workup of postmenopausal bleeding. Investigators from only 13 of the 79 studies identified as relevant provided patient-level data on a total of 2,896 total patients. Endometrial cancer was diagnosed by endometrial biopsy in 259 patients (9%). The sensitivities and specificities of 3-, 4-, and 5-mm endometrial thickness are as follows:

- 3-mm cutoff: sensitivity 98%, specificity 35%
- 4-mm cutoff: sensitivity 95%, specificity 47%
- 5-mm cutoff: sensitivity 90%, specificity 54%

**Bottom line:** Ultrasound measurement of endometrial thickness using a cutoff of 4 or 5 mm is a common method of evaluating the need for endometrial biopsy in women with postmenopausal bleeding. This reanalysis using patient-level data (which should provide a more precise estimate than aggregate level data) suggests that a 3-mm cutoff would improve sensitivity. However, data from most of the eligible studies were not obtainable and thus were not included. We are not convinced of the validity of these findings and think we should not adjust our interpretation of endometrial thickness based on this study.

Article Reviewer: Mari Egan, MD  
Summary Author: Umang Sharma, MD

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**Tools to quickly identify patients with low health literacy**


This systematic review compared 6 brief instruments that screen for literacy, as compared with the gold standard—Test of Functional Health Literacy in Adults (TOFHLA), a commonly used but somewhat lengthy literacy evaluation. Two short questionnaires—the Newest Vital Sign and Medical Term Recognition Test—performed comparably to the TOFHLA. Two 1-question items, asking about a patient’s comfort with filling out medical forms or whether he or she usually asks someone else to help read medical materials, also had comparable results to the longer gold standards.

**Bottom line:** These 1-question items quickly identify patients with limited health literacy, clearly an important issue. We were unable to find any proven interventions to aid these patients once they are identified, so screening for low health literacy does not currently meet PURL standards for demonstrating an impact on “patient-oriented outcomes.” Nonetheless, it is a reasonable assumption to make and lack of evidence is not evidence against any intervention, so we think these tools may be useful to know.

Article Reviewer and Summary Author: Kate Rowland, MD

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**Peroneal tendonitis**

Inflammation of peroneal longus and/or brevis tendon or tendon sheath. Peroneal tendonitis can be difficult to distinguish from lateral ankle sprains. It is frequently missed and underdiagnosed; especially seen in runners and ballet dancers.

**Diagnostics**

Physical examination
- Tenderness along peroneal tendons
  - Particularly posterior or distal to lateral malleolus
- Assess for warmth or swelling along peroneal tendons
- Pain exacerbated by
  - Passive hind foot inversion and ankle plantar flexion
  - Resisted active hind foot eversion and ankle dorsiflexion
- Note position of forefoot and hindfoot, as cavovarus foot associated with increased peroneal injury

Diagnostic imaging
- X-rays — use to rule out fractures, hypertrophy of peroneal tubercle, or loose bodies
  - MRI is the standard for evaluating tendon disorders

**Therapeutics**

Acute treatment
- Rest, ice, NSAIDs, activity modification
- If pain is severe or for refractory cases:
  - Immobilization in CAM boot
  - Rigid ankle orthosis
  - Short leg walking cast for up to 6 weeks
- Corticosteroid injections not recommended, due to risk of tendon rupture

Long-term care
- Physical therapy, including stretching, strengthening, proprioceptive training
- If foot misaligned, consider orthotics
- Surgical consult if pain persists despite prolonged conservative treatment

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**Intrauterine growth restriction**

Intrauterine growth restriction (IUGR) is defined as a fetus with estimated weight less than the 10th percentile for gestational age. IUGR diagnosis is controversial and varies by country; this summary follows guidelines of the American Congress of Obstetricians and Gynecologists.

**Diagnostics**

Accurate gestational age is crucial.

Screen for risk factors, identify major congenital anomalies:
- Fetal karyotyping if structural abnormality, early or severe IUGR, polyhydramnios
- Infectious disease evaluation — maternal serum studies
  - Check for evidence of seroconversion (cytomegalovirus, rubella, varicella zoster virus)
- Amniotic fluid testing for viral DNA as indicated
- Thrombophilic disorder, especially if recurrent, early, or severe

Ultrasound should be done for high-risk pregnancies or those with discordant fundal heights.

