CLINICAL INQUIRIES

From the Family Practice Inquiries Network

What interventions reduce the risk of contrast nephropathy for high-risk patients?

Evidence-Based Answer

Several interventions may reduce the risk of contrast nephropathy for high-risk patients; however, most evidence uses surrogate markers for clinically relevant outcomes. Because dehydration is a risk factor for developing contrast nephropathy, periprocedural hydration is routinely recommended (strength of recommendation [SOR]: **C**, expert opinion). Single studies have suggested that isotonic saline is associated with less risk than half-normal saline, and hydration with fluids containing sodium bicarbonate is more efficacious than those containing isotonic saline (SOR: **B**, single randomized controlled trial [RCT]).

Oral acetylcysteine lowers the risk of post-contrast elevations in creatinine if taken more than 24 hours before contrast administration (SOR: **A**, RCTs). Acetylcysteine's low cost and favorable side effect profile make it an appealing option. Hypo-osmolar contrast media are less likely to induce contrast nephropathy than hyper-osmolar media (SOR: **A**, RCTs). Finally, hemofiltration might be considered for patients with extremely high risk of developing contrast nephropathy (SOR: **B**, single RCT).

Evidence Summary

Intravascular administration of radiocontrast is frequently associated with acute reductions in renal function, particularly for patients with risk factors (**TABLE 1**). Most studies have used operational definitions of contrast nephropathy based on predefined elevations in serum creatinine from baseline, the great majority of which are transient and clinically insignificant. It is unclear if interventions that reduce the rate of mild creatinine elevations (**TABLE 2**) also reduce the risk of clinically relevant adverse outcomes.

A single RCT showed decreased risk of contrast nephropathy for patients pretreated with intravenous fluids containing sodium bicarbonate compared with those pretreated with a sodium chloride solution (number needed to treat [NNT]=8.4).[2] Another RCT showed that periprocedural hydration with isotonic saline is superior to half-normal saline in preventing contrast nephropathy (NNT=77).[3] Several studies have demonstrated decreased risk of contrast nephropa-

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What are Clinical Inquiries?

Clinical Inquiries answer recent questions from the practices of family physicians. Practicing family physicians choose the most relevant questions submitted through a web-based voting system operated by the Family Physicians Inquiries Network (FPIN; online at www.fpin.org).

FPIN is national, not-for-profit consortium of family medicine departments, community residency programs, academic health sciences libraries, primary care practice-based research networks, and other specialists. Once questions are selected, FPIN editors then organize teams of clinicians and librarians to answer them based on systematic review of the world literature. Answers are developed through an explicit, systematic method:

- FPIN librarians and editors identify questions recently answered in best evidence sources (e.g. Cochrane Reviews, Clinical Evidence, the US Preventive Services Task Force, Evidence Based Guidelines, a published systematic review).
- FPIN librarians then conduct systematic and standardized literature searches of best evidence sources, Medline, and other databases in collaboration with an FPIN clinician or clinicians. If a best evidence source has been identified, the search begins from the date of the search conducted for that source. Otherwise, the searches are comprehensive.
- FPIN clinician authors then choose the highest quality original research sources, and critically appraise the research and integrate the findings in the Evidence Based Answer and Evidence Summary section of Clinical Inquiries. Authoritative sources are also quoted in the "Recommendations from Others" section of the Clinical Inquiry.
- Each Clinical Inquiry is reviewed by 4 or more peers or editors before publication in *JFP*.
- FPIN medical librarians are accountable for the thoroughness of the literature search, for recording the databases searched, search hedges used and the search terms. The details of each search is available to any interested reader (contact managingeditor@fpin.org).
- Finally, a practicing family physician or other clinician writes an accompanying commentary to provide a clinical perspective.

TABLE 1

Risk factors for the development of contrast nephropathy

Advanced age
Diabetes mellitus
Chronic renal insufficiency
Congestive heart failure
Acute myocardial infarction
Cardiogenic shock
Renal transplant
Hemodynamic instability
Dehydration
Low serum albumin
Angiotensin-converting enzyme use
Nonsteroidal anti-inflammatory drug use
Furosemide use
Higher volume of contrast media

Source: Nikolsky et al, *Rev Cardiovasc Med* 2003.[1]

thy for high-risk patients when low-osmolality contrast media are used rather than high-osmolality contrast media (NNT=27).[4] A single study suggested that iso-osmolar contrast media generate less contrast induced nephropathy than low-osmolar contrast media.[5] Because the primary outcome in these studies was a change in serum creatinine, the NNTs listed above may not predict clinical outcomes.

Periprocedural administration of acetylcysteine reduces the risk of contrast nephropathy in high-risk patients (odds ratio=0.56; 95% confidence interval, 0.37–0.84). Oral acetylcysteine is effective if intervention is begun 24 hours before contrast administration.[6] Preliminary evidence shows that intravenous administration of acetylcysteine immediately before contrast administration lowers the risk of contrast nephropathy.[7] Oral acetylcysteine is low in cost and has no known side effects.

