Aggressive diabetes therapy: is it "best practice?"

As a family doctor critically considering the 2003 clinical practice guidelines for non–insulin-dependent diabetes mellitus,[1,2] I have a lot more questions about this "looming epidemic" according to the guidelines' revised definition of this "disease state" than I have answers. Knowing how important wellness is to my patients, I am worried about the number of them who I will now declare "ill." A lot of money will be spent to diagnose, monitor, and treat each of the identified "prediabetics" with less than clear indications that this is indeed best practice and in their best interest.

The guidelines suggest that, when compared with conventional treatment, intensive treatment aimed at lowering glycosylated hemoglobin levels toward the normal range have been associated with a reduction in microvascular complications.

In the UK Prospective Diabetes Study Group, it was hypothesized that improved blood-glucose control might reduce the incidence of diabetes-related end points by 40%. No risk reduction was seen in any of these aggregates, however. Accordingly, the study was extended. (And the aggregate end points were changed.[3])

In 1987, retinal photocoagulation and cataract extraction were added as DM-related end points to the study. Subsequently a 3% decrease in diabetes-related end points was shown, in large part due to the drop in retinal photocoagulation. After 10 years, the intensively and conventionally treated groups had similar incidence of total mortality, myocardial infarction, stroke, blindness in one eye, and renal failure.

The guidelines state: "In the UKPDS, each 1% reduction in mean A_{1c} was associated with a 36% decline in the risk of microvascular complications." "Therapy should be targeted to achieve an A_{1c} less than or equal to 7.0% in order to reduce the risk of complications." These two statements suggest that the patient-oriented evidence that matters (POEM), which is the decline in microvascular complications, can be tied to the disease-oriented evidence (DOE), which is achieving an HbA_{1c} or 7.0%, through intensive therapy. In the UKPDS, however, benefits of individual drugs were not proportional to the decrease in HbA_{1c}.

Fasting blood glucose levels appear to be directly related to cardiovascular events, with increased risk apparent at levels that are within the normal range for people without diabetes. The absolute benefit of lowering A_{1C} levels from 7.0% to 6.0% is expected to be small and must be weighed against the risk of hypoglycemia. Furthermore, the risk of hypoglycemia was threefold higher among participants receiving intensive therapy.

According to the algorithm,[1,2] your 40-year-old patients (who were well until the guidelines appeared) are to be considered for aggressive management of their "prediabetic" state, through tight control of blood sugars, early and repeated testing, and at least two medications. Consider also the impact on their ability to get private health insurance.

Perhaps advertising campaigns that are scaring people into believing that they are going to go blind, lose their legs, and harm their loved ones if they do not get tested for non–insulin-dependent diabetes mellitus at age 40 should stop. Before the clinical practice guidelines become the standard of care, the evidence should be balanced with "best practice" and our fiscal reality.

Finally, I wonder why the evidence is not presented in terms of number needed to treat (NNT), number needed to harm (NNH) in the context of the prevalence of non–insulin-dependent diabetes mellitus. Is it possible that in 2004, the evidence does not support what the 2003 clinical practice guidelines are recommending to family doctors?

—Ajantha Jayabarathan, MD, CCFP
Halifax, NS
by e-mail

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Response

I thank Dr Jayabarathan for her letter. I am delighted that the 2003 Canadian Diabetes Association guidelines[1] are raising awareness about diabetes and stimulating discussion about the management of this multifaceted chronic disease.

As Chair of the 2003 Canadian Diabetes Association's clinical practice guidelines expert committee and as a family physician, I am particularly interested in her interpretation of the guidelines. As approximately 75% of people with diabetes receive care exclusively from their family physicians,[2] special care was taken to ensure that these guidelines were relevant to family practice. Dr Jayabarathan's letter highlights some of the important challenges in treating this disease and some of the misconceptions held by the general public and physicians alike in regard to the seriousness of diabetes.

Diabetes is a major threat to public health and is a problem that is rapidly growing in Canada and indeed worldwide. The Canadian Diabetes Association estimates that more than 7% of the Canadian population (at least 2.2 million people) have diagnosed or undiagnosed diabetes.[1]

The key to stemming this epidemic and the associated morbidity is prevention and early and aggressive intervention, both of which are supported by the literature. Dr Jayabarathan appears to question the appropriateness of lowering the recommended age for screening (from 45 to 40) and use of the term "prediabetes" to describe the dysglycemic states of impaired fasting glucose and impaired glucose tolerance. Dr Jayabarathan is concerned that previously "well" patients will now be considered "ill" and wonders whether the aggressive therapies recommended by the guidelines are "in the patient's best interest."

Screening is "case finding": finding an individual with a given disease or condition. Individuals found to have prediabetes or diabetes have the opportunity to make lifestyle changes, receive treatment and regular screening to *maximize* the odds of staying well, and not developing complications. Unfortunately, this diagnosis is all too often delayed, as evidenced by the 20% to 50% of people who present with complications at diagnosis.[3,4] Yes, diabetes is an intensive disease to manage, but surely early intensive intervention to reduce the risk of premature death, cardiovascular disease, dialysis, blindness, or amputation *is* in a patient's best interest.