Biophysical profile (BPP) and Doppler ultrasound are not indicated for initial diagnosis of IUGR.

**Therapeutics**

Appropriately timed delivery is the only intervention that improves morbidity of IUGR infant.

Antenatal surveillance — indicated once diagnosis confirmed to assess fetal growth rate, fetal well-being, and amniotic fluid volumes to minimize complications.
- Optimal methods of antenatal surveillance reviewed online
- Fetal blood sampling to assess acid–base status, to assist timing of delivery
  - 9%–14% procedure-related loss, so repeat use is limited

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What is the best method to reduce postpartum morbidity among women with prolonged obstructed labor?

Evidence-Based Answer

Intrapartum Sims' posturing of the woman on the same side as the fetal spine enhances rotation of the fetal head from occiput posterior (OP) to occiput anterior (OA) and successful vaginal delivery. (SOR: A, based on a systematic review.) Manual rotation of the fetal head from OP/occiput transverse (OT) to OA reduces cesarean section rate, third or fourth degree laceration, postpartum infection, and hemorrhage. (SOR: B, based on a single retrospective cohort study.) Vacuum-assisted vaginal delivery is associated with fewer third or fourth degree lacerations than use of forceps, regardless of head position. (SOR: B, based on a single retrospective cohort study.) In a nonhospital setting, midwife adherence to the World Health Organization (WHO) partograph leads to early hospital referral and reduces incidence of obstructed labor. (SOR: B, based on a single RCT.)

Prolonged obstructed labor refers to slow or absent progress of labor caused by structural factors, which can result in significant maternal morbidity.

In 2007, a systematic review of 5 RCTs examined the effect of maternal posturing (antepartum or intrapartum) on successful rotation of the fetus from the OP to OA position.1 Of the 3 studies that looked at the efficacy of hands-and-knees posturing, 2 showed no benefit and the third study did not assess fetal position at the time of labor.

The 2 remaining studies showed improved outcomes as a result of maternal intrapartum Sims’ posturing toward the side of the fetal spine. A 1997 study compared 120 patients in the intervention group (Sims’ posture on same side of fetal spine) versus 120 in any other position. Vaginal delivery in the OA position occurred in 88.3% of intervention group compared with 20% of controls (P<.001; NNT=2). In a 2001 study, 50 patients assumed a lateral position on the same side as the fetal spine (group A) and 50 patients assumed a lateral position opposite to the side of the fetal spine (group B). Successful rotation to OA occurred in 54% of group A compared with 24% in group B (P<.005; NNT=4). Vaginal delivery occurred in 68% of group A compared with 44% in group B (P<.005).1

A recent retrospective cohort study compared mode of delivery and maternal morbidity in 3,258 women with persistent OP/OT position. Manual rotation was attempted in 731 patients during the second stage of labor, while 2,527 underwent expectant management.2

Delivery in the OA position occurred in 74% after a trial of manual rotation. The manual rotation group was less likely to deliver by cesarean section (adjusted odds ratio [AOR] 0.12; 95% CI, 0.09–0.16), experience third or fourth degree perineal laceration (AOR 0.64; 95% CI, 0.47–0.88), contract chorioamnionitis (AOR 0.68; 95% CI, 0.50–0.92), or have a postpartum hemorrhage (AOR 0.75; 95% CI, 0.62–0.98). Manual rotation was associated with an increased risk of cervical laceration (AOR 2.46; 95% CI, 1.1–5.4).2

A 2004 retrospective cohort study of 1,802 deliveries compared incidence of rectal sphincter injuries in forceps vs vacuum deliveries. The subjects were further stratified into OA (1,438) and OP (364) positions.3

OA deliveries with forceps had 53.8% rectal sphincter injuries compared to 26.6% with vacuum (OR 3.25; 95% CI, 2.52–4.21). OP deliveries with forceps had 71.6% rectal sphincter injuries compared to 33.1% with vacuum (OR 5.25; 95% CI, 3.02–9.10).3

A 2004 RCT studied the use of the WHO partograph in out-of-hospital labor management by midwives in Indonesia. The intervention group consisted of 304 women, managed by partograph and the associated management protocol. The control group consisted of 322 laboring women who were not managed by the partograph.4

In the intervention group, 55 women were referred to hospital care, compared with 30 controls (AOR 4.23; 95% CI, 2.1–8.71). Eleven women in the intervention group experienced obstructed labor, compared with 20 control subjects (AOR 0.38; 95% CI, 0.15–0.96).4

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Are adults with nocturia more likely to have obstructive sleep apnea than adults without nocturia?