A single RCT suggests that hemofiltration initiated 4 to 6 hours before contrast administration reduces the incidence of contrast nephropathy among high-risk patients.[8] The study was unusual in that patients in the intervention group experienced statistically significant reductions in several clinically relevant outcomes, including in-hospital mortality and cumulative 1-year mortality (in-hospital mortality, NNT=8.3; cumulative 1-year mortality, NNT=5). Hemofiltration is expensive and is not available in many institutions.

Recommendations from Others

The American College of Radiology recommends using low-osmolality contrast media for patients with renal insufficiency, particularly those with diabetes.[9] Clinical Evidence found support for the use of low-osmolality contrast media, periprocedural hydration, and acetylcysteine as interventions to reduce the risk of contrast nephropathy.[10]

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TABLE 2

Interventions to reduce risk of contrast nephropathy

INTERVENTION	SOR	PROTOCOLS
Acetylcysteine (oral)	A	Acetylcysteine 600 mg PO twice daily is generally given for 2 days beginning on the day prior to the procedure.[6]
Hypo-osmolar contrast media	A	A variety of protocols have been demonstrated to be effective.[4]
Acetylcysteine (IV)	B	150 mg/kg of acetylcysteine was given in 500 mL of normal saline over 30 min immediately before contrast followed by 50 mg/kg of acetylcysteine in 500 mL of normal saline over 4 h.[7]
Iso-osmolar contast media	B	Varying volumes of iodixanol, an iso-osmolar contrast medium, were used rather than iohexol, a low osmolar contrast medium.[5]
Sodium bicarbonate	B	Patients were given 4.23% dextrose in H_20 with 154 mEq of sodium bicarbonate added per liter. Fluids were begun 1 hour prior to contrast administration running at 3 mL/kg/hr for 1 hour and then at 1 mL/kg/hr until 6 hours after contrast administration.[2]
Isotonic saline	B	0.9% sodium chloride was run at 1 mL/kg/hr beginning at 8 a.m. on the morning of the procedure or as early as possible prior to emergency procedures. The infusion was discontinued at 8 a.m. on the morning following the procedure.[3]
Hemofiltration	B	Hemofiltration was started 4 to 6 hours before the procedure. It was resumed after the procedure was completed and continued for 18 to 24 hours.[8]

SOR, strength of recommendation. (For more on evidence ratings, see "Evidence-based medicine terms" on page 381.

■ Clinical Commentary

Avoid radiocontrast agents when possible; consider hydration and acetylcysteine

The best prevention of contrast nephropathy is to avoid radiocontrast agents whenever possible. Ultrasound, MRI, or CT scanning without radiocontrast can often provide adequate information. However, when contrast agents must be used for high-risk patients, lower doses and iso-osmolal nonionic agents should be considered, and serial studies should be spaced out.

Adequate hydration and avoidance of drugs with renal effects, including nonsteroidal anti-inflammatory drugs, diuretics, and angiotensin-converting enzyme inhibitors, can decrease the risk of contrast nephropathy for patients requiring a contrast study. Patients can be hydrated and their medicines held starting the day before the procedure. For patients with any risk factors for contrast nephropathy, acetylcysteine should also be administered. Sodium bicarbonate can also lower the risk of nephropathy by administering it at the time of the procedure.

Contrast nephropathy has often been defined as an immediate increase in creatinine greater than 25%. The clinical significance of small transient elevations in creatinine is unclear. Furthermore, the wide variability reported in the incidence of contrast nephropathy results from differences in the presence of risk factors. Therefore, it is important to assess each patient's risk individually and undertake additional preventive measures accordingly.

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What interventions can help patients stop using chewing tobacco?

Evidence-Based Answer

Nicotine replacement therapy (NRT), including gum and patches, decreases cravings and short-term abstinence rates, but does not improve long-term abstinence (strength of recommendation [SOR]: **B**, meta-analysis of small randomized controlled studies [RCT]).

It is unclear if bupropion has an effect on cessation rates (SOR: **B**, small RCTs with conflicting results). Behavioral interventions increase abstinence rates for smokeless tobacco users (SOR: **B**, meta-analysis of small RCTs).

Evidence Summary

Use of smokeless tobacco can lead to nicotine dependence and cause periodontal disease, leukoplakia, cancer, and possibly cardiovascular disease.[1–3] Patients who abruptly stop using smokeless tobacco may experience withdrawal symptoms similar to that observed in smokers.[3]

Nicotine gum

A small double-blind study randomized 79 male smokeless tobacco users to chew nicotine gum (0 mg, 2 mg, or 4 mg) for 5 days.[4] Sixty patients completed the study. No significant differences in withdrawal symptoms, including cravings, concentration, or restlessness, were noted among the 3 groups ($P>.05$). However, further analysis demonstrated that patients with high blood levels of cotinine who received nicotine gum 2 mg experienced decreased cravings compared with placebo ($P<.001$), and a trend towards decreased cravings with 4 mg gum was noted ($P<.06$). Limitations of this study: quit rates were not reported, participants did not have to be motivated to quit smokeless tobacco in order to enroll, and it is not known if patients were counseled about the appropriate "chew and park" technique for nicotine gum.

