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Perioperative Use of Arginine-supplemented Diets: A Systematic Review of the Evidence

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Infections are the most frequent cause of morbidity after surgery and up to 54% of all hospital-acquired infections occur in high-risk surgical populations. Infections result in prolongation of hospital stay and increased health care costs by up to $10 billion per year in the United States alone. Multifaceted efforts to prevent infection are an essential component of any surgical practice.

Surgical stress predisposes patients to immune dysfunction, placing them at higher risk of infection, risks that are increased even more if the patient is malnourished before surgical insult. Various nutrient and nutritional strategies have been studied to evaluate their effect on immune function and clinical outcomes. One pharmaconutrient that has been the center of much debate in the literature is arginine and arginine-supplemented nutritional formulas. Arginine is an amino acid involved in multiple metabolic processes. It is a precursor of the formation of polyamines and hydroxyproline, which is important for connective tissue repair, and is the precursor for the formation of nitric oxide, an important signaling molecule. In addition to these vital roles, arginine is an essential metabolic substrate for immune cells and required for normal lymphocyte function.

Arginine deficiency after surgical stress was reported more than 30 years ago, although the mechanisms behind this have until recently remained unknown. More than 20 years ago, supraphysiologic concentrations of arginine were added to the diets of critically ill and surgical patients. These diets were aimed at “enhancing immune function” and also contained increased amounts of omega-3 fatty acids, nucleotides, and other nutrients. These nutrients were eventually incorporated into commercial diets without a rigorous evaluation of their individual effects or side effects in different patient populations. In 2001, Heyland and others reported a meta-analysis suggesting that these arginine-supplemented diets were not beneficial in critically ill patients and could even potentially adversely affect outcomes in this population. In contrast, patients undergoing elective surgery appeared to exhibit a benefit, with a possible decreased rate of infection. The treatment effect of these diets was systematically different in critically ill patients compared with elective surgery patients, and it became apparent that a dedicated meta-analysis should be done separately for patients undergoing elective surgery. Although subsequent meta-analyses have recently been done, they were limited in scope, not including all pertinent articles, included unpublished and duplicate publications, and combined studies with different study designs in evaluating the role of perioperative nutrition. The purpose of this review is to provide an up-to-date systematic review on all studies of arginine-supplemented diets in elective surgical patients. With a larger database, we might be able to shed some light on the perioperative role of such diets.

METHODS
Study identification
We conducted a systematic review of the published literature to identify all relevant trials. Using text word or MeSH headings containing “randomized,” “blind,” “clinical trial,” “nutrition,” “arginine,” “glutamine,” “omega-3 fatty acids,” “fish oil,” “nucleotides,” “immune,” “immunonutrition,” we performed computerized searches for relevant articles on MEDLINE, EMBASE, BIOSIS, CINAHL electronic databases Cochrane Controlled Trials Registe: from 1990 to March 2010. We also searched our personal files and reference lists of review articles and original studies. There were no language restrictions.

Study selection criteria
Citations were classified as primary studies, review articles, or other. All primary studies were retrieved and reviewed independently. We included primary studies if they were randomized clinical trials (RCTs); studied elective surgical
in adults; compared enteral nutrition supplemented with arginine with or without other immune-modulating agents with standard enteral nutrition; and included clinically important outcomes such as mortality, infectious complications, and hospital length of stay.

To select studies with the greatest validity with respect to relative treatment effect, we included only RCTs. We excluded the studies reporting only nutritional or immunological outcomes. We defined elective surgical patients as those undergoing a scheduled surgical procedure whether they were cared for in a critical care environment or not. We excluded studies of critically ill patients who underwent urgent or emergent operations (ie, trauma, ruptured aneurysms, etc.).

Using a scoring system that we have used in previous studies, we scored the methodological quality of individual studies considering the extent to which randomization was concealed, if the study was double-blinded and the analysis was based on the intention-to-treat principle and other key features of high-quality studies, and abstracted necessary data in duplicate and independently. Disagreement in the individual scores of each of the categories (ie, 0, 1, or 2) was resolved by consensus (see Appendix, available online only, for methodological scoring tool). We attempted to contact the authors of included studies and requested additional information not contained in published articles.