**Evidence-Based Answer**

There appears to be an association between frequency of nocturia and the severity of sleep apnea in both older men and women. (SOR: B, based on 2 cohort studies.) It is unclear under what conditions a complaint of nocturia should prompt an evaluation for sleep apnea.

In a prospective cohort study, 58 independent older adults (median age 77.7 years, 76% female) with severe sleep-disordered breathing were asked to keep a voiding diary for 72 hours and then undergo a sleep study. The subjects were grouped according to their apnea-hypopnea index (AHI), defined by the number of apneas and hypopneas that occurred during each hour of sleep. Overall, 45% of subjects had an AHI <10, 36% had an AHI 10 to 24, and 19% had an AHI >25. The mean number of nocturia episodes was significantly greater in the group with an AHI >25 (2.6 episodes) than the other 2 groups (1.6–1.7 episodes; \( P = .028 \)).

In a prospective longitudinal cohort study, 100 perimenopausal women were identified with nocturia and compared with 200 women without nocturia. The women were asked to complete a questionnaire that included obstructive sleep apnea symptoms, measured using the multivariable apnea risk assessment (MAP) index. Scores on the MAP range from 0 to 1 and a mean score of 0.50 has an 80% positive predictive value for diagnosing obstructive sleep apnea. In the women with nocturia, the mean MAP index score was 0.9, compared with 0.34 in the women without nocturia (OR 2.18; 95% CI, 1.58–3.02).

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How often do you need to change a PICC line?

**Evidence-Based Answer**

There is no need to routinely change a peripherally inserted central catheter (PICC) line to prevent infections. As long as the PICC line is functioning and there is no evidence of line-associated local or systemic infection, the PICC line can remain in place until it is no longer needed. (SOR: B, based on a single RCT and an evidence-based guideline with moderate level of evidence.)

In the United States, more than 5 million central venous catheters (CVCs), including PICC lines, are used every year. Line protocols are in place to minimize serious complications, catheter-related bloodstream infection among them.

A 2004 RCT compared the routine removal of central lines (standard-of-care group) with watchful waiting in 64 stable intensive care unit (ICU) patients (80 CVCs total) with fever and suspected catheter-related infection who did not meet criteria for severe sepsis or have erythema at the insertion site. Patients in the watchful waiting group did have the catheter removed if they became hemodynamically unstable or bacteremia developed, or after 5 days of observation if the treating physician desired line removal.

In the standard-of-care group 38 of 38 CVCs were removed, compared with 16 of 42 in the watchful waiting group (\( P < .01 \)). No difference was noted in confirmed catheter-related bloodstream infections (5% in the standard-of-care group vs 7% in the watchful waiting group; \( P > .2 \)). In addition, no difference was noted in duration of hospital stay (42 vs 34 days, respectively; \( P > .2 \)) or ICU mortality (31% vs 25%, respectively; \( P > .2 \)).

An evidence-based guideline by the Hospital Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention, in conjunction with multiple professional organizations, updated a guideline on the prevention of intravascular catheter-related infections in 2002. The guideline states that replacement of CVCs—including PICC lines—is not needed to prevent catheter-related infections when catheters are functioning and have no evidence of causing local or systemic problems (level of evidence IB, moderate evidence from at least 1 or more properly randomized control trial).
The guideline also states that it is unnecessary to remove or replace a PICC line on the basis of fever alone. Catheter removal should be based on clinical judgment if infection is evident from another source or a noninfectious cause of fever is suspected (level of evidence II, based on at least 1 or more well-designed clinical trial, without randomization from cohort or case-controlled studies).2

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Which systemic opioid is best for the management of labor pain?

Evidence-Based Answer
It’s unclear. Fentanyl may provide better pain relief, but is associated with more sedation than intravenous (IV) meperidine. (SOR: A, based on a systematic review.) Remifentanil administered IV as patient-controlled analgesia (PCA) is associated with lower pain scores and fewer conversions to epidural anesthesia than IV meperidine. (SOR: C, based a small RCT and a small observational study.)