Another study randomized 234 male smokeless tobacco users to receive group behavioral treatment plus nicotine gum 2 mg (B/NRT); group behavioral treatment plus placebo (B/Pl); minimal contact plus nicotine gum 2 mg (MC/NRT); or minimal contact plus placebo (MC/Pl).[5]

Group behavioral treatment consisted of 8 group counseling sessions 45 to 60 minutes in length; minimal contact involved 4 brief one-on-one sessions with a nurse. Patients chewed a minimum of 6 pieces of nicotine or placebo gum per day.

At 4 weeks, point prevalence abstinence rates were as follows: B/NRT, 63.6%; B/Pl, 66%; MC/NRT, 35.3%; and MC/Pl, 48.1% ($P<.01$). Abstinence rates remained significantly different at 1 and 6 month follow-ups, but not at 12 months. Post-hoc logistic regression favored group behavioral therapy plus NRT at 6 months. Moreover, survival analysis of continuous prevalence rates demonstrated that the least effective treatment was minimal contact plus NRT.

The authors theorized that nicotine gum may actually worsen risk of relapse in smokeless tobacco users due to behavioral similarities associated with use, but that behavioral treatment may help regain abstinence after a lapse. Gum users experienced lessened withdrawal symptoms including cravings, irritability, anxiety, and difficulty concentrating ($P<.01$). Results indicate that behavioral interventions may be more effective than NRT; however, low doses of nicotine gum were used.

Nicotine transdermal patches

A randomized double-blind study examined nicotine transdermal patches in smokeless tobacco users.[6] Researchers recruited 422 participants from a Minnesota college campus and surrounding metropolitan area through advertisements; they were randomly assigned to nicotine patch plus mint snuff (a nicotine-free product), nicotine patch and no mint snuff, placebo patch plus mint snuff, or placebo patch and no mint snuff. The patch was dosed as 21-mg patch for 6 weeks, 14-mg patch for 2 weeks, and 7-mg patch for 2 weeks. All patients participated in 8 weekly individual 10-minute sessions with a therapist.

Continuous 10-week abstinence rates were 69% for nicotine patch and mint snuff, 58% for nicotine patch and no mint snuff, 46% for placebo patch and mint snuff, and 51% for placebo patch and no mint snuff ($P=.002$). After 15 weeks the abstinence rates were no longer different between the treatment groups. Patch users experienced lower total withdrawal scores ($P=.002$) as well as decreased craving ($P<.001$), irritability ($P<.001$), and restlessness ($P=.019$). Total with-

drawal scores were not improved for mint snuff users; however, subsets of total withdrawal scores were lower for cravings (P=.005), irritability (P=.046), and anxiety (P=.012).

Meta-analysis

The Cochrane Database of Systematic Reviews published a meta-analysis of 6 studies that examined NRT or bupropion in smokeless tobacco users.[3] The primary outcome for the meta-analysis was tobacco abstinence 6 months or more after the intervention. Neither nicotine patches (odds ratio [OR]=1.16; 95% confidence interval [CI], 0.88–1.54) nor nicotine gum (OR=0.98; 95% CI, 0.59–1.63) were shown to improve abstinence over placebo at 6 months. The authors highlight the need for larger studies that compare different NRT products, doses, and duration.

One small randomized trial of bupropion was included, but it found no effect on tobacco abstention (OR=1.00; 95% CI, 0.23–4.37). Another small RCT found an effect; however, it was excluded from the meta-analysis because subjects were followed for only 3 months. The meta-analysis also concluded that behavioral interventions appear to be effective for increasing tobacco abstinence rates. Results were heterogeneous, and study quality was mixed. One post-hoc finding appeared to show that most effective behavioral interventions were coupled with an oral exam with direct feedback.

Recommendations from Others

The United States Department of Health and Human Services recommends that smokeless tobacco users should be treated with the same counseling and interventions utilized for smokers, but commented that evidence is currently insufficient to suggest that NRT increases long-term abstinence.[7] British guidelines concluded that no evidence clearly shows that nicotine gum or patches are effective cessation aids for smokeless tobacco users.[2]

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Clinical Commentary

NRT not recommended for smokeless users; try bupropion, behavioral therapy

Smokeless tobacco users are a special tobacco user population with a limited research base. Although it seems counterintuitive, nicotine replacement therapy (nicotine gum and the nicotine patch) is not recommended for this population. Using the tobacco use and quit history, treatment may include bupropion while employing standard behavioral therapies: intra-treatment social support, extra-treatment social support, and problem solving skills training. After setting a quit date, prepare the patient for the quit, and following the quit attempt focus on relapse prevention. Frequent follow-up visits provide intra-treatment social support and promotes development of extra-treatment (eg, telephone or computer based quit lines or individuals) social support while providing practical problem solving.

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Does furosemide decrease morbidity or mortality for patients with diastolic or systolic dysfunction?

Evidence-Based Answer

No large-scale randomized, placebo-controlled trials evaluate furosemide's effect on mortality and long-term morbidity in diastolic or systolic dysfunction. In short-term studies, furosemide reduces edema, reduces hospitalizations, and improves exercise capacity in the setting of systolic dysfunction (strength of recommendation [SOR]: **B**, based upon low-quality randomized controlled trials). Furosemide and other diuretics reduce symptomatic volume overload in diastolic and systolic dysfunction (SOR: **C**, based on expert opinion).