Data synthesis
Among the primary outcomes of interest was the number of patients with new infectious complications. We used definitions of infectious complications as defined by the original authors, which usually included pneumonia, intra-abdominal abscess, sepsis, line sepsis, wound infection, anastomotic leak, fistula formation, and urinary tract infection. We included only infectious complications when we could abstract the number of patients with such complications. Secondary outcomes included hospital length of stay and mortality. We combined data from all studies to estimate the pooled risk ratio (RR) with 95% confidence intervals for death and infectious complications and overall weighted mean difference (WMD) with 95% confidence intervals for hospital length of stay.

All analyses, except the test for asymmetry, were conducted using Review Manager 5. Pooled RRs were calculated using the Mantel-Haenszel estimator and WMDs were estimated by the inverse variance approach. The random effects model of DerSimonian and Laird was used to estimate variances for the Mantel-Haenszel and inverse variance estimators. RRs are undefined and excluded for studies with no event in either arm. When only 1 group has 0 events then ½ was added to each cell to allow estimation. The presence of heterogeneity was tested by a weighted Mantel-Haenszel chi-square test and quantified by the ² statistic as implemented in Review Manager 5. The possibility of publication bias was assessed by generating funnel plots and testing asymmetry of outcomes using methods proposed by Rucker and colleagues. We considered p < 0.05 to be statistically significant.

We combined experimental arms for the purposes of the overall analysis for studies that randomized patients to more than 2 groups of interest. On review of the data set, we identified 2 studies that had used considerable amounts of glycine in an effort to create isonitrogenous enteral formulas in the control groups. To explore whether this amino acid supplementation affected the results of the meta-analysis, a sensitivity analysis was undertaken by repeating the analysis with these studies excluded.

Earlier hypotheses testing
In addition to the primary outcomes of interest in the overall patient groups, a priori, we identified 4 questions or subgroup analysis that we wished to explore within the context of the data set. The first was an analysis by type of surgery. As a larger number of studies were done in the context of gastrointestinal (GI) surgery, we planned to compare studies that principally enrolled patients having GI surgery and those having other surgical procedures. Second, within the group of patients having GI surgery, there seemed to be 2 different cohorts. We compared outcomes for those having only upper GI surgery with those studies that included only patients having lower GI surgery with those with mixed upper and lower GI surgery. Third, many formulations of arginine-supplemented diets have been studied. These have varying concentrations of arginine, and contain different additional supplemental agents. The most frequently used product in these studies is Impact (Nestle, Inc.). We compared studies that used Impact in the experimental group with those that used other arginine-supplemented formulations. Finally, one of the outstanding issues for perioperative supplementation is whether it is more important to give the supplements before or after the surgery, or both. Unfortunately, there has been no consistent study design used to answer this question. We grouped like studies based on whether the experimental diet was
Table 1. Classification of Studies of Perioperative Arginine-Supplemented Diets

<table>
<thead>
<tr>
<th>Experimental</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>A1</td>
<td>Arginine</td>
</tr>
<tr>
<td>B1</td>
<td>Arginine</td>
</tr>
<tr>
<td>C1</td>
<td>Arginine</td>
</tr>
<tr>
<td>C2</td>
<td>Arginine</td>
</tr>
<tr>
<td>C3</td>
<td>Arginine</td>
</tr>
<tr>
<td>D1</td>
<td>Nothing</td>
</tr>
</tbody>
</table>

Individual studies included in this meta-analysis were categorized depending on whether they were administered arginine in a preoperative or postoperative setting or both, by what was administered to the control group.

EN, enteral nutrition.

RESULTS

Initial screening for eligibility resulted in 54 published RCTs of arginine-supplementation in surgical patients. Of these, 35 included elective surgery patients only, met all other inclusion criteria, and were included in the current review (see Tables 2, 3, and 4).80-84 We excluded RCTs for the following reasons: use of nonstandard therapy in the postoperative control group (fasting/oral intake/IV fluids/omega-3 fatty acids),55-57 duplicated publications,85-87 pseudorandomization,88-89 and absence of clinically important outcomes.90-92 The authors reached 100% agreement for inclusion of articles in this systematic review. There was no clear asymmetry or suggestion of publication bias for the outcomes of infectious complications (n = 28 studies; p = 0.70), mortality (n = 21; p = 0.21) and hospital length of stay (n = 29 studies; p = 0.22) (data not shown).