Dr Jayabarathan's interpretation of the UKPDS is rather unusual, and, unfortunately, a detailed response to her statements is beyond the scope of this letter. Major trials (of which the UKPDS is but one) have shown conclusively that achieving and maintaining the glycemic,[4-6] blood pressure,[7,8] and lipid[9,10] targets recommended in the guidelines can delay the onset or prevent the progression of microvascular and macrovascular complications of diabetes.

Recent data from Ontario indicate that the life expectancy of people with diabetes is 13 years less than people without diabetes,[11] with cardiovascular disease accounting for 70% to 80% of all deaths among people with diabetes.[12,13] In addition, diabetes shifts the age at which acute myocardial infarction is seen by 15 to 20 years earlier.[13] The 2003 guidelines address the centrality of the diabetes-cardiovascular connection, emphasizing not only the management of cardiovascular complications, but also their prevention. However, prevention begins with identification—hence the importance of identifying those at risk. A meta-analysis of published data from 20 studies of 95783 persons followed for 12.4 years demonstrated that a fasting glucose level of 6.1 mmol/L and 2-hour glucose level of 7.8 mmol/L were associated with a 33% and 58% increase in cardiovascular event risk, respectively, when compared with a glucose level of 4.2 mmol/L.[14] In addition, large, well-designed trials have demonstrated conclusively that diabetes can be prevented.[15-17] Identifying people with prediabetes allows family physicians and patients to intervene with strategies not only to reduce the risk of progression to frank diabetes, but also to modify cardiovascular risk factors.

Guidelines are only guidelines, and recommendations will always need to be considered in the context of individual patients. However, Canadian

patients deserve care that is founded on the best evidence available. Cost-to-benefit ratio discussions were deliberately avoided in the 2003 guidelines, as Canadian data are absent, and most literature in this area is based on economic models from other countries that are not relevant to the Canadian health care system. The evidence clearly demonstrates that early identification of risk and aggressive therapeutic interventions reduce morbidity and mortality. Yet, as Dr Jayabarathan points out, comprehensive diabetes care is expensive. It is important to note, however, that the 2003 guideline recommendations are based on evidence, not on the prevailing political approach to disease management. In 2004, it appears that policies on drug and other treatment coverage are out of step with the evidence.

Finally, Dr Jayabarathan questions whether the more than 900 references in the guidelines constitute sufficient evidence on which to base our recommendations, then suggests we should ignore the available evidence and rely on "best practice" and "fiscal realities" to guide how we manage our patients. The CDA guidelines will not satisfy her wish for a best practice guide based on cost-to-benefit ratios, but the guidelines do offer those physicians who are committed to practising evidence-based medicine a wealth of information on how to prevent, detect, and manage this complex, prevalent, and serious disease.

—Stewart B. Harris, MD, MPH, FCFP, FACPM

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Unnecessary use of ceftriaxone?

We were disappointed with the short report[1] published in the April issue of *Canadian Family Physician* advocating the broad use of parenteral ceftriaxone in cellulitis resulting from mammal bites. The authors use overly broad inclusion criteria and have no appropriate control group. They demonstrate that ceftriaxone is effective for treating cellulitis but fail to show that it has any benefit over other options, including cheaper and easier-to-use oral agents. Unnecessary use of parenteral antibiotics has been identified as a source of increased expense and emergency department visits, as well as avoidable inconvenience and discomfort for patients.[2,3]

The criteria for including patients in this series was "moderate-to-severe acute infections inflicted by dogs or cats…." The authors define moderate-to-severe as "impaired function in the limb and swelling, erythema, or purulent discharge in the bite or scratch area."[1] These criteria would include many patients with uncomplicated mild cellulitis, in addition to the moderate-to-severe infections the study claims to be targeting. The authors do not present any information (such as systemic symptoms, lymphangitis, or size of affected area) to support their claim that the patients they were treating had moderate-to-severe infections. Guidelines for grading the severity of cellulitis do exist and could be used for this purpose.[4-6]

The authors state that the results were excellent, with no hospitalizations and no complications in the patients treated with ceftriaxone. We have no idea how important this finding is. The authors present data from previous studies to suggest this represents an improvement. The historical ranges they present for both hospitalizations (0 to 35%) and complications (0 to 48%), however, are exceedingly wide and include zero. We have no way of knowing whether the populations in these previous studies are anything like the patients they treated with ceftriaxone. Given the poorly defined patient population and the lack of reasonable comparators, it is inappropriate for the authors to suggest this treatment protocol will save money through a "reduced rate of hospitalizations." No data here can reasonably support that conclusion.

Infections following animal bites do indeed harbour different pathogens than those seen in cellulitis due to other causes and do require different antimicrobials. However, following appropriate adjustment of antibiotics, the clinical course of these infections is similar.