There is potential morbidity with the use of high-dose loop diuretics (volume contraction, electrolyte disturbances, and neuroendocrine activation).[1–3] Use of high-dose loop diuretics for systolic dysfunction is associated with increased mortality, sudden death, and pump failure death (SOR: **B**, based on retrospective analyses of large-scale randomized controlled trials). However, diuretic resistance or disease severity may explain these latter findings.

Evidence Summary

Faris et al[4] conducted a meta-analysis of randomized controlled trials that used diuretics (pertanide, furosemide, furosemide-hydrochlorothiazide) in congestive heart failure (**TABLE**).[4] Of the 18 trials, 8 were placebo-controlled and 10 used active controls (diuretics vs angiotensin-converting enzyme [ACE] inhibitors, digoxin, or ibopamine, a dopamine agonist). Three placebo-controlled trials (N=221) showed an absolute risk reduction in death of 8% in diuretic-treated patients (number needed to treat [NNT]=12.5). Four placebo-controlled trials (N=448) showed a significantly lower rate of admissions for worsening failure among diuretic-treated patients (NNT=8.5), and 4 of the active-controlled trials (N=150) showed a nonsignificant trend toward decreased admissions. Six active-controlled studies (N=174) showed significantly increased exercise capacity for patients on diuretics. One of these latter trials also assessed quality of life, edema, and New York Heart Association (NYHA) class, and demonstrated no change in these outcomes in the treatment and placebo groups.[5]

The studies used in this meta-analysis had numerous shortcomings: the individual trials had small numbers of patients (N=14–139), short follow-up periods (typically 4–8 weeks), and inadequate statistical power to clearly demonstrate morbidity/mortality reductions. There was significant heterogeneity between studies. Crossover studies were included, some studies did not clearly report masking and assessment of outcome measures, and assessment of study validity was not clear. Studies employed a variety of diuretic types and doses, used different controls, and did not clarify whether patients' congestive heart failure was caused primarily by diastolic or systolic dysfunction.

It is worth noting that diuretic use also carries some risk. One large retrospective study evaluated 6796 patients using potassium-sparing diuretics vs non–potassium-sparing diuretics in the Studies of Left Ventricular Dysfunction (SOLVD) trial.[6] Rates of hospitalization or death from worsening congestive heart failure were significantly higher in the non–potassium-sparing diuretic population than in the nondiuretic population (relative risk [RR]=1.31, 95% confidence interval [CI], 1.09–1.57; number needed to harm=5.78). This increased risk was not found for patients taking potassium-sparing diuretics (RR=0.99; 95% CI, 0.76–1.30).

Another retrospective study of SOLVD patients found a significant and independent association with increased risk of arrhythmic death among patients taking non–potassium-sparing diuretics (RR=1.33; 95% CI, 1.05–1.69).[7]

A retrospective study of 1153 patients with NYHA Class III to IV heart failure, who were enrolled in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE), found high diuretic doses to be independently associated with mortality (adjusted hazard ratio [HR]=1.37; *P*=.004), sudden death (HR=1.39; *P*=.042), and pump failure death (HR=1.51; *P*=.034).[8]

The authors caution that there is no proof of causation between furosemide and death; diuretic resistance may explain the poor outcomes, or the use of loop diuretics at high doses may be proxy of more severe illness, and thus poorer outcome.

TABLE

Clinical effects of diuretics in congestive heart failure

OUTCOME	TRIAL DESCRIPTION	N	RESULTS (REPORTED AS OR)	95% CI	*P* VALUE	NNT
Death	3 placebo-controlled	221	0.25	0.07–0.84	.03	12.5
Admissions	4 placebo-controlled	448	0.31	0.15–0.62	.001	8.5
	4 active-controlled	150	0.34	0.10–1.21	.10	12.8
Exercise capacity	6 active-controlled	174	0.37	0.10–0.64	.007	*

*Unable to calculate NNT due to lack of uniform reporting of exercise times.
OR, odds ratio; CI, confidence interval; NNT, number needed to treat.
Source: Faris et al, *Int J Cardiol* 2002.[4]

Recommendations from Others

The American College of Cardiology recommends using diuretics in the setting of left ventricular systolic dysfunction and fluid retention (level of evidence [LOE]: **A**), and recommends using diuretics in diastolic dysfunction to control pulmonary congestion and peripheral edema (LOE: **C**).[9]

The European Society of Cardiology notes that no randomized controlled trials have assessed survival effects of diuretics in congestive heart failure, but recommends using diuretics for symptomatic treatment of volume overload (LOE: **A**). This society also cites evidence that diuretic use improves exercise tolerance (LOE: **B**). They recommend that diuretics be used always in addition to an ACE inhibitor, that loop diuretics be used if symptoms are more than mild and if glomerular filtration rate (GFR) <30 cc/min, and that thiazide diuretics can be used with loop diuretics for synergistic effects in severe congestive heart failure.[10]

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Clinical Commentary

Helpful in the acute setting, diuretics shouldn't be used alone chronically

Furosemide and the other loop diuretics are very satisfying to use clinically. The patient in heart failure arrives at the hospital dypsneic, cyanotic, and terrified. After a single large dose of medication, the patient diureses and begins to feel good again quite quickly.