Twenty-eight studies reported infectious complications on a per-patient basis. When they were combined statistically, the results showed that arginine-supplemented diets were associated with considerably reduced overall infectious complications when compared with standard formulas in surgical patients (RR = 0.59; 95% CI, 0.50–0.70; p < 0.00001; Fig. 1). The test for heterogeneity was not significant (p = 0.11, I² = 26%). When the analysis was repeated removing the 2 studies that used substantial amounts of glycine in the control group,20,21 the observations were similar (RR = 0.56; 95% CI, 0.47–0.67; p < 0.00001; test for heterogeneity p = 0.14, I² = 24%).

Overall hospital length of stay, aggregated across 29 studies, was reduced in surgical patients receiving arginine-supplemented diets when compared with patients receiving standard formulas (WMD = −2.38; 95% CI, −3.39 to −1.36; p < 0.00001; Fig. 2). The test for heterogeneity was significant, with an I² test indicating the presence of a large amount of heterogeneity (p < 0.00001, I² = 87%). When the analysis was repeated, removing the one study with glycine in the control group that reported on this variable,20 the observations were similar (WMD = −2.38; 95% CI, −3.42 to −1.34; p < 0.00001, with significant heterogeneity present (p < 0.00001, I² = 88%).

Twenty-one studies reported mortality as one of the outcomes. When their results were statistically aggregated, arginine supplemented diets did not have a significant effect on mortality (RR = 1.08; 95% CI, 0.65–1.80; p = 0.76; Fig. 3). The test for heterogeneity was not significant (p = 0.99, I² = 0%). When the analysis was repeated, removing the one study with glycine in the control group that reported on this variable, the observations were similar, as this study reported no deaths20 (RR = 1.08; 95% CI, 0.65–1.80; p = 0.76; test for heterogeneity was not significant (p = 0.99, I² = 0%).

Subgroup analyses

We compared the treatment effect in studies of GI surgery patients (n = 25) and non-GI surgery patients (n = 10) separately. Of the 25 studies of GI surgery patients, 21 clearly reported on patients with infections, and 7 of the 10 studies of non-GI surgery patients reported this. Arginine-supplemented diets were associated with reduced infectious complications in both subgroups (Fig. 4). When the data for the 21 studies in GI surgery were aggregated, RR = 0.61 (95% CI, 0.50–0.74; p < 0.00001; test for heterogeneity p = 0.09, I² = 31%) and for the 7 non-GI operations, RR = 0.51 (95% CI, 0.35–0.73; p = 0.0001; test for heterogeneity p = 0.75, I² = 0%). The differences between these subgroups was not statistically significant (p = 0.28, see Fig. 4). When the data on hospital length of stay were aggregated, arginine-supplemented diets were associated with a significant reduction in hospital length of stay in the 21 GI studies (WMD = −2.11; 95% CI, −3.30 to −0.92; p = 0.0005; test for heterogeneity p < 0.00001, I² = 90%) and in the 8 non-GI studies, (WMD = −3.68; 95% CI, −4.35 to −3.01; p < 0.00001; test for heterogeneity p = 0.46, I² = 0%). There were significant differences between these 2 subgroups (p = 0.0007, Fig. 5).
Table 2. Randomized Studies Evaluating Preoperative Nutrition in Elective Surgery Patients