A systematic review published in 2002 examined 8 trials (5 double-blind) with 772 women comparing IV meperidine with various IV opioids, including morphine, phenazocine, fentanyl, nalbuphine, and pentazocine. Maternal pain scores were better with IV fentanyl compared with IV meperidine, but this difference was small (WMD −0.20; 95% CI, −0.34 to −0.06). However, more women who took fentanyl reported sedation (20% vs 0%, P=.04). Overall, no other significant difference was found in maternal side effects, labor, delivery, or neonatal outcomes.1

A 2009 review examined the use of remifentanil (Ultiva®) administered by PCA for labor analgesia in 2 studies. A double-blind RCT of 43 patients compared remifentanil PCA with IV meperidine in early labor and found that visual analog pain scores were lower with remifentanil, averaging 36 vs 59 on a 100-point scale, and patient satisfaction was higher, 3.9 vs 1.9 on a 4-point scale (where 1=poor and 4=excellent analgesia). This study also showed fewer patients in the remifentanil group converted to epidural analgesia (11% vs 39%). Fetal heart rates remained “reactive” in 90% of patients in the remifentanil group compared with 38% in the meperidine group. In addition, 8 patients in the meperidine group and none in the remifentanil group had an oxygen saturation of less than 95%.2

An observational study of 18 patients compared remifentanil PCA with intramuscular (IM) meperidine and showed a significantly lower median pain score with IM remifentanil (48 vs 72 on a 100-point scale).2

A 2009 review examined the use of remifentanil PCA with intramuscular (IM) meperidine and showed a significantly lower median pain score with IM remifentanil (48 vs 72 on a 100-point scale).2

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What is the value of a clinical impression of costochondritis in the evaluation of chest pain?

Evidence-Based Answer
Among adult patients presenting to the emergency department with chest pain, approximately 6% of those with tenderness on chest wall examination will be diagnosed with a myocardial infarction. (SOR: B, based on a cohort study.) However, receiving a diagnosis of costochondritis decreases the number of admissions and evaluations for chest pain. (SOR: C, based small observational studies.)

A prospective study enrolled 122 consecutive patients seen in an emergency department with chest pain. Costochondritis was diagnosed by the presence of pain by digital palpation of the chest wall. A total of 36 patients were diagnosed as having costochondritis and the rest of the patients (n=86) were used as controls.1

The costochondritis group had a significantly lower incidence of acute myocardial infarction than the group without costochondritis (6.25% vs 27.54%; P<.01). No significant difference was noted in the onset of pain, history of previous chest pain, risk factors for coronary artery disease, or sedimentation rate.1

A retrospective observational study followed 25 patients ultimately diagnosed with costochondritis. All had originally presented to an emergency department with chest pain and had normal cardiac enzymes and chest radiographs. The patients were identified from hospital computer records and were referred to a rheumatologist, who confirmed the diagnosis. The average time to diagnosis was 9.4 months (range 0–57 months). Healthcare utilization was significantly reduced after the diagnosis of costochondritis (TABLE).²

A cohort study evaluated 40 consecutive patients who had coronary angiography, which showed less than 30% stenosis of all major coronary arteries, who were following up at a clinic for evaluation of their (noncardiac) chest pain. They were compared with 40 controls with known coronary artery disease with at least 60% stenosis of one major coronary artery.³

Using standard rheumatologic criteria for diagnosis, patients with normal coronaries had higher prevalence of costochondritis (10% vs 0%; \(P<.04\)) and fibromyalgia (30% vs 2.5%; \(P<.04\)) compared with the control group.³

### TABLE

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Before diagnosis of costochondritis</th>
<th>After diagnosis of costochondritis</th>
<th>(P)</th>
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<tbody>
<tr>
<td>Chest pain admissions</td>
<td>39</td>
<td>6</td>
<td>&lt;.0001</td>
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<tr>
<td>Minor investigations</td>
<td>169</td>
<td>17</td>
<td>&lt;.0001</td>
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<tr>
<td>Major investigations</td>
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<tr>
<td>Inpatient days</td>
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<tr>
<td>Total expenditure (£)</td>
<td>54,122</td>
<td>2,002</td>
<td></td>
</tr>
</tbody>
</table>

Is there a difference in the absorption of omega-3 fatty acids from different sources?