The practitioner, however, needs to be wary of the resulting impression that diuretics are "good" for heart failure. ACE inhibitors, beta blockers, and (in severe cases) spironolactone are "good" for heart failure because they prolong lives. One must not allow diuretic therapy—started for acute decompensation—to prevent use of more important long-term medications by causing dehydration, hypotension, or electrolyte disturbances.

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What is the best treatment for gastroesophageal reflux and vomiting in infants?

Evidence-Based Answer

The literature on pediatric reflux can be divided into studies addressing clinically apparent reflux (vomiting or regurgitation) and reflux as measured by pH probe or other methods (**TABLES 1 AND 2**). Sodium alginate reduces vomiting and improves parents' assessment of symptoms (strength of recommendation [SOR]: **B**, small randomized controlled trial [RCT]). Formula thickened with rice cereal decreases the number of postprandial emesis episodes in infants with gastroesophageal reflux disease (GERD) (SOR: **B**, small RCT).

There are conflicting data on the effect of carob bean gum as a formula thickener and its effect on regurgitation frequency (SOR: **B**, small RCTs). Metoclopramide does not affect vomiting or regurgitation, but is associated with greater weight gain in infants over 3 months with reflux (SOR: **B**, low-quality RCTs).

Carob bean gum used as a formula thickener decreases reflux as measured by intraluminal impedance but not as measured by pH probe (SOR: **B**, RCT). Omeprazole and metoclopramide each improve the reflux index as measured by esophageal pH probe (SOR: **B**, RCT).

Evidence is conflicting for other commonly used conservative measures (such as positional changes) or other medications for symptomatic relief of infant GERD. There is very limited evidence or expert opinion regarding breastfed infants, particularly with regard to preservation of breastfeeding during therapy.

Evidence Summary

Regurgitation ("spitting up") and gastroesophageal reflux are common in infants. In a cross-sectional survey of 948 parents of healthy infants aged 0 to 13 months, regurgitation occurred daily in half of infants from birth to 3 months old, peaked to 67% at age 4 months, and was absent in 95% by age 12 months.[1] Gastroesophageal disease (GERD) is characterized by refractory symptoms or complications (pain, irritability, vomiting, failure to thrive, dysphagia, respiratory symptoms, or

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TABLE 1

Interventions that affect vomiting or regurgitation

INTERVENTION	TRIAL DESCRIPTION	EFFECT
Carob bean gum* 0.4 g/100 cc	Unblinded crossover RCT (n=14 infants w/regurgitation). Reflux episodes measured by intraluminal impedance and visual regurgitation score.[5]	**Improved.** *Carob bean gum:* 15 regurgitations/342 hrs. *Standard formula:* 68 *P*<.0003
	RCT, thickened vs. standard formula (n=20). Outcome: regurgitation score, parental diary.[6]	**No improvement.** *Thickened formula:* 2.2≠ 1.92 regurgitation score. *Control formula:* 3.3 ≠ 1.16. *P*=.14
	Crossover RCT (n=24). Formula thickened with carob bean gum vs rice cereal. Outcomes: symptom scores and emesis episodes[7]	**Improved.** Both groups showed improved symptom scores and decreased emesis, but carob bean gum was superior to rice cereal-thickened formula.
Sodium alginate† 225 mg/115 cc or 450 mg/225 cc	Double-blind multicenter RCT of alginate vs placebo added to formula or breast milk (n=88). Intention-to-treat analysis.[9] Funded by manufacturer. 25% dropout rate. Breastfed infants included, but results not reported separately.	**Improved.** *Alginate:* from 8.5 vomiting/regurgitation episodes to 3 per 24 h. *Placebo:* from 7 episodes to 5 per 24 h. *P*=.009
Rice cereal (see also Carob bean gum, above)	RCT of thickened vs unthickened formula (n=20). Emesis episodes per 90-min postprandial period.[4]	**Improved.** Thickened formula: 1.2 +/- 0.7 emesis episodes per 90 minutes postprandial Placebo: 3.9 +/- 0.9 emesis episodes P=0.015
Metoclopramide 0.1 mg/kg 4 times daily	Crossover RCT (n=30). Metoclopramide vs placebo for 7 days. Mean daily symptom count (included vomiting and regurgitation).[10]	**No improvement.** *Placebo:* Symptom count for Placebo 6.5 ≠ 1.3 per day Metoclopramide 5.6 ≠ 1.2 *P*=.19 Subgroup analysis infants >3 mo showed greater weight gain for treated infants.

* Used in the UK (Instant Carobel); not widely available in US
† Available in UK as Gaviscon Infant.

esophagitis) and occurs in the minority of infants with reflux.[2] This distinguishes the "happy spitter," whose parents may simply require reassurance, from infants who require treatment.

Unfortunately, most of the available studies do not make this distinction in their subjects. Also, available data primarily regard formula-fed infants, and are insufficient to make recommendations for breastfed infants. Esophageal pH probe monitoring is the gold standard for measuring reflux in research; however, its correlation with symptoms is questionable and it is infrequently used in clinical practice.[3] Therefore, recommendations are focused primarily on treating only clinically-evident reflux (emesis and regurgitation).

