trol, diminish the risk of gout, reduce the patient's pill burden, and possibly confer additional clinical benefits.

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1. Neogi T. Gout. N Engl J Med 2011;364:443-52.
2. Messerli FH, Makani H, Benjo A, Romero J, Alviar C, Bangalore S. Antihypertensive efficacy of hydrochlorothiazide as evaluated by ambulatory blood pressure monitoring: a meta-analysis of randomized trials. J Am Coll Cardiol 2011;57:590-600.
3. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Comparative effects of ticrynafen and hydrochlorothiazide in the treatment of hypertension. N Engl J Med 1979;301:293-7.
4. Eriksson JW, Jansson PA, Carlberg B, et al. Hydrochlorothiazide, but not candesartan, aggravates insulin resistance and causes visceral and hepatic fat accumulation: the Mechanisms for the Diabetes Preventing Effect of Candesartan (MEDICA) Study. Hypertension 2008;52:1030-7.
5. Shahinfar S, Simpson RL, Carides AD, et al. Safety of losartan in hypertensive patients with thiazide-induced hyperuricemia. Kidney Int 1999;56:1879-85. [Erratum, Kidney Int 2000;57:370.]

THE AUTHOR REPLIES: For patients with gout and untreated hypertension, I agree it would be prudent to avoid hydrochlorothiazide. Frequently, though, clinicians are faced with patients with gout who are already taking thiazide-type diuretics. Diuretics continue to be recommended as first-line agents for hypertension, given their demonstrated efficacy, which is similar to that of other agents in reducing the rates of cardiovascular end points such as coronary heart disease, congestive heart failure, and stroke, as well as their low costs and similar class effects at low doses.[1,2]

For patients taking a stable dose of a thiazide, intermittent use, as compared with consistent daily use, confers an increased risk of gout attack.[3] Given the cardiovascular risks associated with hypertension and the high prevalence of inadequate blood-pressure control,[4] I would not necessarily recommend the alteration of a regimen that is appropriately controlling a patient's hypertension. Since poorly controlled gout is most commonly related to underdosing of urate-lowering therapy and poor adherence,[5] I would optimize urate-lowering therapy before making changes that might adversely affect blood-pressure control. For patients who are refractory to appropriate maximal urate-lowering therapy, switching to an alternate antihypertensive agent (e.g., the uricosuric losartan) with close monitoring of blood-pressure control would be appropriate. Decision analysis and cost-effectiveness studies are warranted to guide optimal management.

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Since publication of her article, the author reports no further potential conflict of interest.

1. Rosendorff C, Black HR, Cannon CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. Circulation 2007;115:2761-88. [Erratum, Circulation 2007;116(5):e121.]
2. Psaty BM, Lumley T, Furberg CD. Meta-analysis of health outcomes of chlorthalidone-based vs nonchlorthalidone-based low-dose diuretic therapies. JAMA 2004;292:43-4.
3. Hunter DJ, York M, Chaisson CE, Woods R, Niu J, Zhang Y. Recent diuretic use and the risk of recurrent gout attacks: the online case-crossover gout study. J Rheumatol 2006;33:1341-5. [Erratum, J Rheumatol 2006;33:1714.]
4. Hyman DJ, Pavlik VN. Characteristics of patients with uncontrolled hypertension in the United States. N Engl J Med 2001;345:479-86. [Erratum, N Engl J Med 2002;346:544.]
5. Edwards NL. Quality of care in patients with gout: why is management suboptimal and what can be done about it? Curr Rheumatol Rep 2010 December 14 (Epub ahead of print).

Necrotizing Enterocolitis

TO THE EDITOR: In their informative review of necrotizing enterocolitis, Neu and Walker (Jan. 20 issue)[1] seem to be unduly selective in summarizing the evidence about probiotics,[2] by omitting two systematic reviews.[3,4] One review, in which methods that follow Cochrane guidelines were used to evaluate 11 randomized, controlled trials involving 2176 preterm infants, showed that probiotics reduced the rate of death from any cause by over one half (risk ratio, 0.42; 95% confidence interval [CI], 0.29 to 0.62; P<0.00001) and reduced the rate of necrotizing enterocolitis by two thirds (risk ratio, 0.35; 95% CI, 0.23 to 0.55; P<0.00001).[3] A Cochrane review showed similar effects[4] and recommended a change in practice for infants with a birth weight over 1000 g. Neu and Walker noted that there was an increased rate of sepsis in association with probiotics in one trial, but

neither meta-analysis showed an increased rate of sepsis.[3,4]

These results have implications with respect to transparency and parents' preferences.[5] If clinicians and parents remain uncertain of the evidence, further randomized trials that include a placebo control group are needed. However, institutional review boards and ethics committees should ensure that parents in the United States and elsewhere receive balanced, complete information about the risks and benefits of probiotics.[2,5]

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1. Neu J, Walker A. Necrotizing enterocolitis. N Engl J Med 2011;364:255-64.
2. Tarnow-Mordi WO, Wilkinson D, Trivedi A, Brok J. Probiotics reduce all-cause mortality and necrotizing enterocolitis: it is time to change practice. Pediatrics 2010;125:1068-70.
3. Deshpande G, Rao S, Patole S, Bulsara M. Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. Pediatrics 2010;125:921-30.
4. AlFaleh KM, Bassler D. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev 2008;1:CD005496.
5. Neu J, Shuster J. Non-administration of routine probiotics unethical — really? Pediatrics 2010;126(3):e740-e741.