**Evidence-Based Answer**

Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) absorption is similar when administered as fatty fish or supplemented through fish oils. (SOR: B, based on small RCTs.) DHA and EPA absorption may be enhanced by administering emulsified fish oil. (SOR: B, based on 2 single-dose RCTs.)

In an unblinded 16-week RCT, equivalent doses of EPA and DHA were provided to 23 patients as either 3 servings of albacore tuna and 1 serving of salmon or 17 doses of a fish oil supplement every 2 weeks (daily average combined EPA and DHA: 485 and 482 mg, respectively).¹

Both sources resulted in similar absorption at 16 weeks, as measured by the increase in EPA and DHA content in red blood cell membranes (from 4.02 to 6.17 g/100 g in the fish group vs from 4.33 to 6.16 g/100 g in the capsule group; \(P=NS\)) and the plasma phospholipid fraction (3.75 to 6.8 g/100 g vs 3.41 to 5.55 g/100 g; \(P=NS\)).¹

In contrast, in an unblinded, 8-week RCT, 71 patients received 400 g cooked salmon, smoked salmon, or cooked cod weekly, 15 mL cod liver oil (CLO) daily, or placebo. EPA increased in the serum (in mmol/L) for every gram of EPA taken daily in a linear fashion—smoked salmon: 0.26; salmon fillet: 0.39; CLO: 0.14. Similarly, DHA increased as follows—smoked salmon: 0.10; salmon fillet: 0.16; CLO: 0.04. The cooked cod and placebo groups did not have increases in serum EPA or DHA.²

In a randomized, single-dose, crossover RCT involving 10 patients, a 4-g dose of fish oil was provided as a
flavored emulsified oil and in an oil-filled capsules. The mean change in plasma phospholipid fatty acids was 0.67% with emulsified oil versus 0.45% with oil-filled capsules (P<0.01).

In a randomized, single-dose, crossover RCT, 24 patients received a mixture of fish, borage, and flaxseed oils as the natural and emulsified form. The area under the curve (AUC), measuring the extent of absorption, for EPA in plasma was 414.2 hr·mg/L with emulsified oil compared with 139.3 hr·mg/L with natural oil. The AUC for DHA in plasma was 219.4 hr·mg/L with emulsified oil compared with 97.1 hr·mg/L with natural oil.

Physical examination findings that helped differentiate pseudo-VN from true VN were a normal (negative) head impulse test of vestibulo-ocular reflex function (ie, no corrective re-fixation eye saccades after the examiner thrusts the patient's head to either side) and no unilateral paresis with caloric testing.

A subsequent prospective, cross-sectional cohort study evaluated the overall sensitivity and specificity of a 3-step bedside oculomotor examination to differentiate stroke from acute peripheral vestibular disease in patients with high risk for stroke presenting with acute onset of vertigo, nystagmus, nausea/vomiting, head-motion intolerance, and unsteady gait. The reference standard was confirmation of an acute stroke by diffusion-weighted MRI. Of the 101 patients (65% men, mean age 62 years) in this cohort, 25 had peripheral disease and 76 had a central lesion.

The combination of a normal (ie, negative) horizontal head impulse test; direction-changing nystagmus on eccentric gaze; and skew deviation (vertical ocular misalignment) was 100% sensitive and 96% specific for the presence of a central lesion (positive likelihood ratio [LR+] , 25; 95% CI, 3.7–170) and had a negative LR of 0.00 (95% CI, 0.00–0.11).

A prospective comparison study assessed the sensitivity of MRI versus noncontrast CT in 356 patients (mean age 76 years) for the detection of clinically suspected acute stroke. The study included all stroke syndromes and all patients received both tests. MRI readings included both diffusion-weighted imaging and gradient-echo imaging. Acute stroke was the final diagnosis by treating physicians in 217 patients.

Compared with the final diagnosis, MRI had a sensitivity of 83% (95% CI, 78%–88%) and a specificity of 97% (95% CI, 92%–99%). Noncontrast CT had a sensitivity of 26% (95% CI, 20%–32%) and specificity of 98% (95% CI, 93%–99%).

How are central causes of vertigo distinguished from peripheral causes?

