4.1.d Composition of Enteral Nutrition: Immune Enhancing Diets: Ornithine Ketoglutarate (OKG) March 2013

There were no new randomized controlled trials since the 2009 update and hence there are no changes to the following Summary of Evidence

Recommendation: *There are insufficient data to make a recommendation regarding the use of ornithine ketoglutarate for burn patients and other critically ill patients.*

Discussion: The committee noted the lack of a treatment effect with respect to mortality from 3 studies in burn patients. Concerns were raised re: OKG being a precursor to arginine (in addition to glutamine) and safety issues surrounding this in critically ill patients (see section 4.1 (a) Diets supplemented with arginine). The positive treatment effect on non-clinical outcomes such as improved nutrition indices and wound healing was noted, however the inconsistencies in the scoring of wound healing limits the importance of this. Given these concerns and the unknown nature of the feasibility and cost of using OKG, the committee decided not to put forward a recommendation for the use of OKG.

Semi Quantitative Scoring

Values	Definition	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	0
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	1
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
Homogeneity or Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	1
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	1
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	unknown
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, heterogeneous patients, diverse practice settings =3.	1
Cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	1
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	unknown
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	unknown

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Question: Does supplementation of enteral nutrition with ornithine ketoglutarate (OKG) result in better outcomes in the critically ill adult patient?

Summary of evidence: There were three level 2 studies that compared OKG supplementation to placebo in burn patients.

Mortality: All three studies reported on mortality and found no differences between the groups (RR 0.92, 95% CI 0.39, 2.19, p=0.9; figure 1).

Infections: Not reported.

LOS: Not reported.

Other complications: Wound healing times were significantly shorter (Coudray-Lucas $p<0.05$) and wound healing scores were significantly higher (Donati) in the groups receiving OKG. Improved nutritional indices were seen in the groups receiving OKG in all three studies [a higher increase in serum transthreytin levels from day 4-21 (Coudray-Lucas) and improved nitrogen balance, serum transthyretin and retinol binding protein was also observed in the groups receiving OKG (Donati, DeBandt)].

Conclusions:

1) No difference in mortality in critically ill burn patients receiving EN supplementation of OKG
2) EN supplementation of OKG may be associated with improved nutritional indices and may result in improved wound healing in burn patients.

Level 1 study: if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.
Level 2 study: If any one of the above characteristics are unfulfilled

Table 1. Randomized Studies Evaluating Supplementation Of Enteral Nutrition With OKG In Critically ill Patients

Study	Population	Methods (score)	Intervention	Mortality # (%) Experimental	Mortality # (%) Control	RR (CI)**	Infections # (%) Experimental	Infections # (%) Control
1)De Bandt 1998	Severe Burns ≥ 20 % - 50 % TSBA N = 54	C.Random: not sure ITT: no Blinding: no (5)	OKG 10, 20, 30 gms bolus and continuous vs. soy protein 10, 20, 30 gms* Isonitrogenous, isocaloric	5/32 (16)	2/16 (13)	1.25 (0.27,5.75)	NR	NR
2) Donati 1999	Severe Burns 20-60 % TSBA N = 60	C.Random: not sure ITT: yes Blinding: double (8)	OKG 10 gms BID via boluses for 21 days vs. placebo (20 gm maltodextrine) Non-isonitrogenous ,isocaloric	0/31 (0)	0/29 (0)	0.94 (0.02,45.8)	NR	NR
3) Coudray-Lucas 2000	Severe burns ≥ 25 % TSBA N= 49	C.Random: yes ITT: yes*** Blinding: double (8)	OKG 10 gms BID via enteral route vs. Soy protein mixture 10 gms BID for 3 weeks Isonitrogenous, isocaolric	5/25 (20)	6/24 (25)	0.08 (0.28, 2.28)	NR	NR

C.Random: Concealed randomization
ITT: Intent to treat
NR: Not reported
± : Mean ± Standard deviation
* De Bandt et al: data from the combined OKG group (i.e. continuous and bolus and all doses) is compared to the combined control group.
** RR= Relative risk, CI= Confidence intervals
*** ITT for mortality data, Non ITT for Infectious complications

Figure 1. Mortality