## 8.0 Parenteral Nutrition vs. Standard care May 2015

2015 Recommendation: *Based on 6 level 2 studies, in critically ill patients with an intact gastrointestinal tract, we recommend that parenteral nutrition not be used routinely, but early PN should be considered in nutritionally high-risk patients with a relative contraindication to early EN.*

2015 Discussion: The committee noted the inclusion of the large multicentre trial comparing the use of early PN in critically ill patients with a relative contraindication to enteral nutrition (Doig 2014). They noted that the standard of care group did not really follow standard of care as early EN was not introduced within 48 hours and 40% of the standard care group never received any artificial nutrition. When aggregated with the existing trials, the previous trend towards a reduction in infections with the use of PN was no longer seen and there were no differences in ICU, hospital or 60 days mortality between the two groups. The committee acknowledged that the previous recommendation was based on concerns about the harm from using PN and was limited to studies in which patients had an intact GI tract and hence no absolute contraindications to EN. Given the lower incidence of muscle wasting, fat loss, improvement in quality of life, possible reduction in ventilation associated with early PN and the high internal validity of the Doig 2014 study, it was agreed that a weak recommendation be made for the use of early PN is patients with an intact GI tract but a relative contraindication to EN. However, the committee was concerned this not be misconstrued to prescribe early PN in patients with a relative contraindication in the absence of considering nutritional risk. Early PN in low nutritional risk patients would not be appropriate.

2013 and 2009 Recommendation: *Based on 5 level 2 studies, in critically ill patients with an intact gastrointestinal tract, we recommend that parenteral nutrition not be used routinely.*

2013 and 2009 Discussion: The committee noted that the differences in these aggregated results compared to other meta-analyses (Simpson 2005, Peter 2005, Braunshweig 2001, Koretz 2001) were largely due to the difference in the population studied i.e. inclusion of elective surgery and other hospitalized patients. The current aggregated results in critically ill patients suggest no effect on mortality but that PN may be associated with an increase in infectious complications. Given the concerns about the possibility of harm and higher cost associated with PN when compared to standard treatment, the committee decided to put forward a recommendation against its use in patients with an intact GI tract. It is worthy to emphasize that this recommendation applies to the average critically ill patient with an intact GI tract only and does not pertain to patients with a compromised GI tract in whom PN maybe indicated. The committee noted that although the results of the meta-analysis do not support the use of PN in critically ill patients, prolonged periods of starvation (>2 weeks) is associated with poor outcomes (Sandstrom 1993).

# Semi Quantitative Scoring

| Values | Definition | Score 2009 (0,1,2,3) | Score 2015 (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 (mortality)<br>2 (complications) | 0 (mortality)<br>0 (infections) |
| 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 (mortality)<br>1 (complications) | 1 (mortality)<br>0 (complications) |
| 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 | 2 | 2 |
| Adequacy of control group | Extent to which the control group presented standard of care (large dissimilarities=1, minor dissimilarities=2, usual care=3) | 1 | 1 |
| Biological Plausibility | Consistent with understanding of mechanistic and previous clinical work (large inconsistencies=1, minimal consistencies=2, very consistent=3) | 2 | 2 |
| 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 | 3 |
| Low cost | Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU | 1 | 1 |
| Feasible | Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU | 2 | 2 |
| 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 | 1 | 2 |

## 8.0 Parenteral Nutrition vs. Standard care

Question: Compared to standard care (IV fluids, oral diet, etc.), does parenteral nutrition (PN) result in improved clinical outcomes in critically ill patients with an intact GI tract?

Summary of Evidence: From on a recent meta-analysis of PN vs. standard care in critically ill and surgical patients (Heyland et al, JAMA 1998 Dec 16;280 (23):2013-9), there were 6 out of 26 studies that included patients that would routinely be admitted to the ICU as part of their management. Two of these trials evaluated the use of combination EN + PN and hence were excluded from this section and incorporated into section 7.0 (combination EN + PN). There were 4 level 2 studies that were reviewed and two level 2 studies additionally published since the meta-analysis. The recent Australian trial of early PN was the largest and completed on patients with a relative contraindication to EN.

Mortality: When the 6 studies from this review were aggregated, PN had no effect on mortality (RR 0.92, 0.76, 1.12, p=0.40; figure 1).

Infections: Two studies (Sax 1987, Doig 2013) reported the number of patients with infectious complications and parenteral nutrition was not associated with an increase in infectious complications (RR1.20, 95% CI 0.45, 3.21, p=0.72, $I^2$=32%) (figure 2).

LOS and Ventilator days: Based on 4 studies that reported hospital length of stay, the use of parenteral nutrition had no effect on hospital stay (weighted mean difference, WMD 0.51, -6.93, 7.95, p=0.89; figure 3). Two studies reported on ventilator days and found no differences between the groups. In one study (Doig 2014), early PN patients required fewer days of invasive ventilation (7.73 vs 7.26 days per 10 patient ICU days, risk difference, 0.47; 95% CI, 0.82 to 0.11; p=.01).

Other: An improvement in nitrogen balance in the PN groups was noted in some studies (Abel 1976, Sax 1987, Reilly 1990). Two studies reported higher costs associated with the use of parenteral nutrition. The use of PN was also associated with a higher incidence of other complications (pneumonia, respiratory failure, acute renal failure and catheter related sepsis). In the Doig 2014 study, based on Subjective Global Assessment, patients in the early PN group experienced less muscle wasting (0.43 vs 0.27 score increase per week; mean difference, 0.16; 95% CI, 0.28 to 0.038; p=.01) and fat loss (0.44 vs 0.31 score increase per week; mean difference, 0.13; 95% CI, 0.25 to 0.01; p=.04). The day-60 quality of life Score was also statistically higher in the PN Group, but this was not clinically meaningfully (p=.01).