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Population</th>
<th>Methods score blinding</th>
<th>Intervention</th>
<th>Control</th>
<th>Mortality</th>
<th>Experimental</th>
<th>Control</th>
<th>Infections</th>
<th>Experimental</th>
<th>Control</th>
<th>Hospital stay, d</th>
<th>Experimental</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative arginine versus no arginine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wachter, 1999</td>
<td>UG1 surgery (n = 40)</td>
<td>5</td>
<td>Yes</td>
<td>Impact preop × 5 d + hospital food</td>
<td>Isoenergetic supplement preop + hospital food</td>
<td>2/20</td>
<td>10</td>
<td>2/20</td>
<td>10</td>
<td>5/20</td>
<td>25</td>
<td>5/20</td>
<td>25</td>
</tr>
<tr>
<td>McCarron, 1999</td>
<td>UG1 cancer (n = 51)</td>
<td>7</td>
<td>Yes</td>
<td>1) Formula w/arginine 750 mL/d × 7 d preop 2) Formula with arginine + omega-3 fatty acids (Impact × 7 d preop</td>
<td>3) Standard formula × 7 d preop</td>
<td>1) 1/14</td>
<td>2) 0/13</td>
<td>0</td>
<td>3) 8/11</td>
<td>2) 5/13</td>
<td>34</td>
<td>3) 2/11</td>
<td>18</td>
</tr>
<tr>
<td>Bragg, 2002</td>
<td>Colorectal cancer (n = 200)</td>
<td>12</td>
<td>No</td>
<td>2) Impact preop 1 L/d × 5 d</td>
<td>3) IsoC/IsoN formula preop 1 L/d × 5 d</td>
<td>2) 0/50</td>
<td>3) 0/50</td>
<td>2) 6/50</td>
<td>12</td>
<td>3) 16/50</td>
<td>32</td>
<td>2) 9.5 ± 2.9</td>
<td>3) 12 ± 4.5</td>
</tr>
<tr>
<td>Bragg, 2002</td>
<td>UG1 and LGI cancer malnourished (n = 150)</td>
<td>11</td>
<td>No</td>
<td>2) Impact preop × 7 d + EN standard postop</td>
<td>3) IsoC/IsoN standard EN postop</td>
<td>2) 1/50</td>
<td>3) 2/50</td>
<td>4</td>
<td>2) 8/50</td>
<td>16</td>
<td>32) 12/50</td>
<td>24</td>
<td>2) 13.2 ± 3.5</td>
</tr>
<tr>
<td>Gianotti, 2002</td>
<td>UG1 + LG1 cancer &lt;10% weight loss (n = 805)</td>
<td>8</td>
<td>No</td>
<td>1) Impact preop × 5 d</td>
<td>3) None pre/postop</td>
<td>3) 1/102</td>
<td>1) 1/102</td>
<td>1) 14/102</td>
<td>14</td>
<td>3) 31/102</td>
<td>30</td>
<td>1) 11.6 ± 4.7</td>
<td>3) 14 ± 7.7</td>
</tr>
<tr>
<td>Xue, 2006</td>
<td>Colorectal and gastric GI cancer (n = 60)</td>
<td>11</td>
<td>No</td>
<td>Impact preop, standard EN postop</td>
<td>IsoC/IsoN standard EN formula postop</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>9 ± 3.2</td>
<td>12 ± 3.7</td>
<td></td>
</tr>
<tr>
<td>Okano eto, 2009</td>
<td>Gastric cancer patients (n = 60)</td>
<td>10</td>
<td>No</td>
<td>Impact preop × 7 d + standard postop</td>
<td>Standard EN preop × 7 d + standard postop</td>
<td>NR</td>
<td>NR</td>
<td>2/30</td>
<td>7</td>
<td>8/30</td>
<td>28</td>
<td>23.8 ± 16.6</td>
<td>25 ± 10.6</td>
</tr>
</tbody>
</table>

Perioperative arginine versus preoperative standard and postoperative arginine

| Giger, 2007 | Stomach, pancreas cancer (n = 46) | 10 | No | Impact × 5 d preop + 7d postop | Impact × 7d postop | 3) Impact × 7d postop | 1) 1/14 | 3) 0/15 | 1) 2/14 | 3) 10/15 | 1) 13.7 ± 2.3 | 3) 23.1 ± 3.6 |

EN, enteral nutrition; GI, gastrointestinal; IsoN, isonitrogenous; IsoC, isocaloric; LG1, lower gastrointestinal; NR, not reported; postop, postoperative; preop, preoperative; UG1, upper gastrointestinal.

McCarron: Data for groups 1 and 2 combined in the meta-analysis.

Bragg: Data for Group 1 (receiving Impact perioperatively) shown in comparison C2.

Gianotti: Data for Group 2 (receiving Impact perioperatively) shown in comparison C3.
### Table 3. Randomized Studies Evaluating Perioperative Arginine in Elective Surgery Patients

