WHAT'S HOT IN... MEDICINE , March/April 2009

The Intensive Insulin/Intensive Care Debate Waits for NICE-SUGAR

by David W. Sharp

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Just before a highly cited 2001 paper was timed out of eligibility for the Top Ten, your *Science Watch* columnist got round to a brief mention of it (15[4]: 5, September/October 2004). I refer to the article by Dr. Greta Van den Berghe and her colleagues on the use of tight glycemic control in surgical intensive-care patients (*New Engl. J. Med.*, 345[19]:1359-67, 2001). Mortality was reduced by an intensive regimen of insulin treatment (IIT) to keep blood-glucose levels at or below 110 mg/dL (6.1 mmol/L). However, when these workers looked at medical intensive-care units, the beneficial effect on mortality was not replicated (*New Engl. J. Med.*, 354[5]: 449-61, 2006). Both papers attracted a huge amount of interest, reflected in commentaries, correspondence, and citations.

Another indicator of the importance of the work of this Belgian group has been the setting up of other trials. One of these is itself now climbing the citation ladder (F.M. Brunkhorst, *et al.*, *New Engl. J. Med.*, 358 [2]:125-39, 2008); #18, total cites 80, latest count 26). This German trial looked at patients with severe sepsis in multidisciplinary intensive-care units, noting that it was in patients with sepsis that most of the mortality benefit reported in the 2001 paper had been recorded. The trial, which also compared two approaches to fluid resuscitation, was stopped early on safety grounds. On neither death rates (28-day mortality 24.7% in the IIT group and 26.0% in the conventional-therapy group) nor on a score for organ failure was there a

Medicine Top Ten Papers

Rank	Papers	Cites Sep-Oct 08	Rank Jul-Aug 08
1	R.J. Motzer, *et al.*, "Sunitinib versus interferon alfa in metastatic renal-cell carcinoma," *New Engl. J. Med.*, 356(2): 115-24, 11 January 2007. [10 institutions worldwide] *124NE	65	4
2	B. Escudier, *et al.*, "Sorafenib in advanced clear-cell renal-cell carcinoma," *New Engl. J. Med.*, 356(2): 125-34, 11 January 2007. [15 institutions worldwide] *124NE	58	2
3	S.E. Nissen, K. Wolski, "Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes," *New Engl. J. Med.*, 356(24): 2457-71, 14 June 2007. [Cleveland Clinic, OH] *178DR	50	3
4	G. Hudes, *et al.*, "Temsirolimus, interferon alpha, or both for advanced renal-cell carcinoma," *New Engl. J. Med.*, 356(22): 2271-81, 31 May 2007. [17 institutions worldwide] *172PO	47	†
5	J. Yu, *et al.*, "Induced pluripotent stem cell lines derived from human somatic cells," *Science*, 318(5858): 1917-20, 21 December 2007. [Genome Ctr. Wisconsin, Madison; U. Wisconsin, Madison] *243HE	43	1

significant difference between the two trial arms. A safety concern with IIT is that glucose concentrations may fall too far, and in this trial serious hypoglycemia was roughly four times more common in the patients given IIT.

The type of patient has varied (the latest study from Van den Berghe's group is in pediatric intensive care [D. Vlasselaers, *et al.*, *Lancet*, 373(9663): 547-56, 14 February 2009]); so has the insulin protocol, and also the method of glucose measurement, which may be important (M. G. Scott, *et al., Clin. Chem.*, 55[1]: 18-20, 2009). Last year saw the publication of a meta-analysis on data from no fewer than 29 clinical trials involving 8,432 patients (R. S. Wiener, *et al.*, *J. Am. Med. Assoc.*, 300 [8]: 934-44, 2008). This revealed no difference in in-hospital mortality between tight blood-glucose control (21.6%) and usual care (23.3%) (relative risk 0.93 with a 95% confidence interval of 0.85-1.03) and episodes of hypoglycemia were more than five times more common with IIT. In their own recent reviews Van den Berghe and colleagues agree on the need for more trials but argue that on the basis of the prevailing evidence IIT confers a benefit in sepsis "equal to the benefit found in critical illness without sepsis and critical illness generally" (*Curr. Pharm. Res.*, 14[19]: 1887-97, 2008) and elsewhere that "current evidence favors strict control of blood glucose levels to normoglycemia below 110 mg/dL" (*Horm. Res.*, 71[1]: 2-11, 2009).

6	R. Sladek, *et al.*, "A genome-wide association study identifies novel risk loci for type 2 diabetes," *Nature*, 445(7130): 881-5, 22 February 2007. [14 institutions worldwide] *138CR	39	5
7	T.M. Frayling, *et al.*, "A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity," *Science*, 316(5826): 889-94, 11 May 2007. [19 institutions worldwide] *166HM	34	†
8	L.J. Scott, *et al.*, "A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants," *Science*, 316(5829): 1341-5, 1 June 2007. [12 U.S. and Finland institutions] *173PS	31	7
9	E. Zeggini, *et al.*, "Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes," *Science*, 316(5829): 1336-41, 1 June 2007. [10 U.K. institutions] *173PS	31	6
10	L.D. Wood, *et al.*, "The genomic landscapes of human breast and colorectal cancers," *Science*, 318(5853): 1108-13, 16 November 2007. [14 institutions worldwide] *231OC	31	†

SOURCE: Thomson Reuters *Hot Papers Database*. Read the Legend.

By the end of this year the picture should be a good deal clearer. Recruitment for a trial in 6,100 patients coordinated at the George Institute for International Health in Sydney, Australia, was completed in August, 2008, and the main outcome is 90-day mortality, so the statistical analysis and even the writing up will have been well advanced as *Science Watch* goes to press. In this trial, in over 35 intensive-care units in Australasia and North America, the comparison groups had assigned target blood glucose levels of 4.5-6.0 or 8.0-10.0 mmol/L. Whatever their current views, intensive-care specialists the world over will be awaiting with keen interest the outcome of NICE-SUGAR, the name surely being preferred to Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (T.M. Merz, S. Finfer, *Minerva Anestesiol.*, 20 January 2009: e-pub ahead of print). All that is on record to date by way of results is a rate of hypoglycemic episodes (defined as a drop in blood sugar to 2.2 mmol/L or less and as a serious adverse event) of 8.0 per 100 patients in the group with the lower target blood glucose contrasting with only 0.3 per 100 in the other group (N. Clark, S. Finfer, and the NICE-SUGAR study investigators).

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KEYWORDS: SEPSIS, INTENSIVE INSULIN THERAPY, GRETA VAN DEN BERGHE, F.M. BRUNKHORST, NICE-SUGAR, HYPOGLYCEMIA.

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