Conclusions:

1) Parenteral nutrition has no effect on mortality in critically ill patients.
2) Parenteral nutrition has no effect on infectious complications in critically ill patients.
3) Parenteral nutrition has no effect on hospital stay.
4) Parenteral nutrition was associated with less muscle wasting and less fat loss.

***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 parenteral nutrition vs. standard care in critically ill patients

| Study | Population | Methods (score) | Intervention | Mortality # (%)† | | Infections # (%)‡ | |
|---|---|---|---|---|---|---|---|
| | | | | PN | Control | PN | Control |
| 1) Abel 1976 | Malnourished cardiac surgery patients N=44 | C.Random: not sure ITT: no Blinding: no (4) | PN without lipids after surgery vs D5W | 4/20 (20) | 3/24 (12.5) | NR | NR |
| 2) Sax 1987 | Acute pancreatitis N=54 | C.Random: not sure ITT: yes Blinding: no (8) | PN with lipids after admission vs IV fluids | 1/29 (3) | 1/26 (4) | 4/29 (14) | 1/26 (4) |
| 3) Reilly 1990 | Liver transplant patients malnourished N=18 | C.Random: not sure ITT: yes Blinding: no (7) | PN with lipids after transplant vs D5W | 0/8 (0) | 2/10 (20) | NR | NR |
| 4) Sandstrom 1993 | Major surgery, trauma, 20% malnourished N=300 | C.Random: yes ITT: yes Blinding: no (10) | PN with lipids after surgery vs D5W | 12/150 (8) | 10/150 (7) | NR | NR |
| 5) Xian-Li 2005* | Severe acute pancreatitis N=69 | C.Random: yes ITT: yes Blinding: no | PN with lipids vs IV fluids | 3/21 (14) | 10/23 (44) | Infectious complications** 21 | Infectious complications** 11 |
| 6) Doig 2013 | Multicenter mixed ICUs N=1372 | C.Random: yes ITT: yes Blinding: no (12) | PN 3-in-1 bag (Kabiven G19%) goal to reach target on day 3 as per protocol vs Standard care (attending clinician selected the route, starting rate, metabolic targets, and composition of nutrition to be provided) | ICU 81/678 (11.89) Hospital 140/678 (20.6) Day 60 146/678 (21.5) | ICU 100/680 (14.66) Hospital 151/680 (22.1) Day 60 155/680 (22.8) | Any major infection 74/678 (10.9) Catheter 31/678 (4.55) Bloodstream 39/678 (5.73 Airway/lung 101/678 (14.83) Pneumonia 43/678 (6.31) | Any major infection 78/680 (10.9) Catheter 32/680 (4.55) Bloodstream 33/680 (5.73 Airway/lung 123/680 (14.83) Pneumonia 45/680 (6.31) |

Table 1. Randomized studies evaluating parenteral nutrition vs. standard care in critically ill patients (continued)

| Study | LOS days | | Ventilator days | | Cost | | Other | |
|---|---|---|---|---|---|---|---|---|
| | PN | Control | PN | Control | PN | Control | PN | Control |
| 1) Abel 1976 | Hospital<br>19 ± 6 | Hospital<br>18 ± 6 | 5.25 ± 4.8 | 3.46 ± 2.5 | $12,290 ± 1395 | $9630 ± 1562 | Post-op complications<br>16/20 (80) | 6/24 (25) |
| 2) Sax 1987 | Hospital<br>15 ± 4 | Hospital<br>10 ± 3 | NR | NR | NR | NR | Infected catheters per group<br>28 | 13 |
| 3) Reilly 1990 | Hospital<br>67.3 ± 29<br>ICU<br>3.8 ± 1.0 | Hospital<br>47.2 ± 19<br>ICU<br>6 ± 2.3 | 2.3 ± 0.9 | 3.6 ± 2.7 | NR | NR | NR | |
| 4)Sandstrom 1993 | NR | NR | NR | NR | NR | NR | NR | |
| 5) Xian-Li 2005* | 28.6 ± 6.9 | 39.1 ± 10.6 | NR | NR | NR | NR | NR | |
| 6) Doig 2013 | ICU<br>8.6 (8.2-9)<br>Hospital<br>25.4 (24.4-26.6) | ICU<br>9.3 (8.9-9.7)<br>Hospital<br>24.7 (23.7-25.8) | 7.26 (7.09 - 7.44) | 7.73 (7.55 - 7.92) | NR | NR | Muscle wasting increase in SGA score<br>0.27 | 0.43 (p =0.01)<br>Fat Loss increase in SGA score<br>0.31 0.44 (p=0.04)<br>Quality of Life Score<br>49.8 45.5 (p =0.01) |

* Only data comparing the groups receiving standard PN and IV fluids reported here.
** Not included in meta-analysis as not reported as number of patients with infections.
C.Random: concealed randomization ‡ refers to the # of patients with infections unless specified
ITT: intent to treat † hospital mortality unless otherwise specified
NR: not reported ± ( ) : mean ± Standard deviation (number)

Figure 1. Mortality

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Figure 2. Infections

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## Figure 3. Hospital LOS