Evidence-Based Answer

On bedside examination, the combination of a normal horizontal head impulse test, direction-changing nystagmus on eccentric gaze, and skew deviation (vertical ocular misalignment) has a high sensitivity and specificity for presence of a central lesion in vertiginous patients. (SOR: B, based on a cohort study.) For imaging, magnetic resonance imaging (MRI) is more sensitive than early MRI diffusion-weighted imaging. (SOR: C, extrapolated from a comparison cohort trial that included all stroke syndromes.)

A prospective cohort study evaluated 240 consecutive patients with isolated cerebellar stroke and identified a subset of 25 patients (10.4%; mean age 64 years, 44% women) with symptoms suggestive of vestibular neuritis (VN) rather than cerebellar stroke (pseudo-VN). Isolated spontaneous prolonged vertigo with postural imbalance were the only presenting symptoms in 24 (96%) of the 25 patients. All patients underwent MRI evaluation.
What is the minimum number of days that antibiotics should be given to a patient hospitalized with uncomplicated pneumonia?

Bottom line

Patients hospitalized with community-acquired pneumonia (CAP) should be treated for a minimum of 5 days. (SOR: A, based on meta-analysis of RCTs and an evidence-based guideline.) Clinically, it is important to realize that short-course protocols (especially with levofloxacin) often use higher daily doses than standard protocols. Patients should be afebrile for 48 to 72 hours and have symptom improvement before discontinuing treatment. (SOR: B, based on an evidence-based guideline with a moderate level of evidence.)

Review of the evidence

CAP is a common diagnosis encountered in the inpatient setting. Duration of therapy from 7 to 14 days has been traditionally recommended.¹

In 2008, a meta-analysis of 7 double-blind RCTs (5 involving adults and 2 involving children) compared short versus long antibiotic courses of therapy for CAP. The medications varied from study to study, but compared the same drug at standard dosing for different durations of treatment within each study.¹

No differences were found between short- (adults 3–7 days; children 3 days) and long-course (adults 7–10 days, children 5 days) regimens for clinical success at the end of therapy (5,107 patients [1,095 adults, 4,012 children]; OR 0.89; 95% CI, 0.74–1.07) or at later follow-up, defined as 30 to 45 days (2,762 patients; OR 0.98; 95% CI, 0.80–1.20). In the subset analysis of adult patients only, no difference was seen between short- and long-course therapy (1,095 patients; OR 0.92; 95% CI, 0.58–1.47).¹

A 2005 multicenter, randomized, double-blind, retrospective comparison trial evaluated 5- and 10-day regimens of levofloxacin in a subgroup of 177 patients aged ≥65 years with CAP. Eighty patients received levofloxacin 750 mg/d (IV/PO) for 5 days and 97 received levofloxacin 500 mg/d (IV/PO) for 10 days.²

Unadjusted clinical success rates, defined as resolution of pretherapy symptoms of CAP or improvement without a need for additional antimicrobial therapy, were comparable between the 2 groups: 89% in the 750-mg arm and 91.9% in the 500-mg arm (absolute difference 2.9%, 95% CI, –7.1 to 12.7). The odds ratio for clinical success (500 mg/10 d vs 750 mg/5 d) was 1.39 (95% CI, 0.48 to 4.03).²

Another multicenter, randomized double-blind study of 390 patients (41% hospitalized) examined the efficacy of a short-course, high-dose treatment compared with a longer course, lower dose treatment with levofloxacin IV/PO. The clinical success rates were comparable: 92.4% for the 750 mg/5 d group and 91.1% for the 500 mg/10 d group (95% CI around the difference, –7.0 to 4.4).³

Recommendation

The Infectious Diseases Society of America/American Thoracic Society released an evidence-based guideline in 2007. It recommends patients be treated for CAP for at least 5 days (quality of evidence: level I [high] based on well-conducted RCTs) and should be afebrile for 48 to 72 hours and have no more than 1 CAP-associated sign of clinical instability (temperature >37.8°C, heart rate >100 beats/min, respiratory rate >24 breaths/min, systolic blood pressure <90 mmHg, not tolerating oral intake, abnormal mental status, SaO₂ <90% on room air) before discontinuing antibiotics (quality of evidence: level II [moderate], based on well-designed controlled trials without randomization, including cohort, patient series, and case-control studies).⁴

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REFERENCES

Should we screen patients with chronic pelvic pain for depression?