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Population</th>
<th>Methods coding</th>
<th>Intervention</th>
<th>Experimental control</th>
<th>Mortality experimental control, n (%)</th>
<th>Infections experimental control, n (%)</th>
<th>Hospital stay (d)</th>
<th>Experimental control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braga, 1999&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Stomach, pancreas, colorectal cancer (n = 206)</td>
<td>12 Yes</td>
<td>Impact preop + standard EN postop</td>
<td>IsoC/ImoN EN preop + standard EN postop</td>
<td>0/102 (0)</td>
<td>1/104 (1)</td>
<td>14/102 (14)</td>
<td>3/104 (3)</td>
</tr>
<tr>
<td>Senkal, 1999&lt;sup&gt;23&lt;/sup&gt;</td>
<td>LGI cancer (n = 178)</td>
<td>11 Yes</td>
<td>Impact pre + postop</td>
<td>Standard EN pre + postop IsoN/IsoC</td>
<td>NR</td>
<td>NR</td>
<td>10/78 (1.3)</td>
<td>18/76 (24)</td>
</tr>
<tr>
<td>Snyderman, 1999&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Head and neck cancer (n = 136)</td>
<td>8 Yes</td>
<td>Impact pre + postop</td>
<td>Standard EN formula 5 + 10 d post</td>
<td>0/82 (0)</td>
<td>0/47 (0)</td>
<td>13/82 (23)</td>
<td>19/47 (40)</td>
</tr>
<tr>
<td>Tepaske, 2001&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Cardiac surgery (n = 50)</td>
<td>7 Yes</td>
<td>Impact 5–10 d pre + postop</td>
<td>Standard EN pre + postop</td>
<td>1/23 (4)</td>
<td>1/22 (5)</td>
<td>4/23 (17)</td>
<td>12/22 (55)</td>
</tr>
<tr>
<td>van Bokhorst-De van der Schueren, 2001&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Head and neck cancer, malnourished (n = 56)</td>
<td>6 Yes</td>
<td>1) Arginine formula (12.5 g/L) PRE + postop</td>
<td>Standard EN pre + postop</td>
<td>1) 2/17 (12)</td>
<td>2) 1/15 (7)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ercol, 2001&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Colon disease (n = 28)</td>
<td>9 No</td>
<td>Impact + low-fiber diet 750 mL/d, 6 d pre + post</td>
<td>Standard EN + low-fiber diet 5 + 10 d 3 d post</td>
<td>0/25 (0)</td>
<td>0/25 (0)</td>
<td>1/25 (4)</td>
<td>7/25 (28)</td>
</tr>
<tr>
<td>Sakatani, 2001&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Esophagectomy (n = 30)</td>
<td>6 No</td>
<td>Impact 3 d pre + 14 d post</td>
<td>Standard EN 3 d pre + 14 d post</td>
<td>0/25 (0)</td>
<td>0/25 (0)</td>
<td>1/25 (4)</td>
<td>7/25 (28)</td>
</tr>
<tr>
<td>Tepaske, 2001&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Cardiopulmonary bypass (n = 70)</td>
<td>10 Yes</td>
<td>Impact 5–10 d pre + postop</td>
<td>Standard EN pre + postop</td>
<td>0/25 (0)</td>
<td>0/25 (0)</td>
<td>1/25 (4)</td>
<td>7/25 (28)</td>
</tr>
<tr>
<td>Celik, 2004&lt;sup&gt;30&lt;/sup&gt;</td>
<td>GYN cancer (n = 50)</td>
<td>8 No</td>
<td>Impact preop X 2 days + 7 d postop</td>
<td>Standard EN pre + postop</td>
<td>0/25 (0)</td>
<td>0/25 (0)</td>
<td>1/25 (4)</td>
<td>7/25 (28)</td>
</tr>
<tr>
<td>van Bokhorst-De van der Schueren, 2001&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Head and neck cancer, malnourished (n = 49)</td>
<td>6 Yes</td>
<td>1) Arginine formula (12.5 g/L) PRE + postop</td>
<td>Standard EN postop only</td>
<td>1) 2/17 (12)</td>
<td>2) 1/15 (7)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Braga, 2002&lt;sup&gt;32&lt;/sup&gt;</td>
<td>LGI and LGI cancer, malnourished (n = 150)</td>
<td>11 No</td>
<td>Impact preop X 7 d + IMPACT postop</td>
<td>Standard EN preop</td>
<td>1) 5/50 (0)</td>
<td>2) 3/50 (0)</td>
<td>1) 5/50 (10)</td>
<td>1) 5/50 (24)</td>
</tr>
<tr>
<td>van Bokhorst-De van der Schueren, 2002&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Colorectal cancer (n = 200)</td>
<td>12 No</td>
<td>Impact preop L/d × 5 d postop</td>
<td>None pre/postop</td>
<td>1) 1/50 (2)</td>
<td>2) 1/50 (2)</td>
<td>1) 5/50 (10)</td>
<td>2) 3/50 (6)</td>
</tr>
<tr>
<td>Gianotti, 2002&lt;sup&gt;34&lt;/sup&gt;</td>
<td>LGI + LGI cancer &lt;10% weight loss (n = 305)</td>
<td>8 No</td>
<td>Impact preop X 5 d + 3 d postop</td>
<td>None post-op</td>
<td>2) 2/101 (2)</td>
<td>1) 1/102 (1)</td>
<td>2) 1/101 (1)</td>
<td>1) 1/102 (1)</td>
</tr>
</tbody>
</table>