Five small RCTs studied the practice of using formula thickeners (**TABLES 1 AND 2**). In 1 study, formula thickened with rice cereal decreased emesis episodes.[4] Two studies of carob bean gum–thickened formula vs plain formula yielded conflicting results.[5,6] In the study showing improvement with carob bean gum, the parents were not blinded to the

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TABLE 2

Interventions that affect pH probe/measured reflux

INTERVENTION	DESCRIPTION	EFFECT
Carob bean gum* 0.4 g/100 cc	Unblinded crossover RCT (n=14 infants w/regurgitation). Reflux episodes measured by intraluminal impedance and visual regurgitation score. Limitations: unblinded; small sample size; no breastfed infants included.[5]	**Improved.** *Carob bean gum:* 536 episodes in 342 hours. *Placebo:* 647 episodes. P<.02
	RCT, thickened vs standard formula. Reflux meas. by 24-h pH probe.[6]	**No improvement.** Reflux index for thickened formula, 11.1 ± 6.1. Standard formula, 13.2 ± 4.7. *P*=.41
Rice cereal	RCT of thickened vs unthickened formula (n=20). Reflux measured by scintigraphy.[4]	**No improvement.** *Thickened formula group:* 26.8 ± 5.8 episodes per 90 min postprandial period. *Unthickened formula group:* 27.9 ± 4.0. *P*=NS.
Infant seat at 60°	RCT, positioning in infant seat vs prone. Episodes of reflux measured by pH probe.[3]	**Worsened.** *Infant seat:* 16 ± 2.4 episodes in 2 h. *Prone position:* 10 ± 2.3 episodes. *P*=.002
Head of bed at 30°	Crossover RCT (n=90). Prone position vs prone/head of bed elevated to 30°. Number and length of reflux episodes, measured by pH probe.[8]	**No improvement.** Head-elevated 6.2 ± 0.6 episodes per 2 h. Flat prone 7.8 ± 0.8 episodes per 2 h. *P*=NS. Head-elevated 17.1 ± 2.4 minutes longest episode. Flat prone 17.9 ± 2.2 minutes. *P*=NS.
Pacifier use	RCT (n=48). Seated vs prone position, with or without pacifier; reflux episodes meas. by pH probe.[3]	**Prone: Worsened** from 7.2 ± 1.1 episodes in 2 h without pacifier to 12.8 ± 2.3 w/pacifier. *P*=.04.
Omeprazole (Infants 5–10 kg: 10 mg/d; infants >10 kg: 10 mg bid)	RCT (n=30 irritable infants with reflux or esophagitis). Reflux index (% of time pH <4) meas. by pH probe and "cry/fuss time."[11]	**Irritability unchanged.** Improved pH: *Omeprazole:* Reflux index –8.9% ± 5.6. *Placebo:* Reflux Index –1.9% ± 2. *P*<.001.
Metoclopramide (0.1 mg/kg 4 times daily)	Crossover RCT (n=30). Metoclopramide vs placebo for 7 days. Reflux index measured by pH probe. Wide confidence intervals.[10]	**Improved reflux index.** *Metoclopramide:* 10.3% (95% CI, 2.4–22.8). *Placebo:* 13.4% (95% CI, 2.8–30.5). *P*<.001

treatment, which may have led to bias favoring the treatment.[5] An uncontrolled, comparative trial of carob bean gum vs rice cereal suggested superiority of carob bean gum as a thickener, although both treatments yielded improvement.[7] Carob bean gum is available in the UK as a powder (Instant Carobel) but is not widely available in the US.

Three trials studied the effects of other conservative therapies such as positional changes and pacifiers on reflux measured by pH probe; unfortunately, none assessed clinical outcomes such as emesis or regurgitation.[3] Reflux by pH probe was worsened in a trial studying the infant seat for positioning. In the trial studying elevating the head of the bed to 30° in the prone position, reflux measured by pH probe was also unchanged; prone positioning is no longer recommended due to the risk of Sudden Infant Death Syndrome (SIDS).[8] The trial of pacifier use showed improvement of reflux by pH probe when used in the seated position, but worsening in the prone position. Since pH probe does not necessarily reflect clinical symptoms, the utility of the information from these studies is limited.

Only 1 trial of drugs used to treat infant reflux

measured clinical symptoms. This large manufacturer-sponsored RCT found that sodium alginate[9] significantly reduced emesis episodes in treated infants. Sodium alginate is marketed in the UK as Gaviscon Infant. While this trial included breastfed infants, it did not report the numbers of breastfed infants in the 2 treatment groups or present data separately for breastfed infants. Small RCTs of metoclopramide[10] and omeprazole[11] show significant improvement in reflux index measured by pH probe. However, metoclopramide yielded no improvement in symptom counts, and the omeprazole study resulted in no differences in "cry-fuss time" between treatment groups.

Recommendations from Others

The North American Society for Pediatric Gastroenterology and Nutrition recommends thickening agents or a trial of hypoallergenic formula for vomiting infants.[2] They caution against prone positioning and favor proton pump inhibitors over H2 blockers for symptomatic relief and healing of esophagitis. They found insufficient evidence to recommend surgery over medication.