Without evidence to suggest otherwise, we suspect many of these patients had mild-to-moderate cellulitis and would have responded well to oral antibiotics. Review of the literature suggests that 90% of patients with cellulitis will respond to appropriate initial therapy. Close follow up is indicated to ensure that the 10% that fail to respond are identified, and a decision is made regarding the initiation of parenteral therapy or referral for further assessment.

Using the "study design" and logic employed in this article, one could show that many different parenteral antibiotics treat cellulitis effectively while costing less than a day in hospital. Although ceftriaxone is the appropriate agent in cases where parenteral therapy is indicated, intravenous or intramuscular therapy is not always warranted. Parenteral antibiotics all cost much more than a course of oral therapy and are unnecessary for most patients.

—Sam G. Campbell, MB BCH, CCFP(EM)
—Merril Pauls, MD, MHSC, CCFP(EM)
Halifax, NS
by e-mail

PS: We also note the absence of any reference to whether research ethics approval was obtained before initiation of this treatment protocol.

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Response

I thank Drs Campbell and Pauls for directing us to four papers (all of which were reviews, opinions, and commentaries rather than studies) supporting our determination that parenteral, not oral, antibiotics were warranted for the initial therapy of our patients with infected dog and cat bites. All of our patients had cellulitis for more than 18 hours, severe pain, more than 5 cm breadth of erythema, a rapidly advancing edge of cellulitis, and involvement of the distal aspects of the limbs. According to the authors of the papers cited by Campbell and Pauls (their references 2 to 5), these characteristics define all of our reported patients as Grade (or Class) II to IV and as candidates for parenteral antibiotic therapy.

I agree that antibiotics must be prescribed with care to maximize benefit and minimize risk of side effects and bacterial resistance. Being careful involves choosing antibiotics that have a reasonable chance of success because they target the offending organisms and their dose and route of administration achieve effective concentrations at the site of infection. For infected animal bites, ceftriaxone satisfies both concerns.

Our paper demonstrated ceftriaxone's effectiveness as initial therapy of moderately to severely infected bites, none of which was mild or trivial when classified according to established criteria (their references 2 to 5). It might be that the newer oral fluoroquinolones are as effective as ceftriaxone, less expensive, and more convenient. But it will be important to test that hypothesis by controlled observation in case these new oral agents are less effective or less well tolerated.

—Ross A. Pennie, MD, FRCPC

Beware of "natural" products

The article "Probiotics might not be what they seem"[1] in the April issue brought to light several interesting and important points. It illustrated the unreliable nature of many so-called "natural" and "probiotic" products and the inability of Health Canada to properly regulate and enforce labeling standards. It also illustrated an interest of family physicians in an area of science that has seen exponential growth these past 5 years. Some further insight is required, however, before accepting the article's contents and conclusions.

The term probiotics is defined by a United Nations and World Health Organization Expert Panel as "Live microorganisms which when administered in adequate amounts confer a health benefit on the host."[2] Subsequent guidelines outline further what represents a probiotic.[3] Of the 10 products tested by Dr Huff, sadly none are proven probiotics. In other words, they have not been proven to confer specific health benefits as documented by peer-reviewed clinical studies. Of note, Natural Factors only claim viable count at time of manufacture, thus their claims are not strictly false, just misleading. They also state on their website that "products are manufactured according to Canadian Health Protection Branch Good Manufacturing Practices (GMP), among the highest standards in the world," which could make a purchaser conclude that they are outstanding probiotics, when in fact they have never published clinical evidence on their specific strains. The critical factor that separates good manufacturers from those using good manufacturing processes, is the excipients or encapsulation or packaging that protect the organisms from air and moisture. Some products should be refrigerated but are not for marketing presence in stores, while others could have new beadlike capsules that might not even release the organisms in the gut.

Such is the state of legislation in Canada. There are products being sold here that make illegal claims, yet they are not challenged or removed. This is especially true with Internet claims, where companies, such as Nutrition Now, reference a range of published papers, none of which used Nutrition Now strains, to suggest to consumers that their product will benefit people with high cholesterol, diarrhea, ulcerative colitis, and irritable bowel syndrome. No good data exist for probiotics in irritable bowel syndrome, so it is a pity that Nutrition Now does not spend a portion of their revenues on such clinical studies to verify any clinical benefits. At present, there is essentially only one proven probiotic product available in this country: VSL#3 for inflammatory bowel disease,[4] and possibly Fermalac, albeit with only one clinical trial on its vaginal use.[5] Thus, Dr Huff has uncovered real problems, but her final conclusion needs to be revised, as some probiotics are indeed worthy of recommending, even though few are available in Canada.

—Gregor Reid, PHD, MBA
Director, Canadian Research and Development
Centre for Probiotics,
Lawson Health Research Institute
London, Ont
—Jo-Anne Hammond, MD
London, Ont
by e-mail

Competing interest

Dr Reid's *and* **Dr Hammond's** *research receives support from the Natural Sciences and Engineering Research Council of Canada, Canadian Institutes for Health Research, and Wyeth Ayerst Canada.* **Dr Reid** *owns patents on Lactobacillus strains GR-1 and RC-14.*

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