EN: enteral nutrition; GYN, gynecological; IQR, interquartile range; IsoN, isotonious argineno; IsoC, isocaloric; IsoVol, isovolemic; LGI, lower gastrointestinal; NR, not reported; postop, postoperative; preop, preoperative; UGI, upper gastrointestinal.

14: Snyderman<sup>24</sup>: Data for groups 1 and 2 combined (impact pre + post) and compared with groups 3 and 4 combined (standard pre + post).
15a: van Bokhorst De van der Schueren<sup>26</sup>: Data for Group 3 (control nothing preop and EN postop) appears in C2.
Tepaske<sup>25</sup>: Groups 1 and 2 combined in the meta-analysis.
Celik<sup>27</sup>: Infection data not included in meta-analysis as only reported as wound infection, not total number of infections.
van Bokhorst De van der Schueren<sup>26</sup>: Data for Group 2 (control EN pre- and postop) appears in C1.
Braga<sup>32</sup>: Data for Group 2 (impact preop and standard postop) appears in A1.
Gianotti<sup>34</sup>: Data for Group 1 (impact preop) appears in A1.
Table 4. Randomized Studies Evaluating Postoperative Arginine in Elective Surgery Patients

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Population</th>
<th>Methods Score Blinding</th>
<th>Postoperative arginine versus standard</th>
<th>Intervention</th>
<th>Mortality, n (%)</th>
<th>Infections, n (%)</th>
<th>Hospital stay, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daly, 1990&lt;sup&gt;26&lt;/sup&gt;</td>
<td>UGI surgery (n = 30)</td>
<td>4 No</td>
<td>Arginine 25 g/d with modular feed postop</td>
<td>Glycine 43 g/d modular feed postop</td>
<td>10/16 (63)</td>
<td>9/14 (64)</td>
<td>NR</td>
</tr>
<tr>
<td>Daly, 1992&lt;sup&gt;23&lt;/sup&gt;</td>
<td>UGI cancer (n = 85), 32% weight loss &gt;10%</td>
<td>10 No</td>
<td>Impact via NC postop</td>
<td>Omotic HCI via NC non-IsoN postop</td>
<td>2/41 (5)</td>
<td>0/44 (0)</td>
<td>5/41 (12)</td>
</tr>
<tr>
<td>Daly, 1999&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Esophophageal, pancreatic and gastric cancer (n = 60), 37% weight loss &gt;10%</td>
<td>9 Yes</td>
<td>1) Impact postop and si outpatient 2) Impact postop small bowel</td>
<td>Traumatic postop and as outpatient 3) Traumatic postop small bowel</td>
<td>1/30 (3)</td>
<td>2/30 (7)</td>
<td>1/30 (3)</td>
</tr>
<tr>
<td>Braga, 1996&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Pancreatic, gastric cancer (n = 60), 50% weight loss &gt;10%</td>
<td>9 Yes</td>
<td>Impact postop</td>
<td>Same EN formula w/o arginine and omega-3 fatty acids, with glycine + omega-6 fatty acids IsoN postop</td>
<td>0/20 (0)</td>
<td>0/20 (0)</td>
<td>2/20 (10)</td>
</tr>
<tr>
<td>Schilling, 1996&lt;sup&gt;26&lt;/sup&gt;</td>
<td>GI cancer (upper and lower) (n = 45), body mass index 23–24</td>
<td>6 No</td>
<td>Impact postop via nasojejunal</td>
<td>Frensulin (Standard EN) via nasojejunal postop</td>
<td>NR</td>
<td>NR</td>
<td>3/14 (21)</td>
</tr>
<tr>
<td>Senzaki, 1994&lt;sup&gt;27&lt;/sup&gt;</td>
<td>UGI cancer (n = 154), NRI index 98–100</td>
<td>8 Yes</td>
<td>Impact postop via jejunostomy</td>
<td>Standard EN (min 3.0 L/day) via jejunostomy</td>
<td>3/77 (4)</td>
<td>2/77 (3)</td>
<td>17/77 (22)</td>
</tr>
<tr>
<td>Giancotti, 2001&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Pancreatic duodenectomy, 40%, malnourished (n = 212)</td>
<td>10 No</td>
<td>1) Impact postop</td>
<td>2) Standard EN postop</td>
<td>2/71 (3)</td>
<td>1/73 (1)</td>
<td>6/71 (8)</td>
</tr>
<tr>
<td>Rito, 2001&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Head and neck cancer (n = 44)</td>
<td>6 No</td>
<td>Nutrition Intensive (6.25 g arginine/L) postop</td>
<td>Nutrition Protein Plus IsoC/IsoN postop</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Jiang, 2001&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Upper GI surgery (n = 120)</td>
<td>7 Yes</td>
<td>Impact postop (from day 1–11)</td>
<td>IsoC/IsoN standard EN postop</td>
<td>NR</td>
<td>NR</td>
<td>0/60 (0)</td>
</tr>
</tbody>
</table>