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Clinical Commentary

Lack of age-appropriate RCTs make evidence-based treatment difficult

Gastroesophageal reflux, defined as the passage of gastric contents into the esophagus, is one of the most common gastroesophageal problems in infants. GERD is a pathological process in infants manifested by poor weight gain, signs of esophagitis, persistent respiratory symptoms or complications, and changes in neurologic behavior. Gastroesophageal reflux generally resolves within the first year of life, as the lower esophageal sphincter mechanism matures. Traditionally, these infants have been managed conservatively with feeding schedule modifications, thickened feeds, changes in positions after feeding, and formula changes. Depending on the history and clinical presentation of an infant with GERD, more detailed evaluation and treatment may be necessary.

As per the North American Society for Pediatric Gastroenterology and Nutrition, if an upper gastrointestinal series has ruled out anatomic causes of gastroesophageal reflux, and nonpharmacologic interventions have failed, an acid suppressive agent is usually the first line of therapy. The lack of age-appropriate case definitions and randomized controlled trials, however, make it difficult for those practitioners who treat infants to have a evidence-based protocol for managing GERD.

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Does anticoagulation prevent thrombosis for persons with fractures distal to the hip?

Evidence-Based Answer

Low-molecular-weight heparin (LMWH) prophylaxis significantly reduces the total incidence of deep venous thrombosis (DVT) for patients with lower-limb fractures managed with surgical fixation and cast immobilization (strength of recommendation [SOR]: **A**, based on multiple randomized controlled studies [RCTs]). Evidence is insufficient to show whether LMWH specifically reduces the risk of clinically significant DVTs, and recommendations on its use are conflicting (SOR: **C**, based on expert opinion). Evidence is insufficient to recommend for or against warfarin prophylaxis for DVT in fractures distal to the hip (SOR: **C**, based on expert opinion).

Evidence Summary

Thrombotic complications are common in lower-limb fractures. In 1968, a prospective observational study evaluated the natural history of DVT and pulmonary embolism (PE) in tibial fractures treated with open reduction and internal fixation with early mobilization. Seventy-six consecutive patients with 79 tibial fractures were evaluated with venograms, most within 1 month of injury. The overall incidence of thrombosis was 45%. Half were minor, involving 1 to 3 of the paired deep venous trunks of the lower leg without clinical signs of embolism. Twelve patients (16%) had extensive thrombosis, involving 4 to 6 of the deep venous trunks. Three of these had nonfatal PE diagnosed clinically, and 1 had a fatal PE confirmed at autopsy. The mean age of those with extensive thrombosis or PE was 54 years, and these events were uncommon below age 25 years.[1]

Incidence of DVT and PE was also evaluated in a cohort of 102 unselected patients who underwent operative fixation for lower-limb fractures, excluding patella, ankle, and foot fractures. All underwent venography approximately 9 days after fixation and were followed clinically for 6 weeks. The overall incidence of DVT was 28% (40% with femoral shaft, 43% with tibial plateau, 22% with tibial shaft, and 12% with tibial plafond [distal articular tibia]). Four developed clinical evidence of PE during hospitalization but only 1 had objective confirmation. None of the patients showed clinical evidence of PE as outpatients.[2]

LMWH prophylaxis significantly reduced thrombosis in patients with lower-limb fractures in 3 out of 4 RCTs. The first RCT evaluated 253 patients with lower-limb fractures immobilized in plaster casts after surgical fixation. Half the patients received subcutaneous LMWH (nadroparin [Fraxiparin], a European LMWH similar to enoxaparin), and half received no thrombosis prophylaxis. Based on compression ultrasound at the time of cast removal (17 days postinjury, on average), the overall DVT incidence was 11%. Six patients (5%) receiving LMWH had DVTs vs 21 (17%) in the control group (number needed to treat [NNT]=8 to prevent 1 DVT detectible by compression ultrasound). Two thirds of patients with DVT were asymptomatic. One third had clinical signs of DVT, including 1 patient diagnosed with PE on clinical grounds. There was no difference in bleeding complications between the treatment groups.[3]

A second RCT evaluated LMWH (Mono-Embolex, a European LMWH) prophylaxis in 328 outpatients with lower limb injuries, which included fractures, severe contusions, and ligamentous injuries. All were treated nonsurgically with cast immobilization (mean=18.8 days, range=2–72 days) and 176 patients used daily LMWH injections. All underwent Doppler evaluation for leg thromboses after cast removal, and positive results were confirmed with venograms. Overall, there were no DVTs among the LMWH prophylaxis group and 7 DVTs (4.3%) in the group without LMWH prophylaxis ($P<.006$). Among those with fractures, the untreated DVT rate was 5.9% (vs 0% with LMWH prophylaxis). Those over age 40 who did not use LMWH had a DVT rate of 11.4% (vs 1.7% in younger patients). Without LMWH prophylaxis, casting for more than 10 days approximately doubled the risk of DVT compared with less than 10 days (6.1% vs 3.1%). This study did not report on the anatomic location of DVTs or if they were clinically evident.[4]