Summary
In patients with chronic pelvic pain (CPP), depression is more common than in matched controls and is significantly associated with functional and social impairment and decreased quality of life. No research has specifically assessed the effect of depression treatment on outcomes for patients with CPP. However, screening for depression in such patients is recommended because of the potential effect on functioning and quality of life. (SOR: C, based on extrapolation from limited evidence.)

The evidence
CPP is defined as nonmenstrual pelvic pain lasting >6 months. The source of CPP may include the reproductive organs or the urologic, musculoskeletal, neurologic, gastroenterologic, endocrine, or myofascial systems. A psychological component may also be present in up to 80% of patients. CPP is often refractory to drug or surgical therapy. Although the overlap between depression and CPP is well known, their interaction, effect on quality of life, and implications for treatment are not well understood.

A cross-sectional controlled study that compared 52 women with CPP and 54 controls without CPP (aged 18–45 years) assessed the impact of anxiety and depression on patients’ quality of life. The intensity of pelvic pain was measured using a visual analogue scale; quality of life was measured by the World Health Organization’s Quality of Life survey (WHOQOL); and anxiety and depression were measured by the Hospital Anxiety and Depression Scale (HAD). The WHOQOL measures the domains of physical health, psychological health, social relationships, and environment, each on a 100-point scale. The HAD consists of items measuring depression and anxiety, with a total cutoff score indicating presence of the disorders.

The CPP group reported significantly more depression, as measured by the HAD (40% vs 30%; P=.027). Within the CPP group, those with depression had consistently lower WHOQOL scores than CPP patients without depression. Scores were lower by 16 points in the physical domain (P=.003), 21 points in the psychological domain (P<.0001), 17 points in the social domain (P=.0015), and 13.5 points in the environmental domain (P=.0048).

No significant correlation was noted between chronicity of pain and depression or anxiety compared to those without depression.

In a study of 1,647 OB/GYN patients aged ≥18 years (mean age, 33 years) in 7 different clinics, patients who were waiting to see their health provider were selected to self-report symptoms using the Patient Health Questionnaire (PHQ) and the 20-Item Short Form Health Survey (SF-20). The PHQ assesses DSM-IV criteria for common psychiatric disorders, including depression and anxiety. The SF-20 measures quality of life in the domains of pain, social, emotional, role-functioning, mental functioning, and physical functioning.

Overall, 29% reported moderate, severe, and very severe bodily pain (n=479), as measured by the SF-20, in the previous 4 weeks, and 21% met criteria for depression based on the PHQ. Overall, 10.3% of the sample reported having both moderate to very severe bodily pain and depression. A regression analysis showed patients with depression (OR 19; 95% CI, 12–29) and pain (OR 4.5; 95% CI, 3–6.7) were at greater risk for anxiety. Depression and pain were also associated with decreased role and social functioning, suicidal and death ideation, interpersonal stress, and functional impairment (R² 0.10–0.24).

Depression appears to affect quality of life in patients with CPP; however, additional research is needed to determine if treatment of depression would improve quality of life and outcomes in CPP. A treatment approach for CPP incorporating physical, social, and emotional symptoms is considered optimal, and screening for depression would be an important step in providing biopsychosocial treatment.

REFERENCES
What is the role of montelukast in chronic idiopathic urticaria?

Bottom line
Montelukast, a leukotriene receptor antagonist, provides mild relief but is less effective than antihistamines for treating patients with chronic idiopathic urticaria. (SOR: A, based on consistent RCTs.) Montelukast may provide additional symptom relief as add-on therapy with an antihistamine. (SOR: B, based on conflicting RCTs.)

Evidence summary
Chronic idiopathic urticaria is defined as the regular occurrence of wheals, itching, and erythema most days of the week for more than 6 weeks without an identifiable cause.

Therapy with desloratadine is better than montelukast alone
An RCT (n=160) randomized patients with moderate chronic idiopathic urticaria into 1 of 4 arms: (A) desloratadine, (B) desloratadine plus montelukast, (C) montelukast, and (D) placebo. Efficacy was measured twice daily by a total symptom score (0 to 9, with 9 corresponding to severe symptoms). Baseline symptom scores were similar among the groups (A, 6.4; B, 6.3; C, 6.9; D, 7.1).

