9.4a Composition of Parenteral Nutrition: Glutamine Supplementation March 2013

2013 Recommendation: *Based on 9 level 1 studies and 19 level 2 studies, when parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine should be considered. However, we strongly recommend that glutamine NOT be used in critically ill patients with shock and multi-organ failure (refer to section 9.4 b Combined Parenteral and Enteral Glutamine. There are insufficient data to generate recommendations for intravenous glutamine in critically ill patients receiving enteral nutrition.*

2013 Discussion:
It was noted that with the addition of 11 new trials (Tian 2006, Zhang 2007, Ozgultekin 2008, Yang 2008, Eroglu 2009, Perez-Barcena 2010, Andrews 2011, Cekman 2011, Grau 2011, Wernerman 2011 & Ziegler 2012), there were weaker signals for a reduction in overall mortality & infectious complications and yet a strong treatment effect of IV supplemented glutamine on hospital mortality and ICU and hospital length of stay remained. It was further noted that a few large scale multicenter randomized trials of IV glutamine had failed to demonstrate a convincing positive effect (Andrews 2011, Wernerman 2011, Ziegler 2012). The committee agreed that the REDOXS study (Heyland 2012), which uses combined EN and PN glutamine supplementation at high doses, should not be included in this section due to its different intervention and patient population (shock and multi-organ failure patients). However, it was felt that the results of this 1200 patient multicentre trial, which suggested a significant safety concern, could not be ignored. Coupled with a diminished signal of benefit and a potential increase in harm, the committee downgraded the recommendation for IV glutamine to "should be considered."

2009 Recommendation: *Based on 4 level 1 studies and 13 level 2 studies, when parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine, where available, is strongly recommended. There are insufficient data to generate recommendations for intravenous glutamine in critically ill patients receiving enteral nutrition.*

2009 Discussion: The committee noted that in patients receiving PN, there was a large reduction in mortality, hospital length of stay and a moderate reduction in infectious complications associated with the use of parenteral glutamine. There was concern about the large heterogeneity seen in the aggregated data on hospital length of stay. Given the similar signals on reduced mortality and infections from majority of the studies from various settings, the likelihood of the results being replicated in other settings is good. The cost and lack of availability of parenteral glutamine limits the applicability of this intervention. The committee decided that the range of glutamine of 0.2-0.57 gm/kg/day, as used in the studies reviewed, would be reasonable (see table 1). Based on the three trials in which EN was used predominantly, whether parenteral glutamine has an effect in patients fed enterally is unknown. The effect of enteral glutamine is discussed separately (section 4.1(e)).

Semi Quantitative Scoring

Value	Definition	2009 Score (0,1,2,3)	2013 Score (0,1,2,3)
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	2 (infection) 3 (mortality)	1 (infection) 1 (mortality)
Confidence interval	95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval	3 (infection) 3 (mortality)	2 (infection) 2 (mortality)
Validity	Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of outcomes--a higher score indicates presence of more of these features in the trials appraised	2	2
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	3	1 (infection) 3 (mortality)
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	2	2
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	3	3
Generalizability	Likelihood of trial findings being replicated in other settings (low likelihood i.e. single centre =1, moderate likelihood i.e. multicentre with limited patient population or practice setting =2, high likelihood i.e. multicentre, heterogenous patients, diverse practice settings =3.	2	1
Low cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	2	2
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	0 (not available in Canada)	0 (available with difficulty)
Safety	Estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm	2	1