The third RCT evaluated reviparin (another European LMWH) vs placebo in 440 outpatients with lower limb injuries, of whom 293 had fractures. About half had surgical management and all

were treated with a plaster cast or brace for an average of 44 days. Most were ambulatory with crutches. All underwent venography within a week of cast removal. The DVT rate for fracture patients using reviparin was 10.4%, vs 18.2% among those without LMWH prophylaxis (absolute risk reduction=7.8%; NNT=12.8). Three fourths of the DVTs were in distal veins, and 21% of the DVTs in the LMWH patients occurred in deep veins compared with 34% in patients without. Two pulmonary emboli occurred, both in patients without LMWH prophylaxis.[5]

The final RCT evaluated tinzaparin (yet another European LMWH) in 300 adult outpatients immobilized in plaster for at least 3 weeks. Most patients (205 out of 300) underwent venography, and the overall DVT rate was 10% (tinzaparin) vs 17% (controls). Among the 150 fracture patients who underwent venography, the DVT rate was 11% (tinzaparin) vs 13% (controls). This difference was not significant, probably due to insufficient numbers. None of the DVTs was clinically detectable.[6]

In hip fracture and hip arthroplasty, warfarin and LMWH are both effective in preventing thrombosis. No studies have specifically evaluated warfarin prophylaxis in lower extremity fractures or compared it with LMWH.

Recommendations from Others

The American College of Chest Physicians (ACCP) says that LMWH prophylaxis reduces the risk of asymptomatic DVTs and is standard of care in Europe. The ACCP does not recommend thromboprophylaxis for isolated lower extremity fractures in the US because of cost and insufficient evidence of clinically important reduction in venous thromboembolism (VTE). However, ACCP lists unspecified "lower extremity or pelvic fracture" as a risk factor for VTE, and does recommend that trauma patients with at least 1 risk factor for VTE receive thromboprophylaxis. They make no recommendation about the use of warfarin.[7]

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Clinical Commentary

Although LMWH costs more than daily warfarin, it has fewer complications

LMWH has largely replaced warfarin for DVT prevention in lower extremity fractures in our clinic. Subsequently, screening for warfarin's drug-drug interactions and measuring the PT/INR levels to adjust patient doses are no longer needed. LMHW provides effective DVT prevention without laboratory monitoring. Even though LMWH costs significantly more than daily warfarin, the complications associated with warfarin use, or no prophylaxis therapy at all, could be substantially greater. We do not typically use prophylactic anticoagulation on ankle fractures, but we do routinely put high-risk patients with tibia, fibula, and femur fractures on aspirin and LMWH. In our experience, we have not had a patient develop a DVT while on LMWH prophylaxis.

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How does tissue adhesive compare with suturing for superficial lacerations?

Evidence-Based Answer

Tissue adhesives are effective and yield results comparable to those with conventional suturing of superficial, linear, and low-tension lacerations. The cosmetic outcome is similar; wound complications, such as infection and dehiscence, may be lower with tissue adhesives. Wound closure of superficial lacerations by tissue adhesives is quicker and less painful compared with conventional suturing (strength of recommendation: **A**, systematic reviews of randomized trials).

Evidence Summary

Multiple studies and reviews have compared tissue adhesives with sutures or adhesive strips for wound closure. A Cochrane review found 10 studies, which included 970 patients in the emergency-room setting. Review of these articles found no significant difference in cosmetic appearance between tissue adhesive closure and standard suture closure with a 3-month follow-up period in acute, linear wounds under low tension. Wound erythema (number needed to treat [NNT]=10) and dehiscence rates (NNT=25) were lower for tissue adhesives.[1] In the 6 studies that reported time data, treatment with tissue adhesive took 4.7 fewer minutes. In all 6 studies that reported patients' perception of pain, pain was significantly less with tissue adhesive (weighted mean difference=13.7 mm [on 100-mm scale]; 95% confidence interval [CI], –20.0 to –6.9).

A multicenter, randomized trial studied 924 wounds (383 traumatic, 541 surgical) and reported no difference in cosmetic appearance upon grading by both a clinician and the patients themselves.[2] This study was not included in the Cochrane review because of the inclusion of surgical wounds. In a clinical trial reported after the Cochrane review, Holger and colleagues[3] studied tissue adhesives against standard wound closure using either nylon or absorbable gut sutures. The study included 145 patients, 84 of whom had at least a 9-month follow-up. No significant difference was noted in a visual analog grading scale, with a 10- to 15-mm difference (out of 100 mm) considered significant.[3] Tissue adhesive closure was, on average, 5.7 minutes faster than standard wound closure with sutures for superficial lacerations. Pain outcomes in the studies showed that closure with tissue adhesive was less painful due to the lack of a need for anesthesia.[4]

Recommendations from Others

No major guidelines were found regarding the use of skin adhesives for wound closure.

Clinical Commentary

Skin adhesives offer reduced pain and less time spent closing the wound

Skin adhesives should be considered for closure of superficial cuts because skin adhesives are comparable to sutures in both cosmetic outcome and complication rates. Additionally, skin adhesives offer the patient benefits of reduced pain and less time spent in closing the wound. Although the cost of the tissue adhesives is higher than conventional sutures, follow-up visits for suture removal are not needed, reducing medical service time during the wound check visit.

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