After 6 weeks, a lower mean symptom score was observed in all treatment groups compared with placebo (A, 1.5; B, 1.5; C, 2.7; D, 3.3; ANOVA P<.05). Any therapy with desloratadine was significantly better than montelukast alone (P<.001 for each comparison). The difference in symptom scores between desloratadine and combination therapy (groups A and B) was insignificant.

The authors did not state if they used intention-to-treat analysis. A major limitation of this study was an exceptionally high dropout rate in the montelukast and placebo arms (67.5% and 87.5%, respectively).

Montelukast increases symptom relief
A double-blind RCT (n=81) compared desloratadine, desloratadine with montelukast, and placebo for patients with chronic idiopathic urticaria. Efficacy was measured by a total symptom score of 0 to 12, with 12 being the most severe.

Results from 76 patients showed that both treatment regimens achieved significant improvement in overall urticarial symptoms versus placebo after 6 weeks. The combination arm had a mean symptom score reduction of 88.5% from baseline, while the desloratadine-only arm had a 69% reduction (P<.05; NNT=5). Seventy-three percent of patients in the combination therapy arm experienced complete symptom relief, versus 16% in the desloratadine-only arm (P<.05; NNT=1.8), suggesting montelukast is effective as add-on therapy for chronic idiopathic urticaria. One patient in the combination arm, 2 in the desloratadine-only arm, and 2 in the placebo arm discontinued treatment during the first study week for various reasons.

Recommendation
Currently guidelines recommend antihistamines as first-line agents for chronic idiopathic urticaria. For patients whose urticaria is refractory to antihistamines alone, montelukast may be considered as adjunctive therapy.

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REFERENCES

Evidence-Based Practice learning objectives
1 To become knowledgeable about evidence-based solutions to commonly encountered clinical problems
2 To understand how ground-breaking research is changing the practice of family medicine
3 To become conversant with balanced appraisals of drugs that are marketed to physicians and consumers.
1. How often should Prolia be administered for the treatment of osteoporosis?
   a. Daily
   b. Monthly
   c. Every 6 months
   d. Annually

2. For a patient in labor with a fetus in the occiput posterior position:
   a. Maternal intrapartum Sims’ positioning toward the side of the fetal spine reduces cesarean section rates
   b. Use of forceps is associated with less perineal trauma than vacuum
   c. Manual rotation is associated with an increased risk of chorioamnionitis
   d. Manual rotation is associated with an increased risk of postpartum hemorrhage

3. On physical examination, a central cause for vertigo is most strongly suggested by:
   a. A normal (negative) head thrust test
   b. Presence of direction-changing nystagmus
   c. Presence of vertical ocular misalignment
   d. The combination of all of the above findings

4. Which of the following statements is true regarding eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplementation?
   a. Fish oil capsules do not increase fatty acid content of red blood cells
   b. Emulsification of fish oil may increase systemic absorption
   c. Cod fillets will increase EPA and DHA levels compared with cod liver oil
   d. Dietary intake of fish is superior to supplementation to increase EPA and DHA concentrations

5. Which statement is true regarding systemic opioids for the management of labor pain?
   a. Intravenous (IV) meperidine is the most effective parenteral narcotic agent for managing labor pain
   b. Remifentanil via patient-controlled analgesia is effective for managing labor pain
   c. Fentanyl IV is less sedating than meperidine IV
   d. Fentanyl IV is less effective than meperidine IV

6. Adults with nocturia:
   a. Should always be screened for obstructive sleep apnea
   b. May be at a higher risk for obstructive sleep apnea
   c. Are not at risk for obstructive sleep apnea
   d. Are at reduced risk for obstructive sleep apnea

7. How long should patients hospitalized with uncomplicated pneumonia be treated with antibiotics?
   a. A minimum of 14 days of total antibiotic therapy (IV/PO)
   b. A minimum of 5 days of total antibiotic therapy (IV/PO)
   c. A minimum of 3 days of IV antibiotic therapy
   d. Until the patient is afebrile for 24 hours with symptom improvement

8. When evaluating a patient for chest pain in an emergency department:
   a. Eliciting pain on palpation of the chest rules out coronary artery disease
   b. Eliciting pain on palpation of the chest reduces (but does not eliminate) the probability of coronary artery disease
   c. A prior diagnosis of costochondritis increases the chance that patients will come to the emergency department for minor chest pain episodes
   d. Patients with a history of costochondritis are more likely to have underlying atherosclerosis
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