TO THE EDITOR: The statement in the review by Neu and Walker that there was a higher incidence of sepsis among infants who received probiotics, especially infants with a birth weight of less than 750 g, was of concern to us. Since death is a competitive factor for sepsis, consideration of the composite outcome of sepsis or death, in addition to consideration of sepsis alone, is helpful. Table 1 summarizes the data from our trial, which evaluated the composite outcome of sepsis or death; the rate did not differ significantly between groups.[1] Hammerman, the corresponding author of another study on oral probiotics for the treatment of necrotizing enterocolitis in very-low-birth-weight infants, was kind enough to provide the original data from the clinical trial[2]; when the data from that study were combined with those from our trial, the trend was similar to that in our trial alone (Table 1).

We believe that the data are compelling and should be available to clinicians worldwide as they make their decisions regarding the use of probiotics in small preterm infants. Although the concerns of the authors and the Food and Drug Administration are noteworthy, the devastating disease burden of necrotizing enterocolitis and the relative safety of probiotics make continued delays in routine administration of probiotics increasingly difficult to justify.

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Table 1. Outcomes in Preterm Infants with Birth Weight of 750 g or Less in Trials of Oral Probiotics to Prevent Necrotizing Enterocolitis (NEC).

Outcome	Taiwan Multicenter Trial*			Combined Data†		
	Oral Probiotics (N=33)	Control (N=18)	P Value	Oral Probiotics (N=34)	Control (N=24)	P Value
	no. (%)			*no. (%)*		
Sepsis	12 (36)	1 (6)	0.02	12 (35)	6 (25)	0.4
NEC	1 (3)	2 (11)	0.24	1 (3)	4 (17)	0.06
Death	1 (3)	4 (22)	0.03	1 (3)	7 (29)	0.004
Sepsis or death	13 (39)	5 (28)	0.24	13 (38)	13 (54)	0.23
NEC or death	2 (6)	6 (33)	0.01	2 (6)	11 (46)	<0.001

* Data are from Lin et al.[1]
† Data are from Lin et al.[1] and Bin-Nun et al.[2] There were no events of NEC, sepsis, or death in the probiotics group in the study by Bin-Nun et al.

1. Lin HC, Hsu CH, Chen HL, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial. Pediatrics 2008;122:693-700.
2. Bin-Nun A, Bromker R, Wilschanski M, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight infants. J Pediatr 2005;147:192-6.

THE AUTHORS REPLY: We agree with Tarnow-Mordi et al. that several randomized, controlled trials and meta-analyses point to the possibility that the development of neonatal necrotizing enterocolitis can be prevented with the use of probiotics. There has been extensive debate as to whether the current evidence supports the routine use of probiotics for this condition. Major concerns about the inclusion of multiple probiotic preparations and about the methodology of meta-analysis, as well as about the level of evidence from the individual studies, have been expressed in the literature.[1-4] We believe that the fact that there is controversy regarding the use of probiotics should be clearly stated for parents, investigational review boards, and other interested parties. Equipoise should be maintained to allow for additional investigation through adequately powered studies that have a primary outcome of necrotizing enterocolitis. We continue to agree fully with committees on nutrition from both Europe and America that have urged caution and have proposed that additional confirmatory studies be performed before a change in practice to include the routine use of probiotics for the prevention of necrotizing enterocolitis in the neonatal intensive care units is recommended.

In response to Lin et al.: the secondary data analysis pertaining to sepsis and adjustment for death is of interest, but the concern that sepsis developed in 12 babies in the probiotic group, as compared with only 1 in the control group, remains, especially since there is no clear evidence of the cause of death in the groups. A recent study in Brazil might have suggested that there was lower mortality among babies assigned to a probiotic group, but the majority of deaths in this study occurred before the babies were even started on probiotics.[5] The cause of death for preterm infants born at an extremely low birth weight is often the removal of life support because of severe intracranial hemorrhage, which is likely to have little relevance to the use of probiotics. To determine whether there is a reasonable pathophysiological explanation to link the outcome to the use of probiotics, future studies will need to state the cause of death clearly.

As suggested in our review, before routine probiotic prophylaxis can be recommended to neonatologists, it is important to have additional evidence provided in support of efficacy, as well as information on both the short-term and long-term safety of a single agent or set of agents that is chosen for use.

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1. Deshpande G, Rao S, Patole S, Bulsara M. Updated meta-analysis of orobiotics for preventing necrotizing enterocolitis in preterm neonates. Pediatrics 2010;125:921-30.
2. Tarnow-Mordi WO, Wilkinson D, Trivedi A, Brok J. Probiotics reduce all-cause mortality and necrotizing enterocolitis: it is time to change practice. Pediatrics 2010;125:1068-70.
3. Soll RF. Probiotics: are we ready for routine use? Pediatrics 2010;125:1071-2.
4. Neu J. Routine probiotics for premature infants: let's be careful! J Pediatr 2011;158:672-4.
5. Braga TD, da Silva GA, de Lira PI, de Carvalho Lima M. Efficacy of Bifidobacterium breve and Lactobacillus casei oral supplementation on necrotizing enterocolitis in very-low-birth-weight preterm infants: a double-blind, randomized, controlled trial. Am J Clin Nutr 2011;93:81-6.

More on DSMBs

TO THE EDITOR: Merck, sponsor or financial supporter of Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) (ClinicalTrials.gov number, NCT00092677), Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) (NCT00202878), and Study of Heart and Renal Protection (SHARP) (NCT00125593), agrees with the importance of an independent data and safety monitoring board (DSMB), a point made by Drs. Drazen and Wood (July 29, 2010, issue).[1] We disagree, however, with their suggestion that Merck failed to give the DSMBs full independence, for the following three reasons:

In January 2008, the SEAS DSMB informed