Postoperative arginine versus standard.

| de Luis, 2002<sup>30</sup> | Head and neck cancer (n = 47) | 10 Yes | Arginine-enhanced EN + fiber postop | Isoal/IsoN + fiber postop | 3 months 3/23 (13) | 3 months 2/24 (8) | 5/23 (22) | 4/24 (17) | NR | NR |
| de Luis, 2004<sup>30</sup> | Head and neck cancer (n = 90) | 9 Yes | Arginine-enhanced EN + fiber postop | Isoal/IsoN + fiber postop | NR | NR | 2/45 (4) | 4/45 (9) | 25.8 ± 15 | 35.0 ± 24.6 |
| Ferreras, 2005<sup>30</sup> | Gastric cancer (n = 66) | 9 Yes | Impact postop | Isoal/IsoN postop | 1/30 | 2/30 | 2/30 (7) | 9/30 (30) | 13 (mean) 11–22 (range) | 15 (mean) 10–22 (range) |
| Lobo, 2006<sup>31</sup> | Rectectomy for pancreas, stomach, esophageal cancer (n = 120) | 8 Yes | Stressen feed w/arginine, glutamine, omega-5 PUFA postop | IsoC/IsoN control (Nutrition high protein) postop | 6/54 (11) | 6/54 (11) | At 30 d 32/54 (59) | At 30 d 33/54 (61) | 14.5 (12–23) | 17.5 (13–23) |
| de Luis, 2007<sup>32</sup> | Head and neck cancer (n = 72) | 8 No | EN diet w/arginine 8.5 g/L postop | IsoC/IsoN postop | NR | NR | 2/55 (6) | 2/57 (3) | 27.9 ± 21 | 28.2 ± 12 |
| Casas-Rodeiro, 2008<sup>33</sup> | Oral and laryngeal cancer (n = 44) | 7 No | 1) EN w/arginine postop 2) EN w/arginine + omega-3 PUFA postop | IsoC/IsoN postop | NR | NR | NR | NR | 1/22.5 ± 10.0 | 21/8.6 ± 7.8 |
| Klek, 2008<sup>34</sup> | Pancreatic and gastric cancer resections (n = 196) | 6 Yes | Recomb 20 mL/h; dl; 50 mL/h 2 75 mL/h 3 100 mL/h until dl 7 postop | Pepsiorb, same schedule as experimental group | 1/92 (1) | 1/91 (1) | 17/92 (23) | 21/92 (23) | 12.9 ± 8.0 | 12.4 ± 5.9 |
| Klek, 2008<sup>34</sup> | Pancreatic and gastric cancer resections (n = 192) | 9 No | Stressen w/arginine, glutamine, omega-3 PUFA postop | Pepsiorb postop | 1/52 (2) | 1/52 (2) | 13/52 (25) | 15/53 (28) | 13.1 ± 4.1 | 12.4 ± 3.9 |

(continued)
Outcomes were also analyzed separately for studies of upper GI operations only (n = 18), lower GI operations only (n = 2), and studies of mixed (both upper and lower GI surgery) (n = 5). When the 16 trials of patients with upper GI surgery only that reported on infectious complications were aggregated, patients receiving arginine-supplemented diets experienced fewer infectious complications than those receiving standard diet therapies (RR = 0.69; 95% CI, 0.55–0.87; p = 0.002; test for heterogeneity p = 0.15, I² = 27%). In the one study of lower GI surgery, RR = 0.34 (95% CI, 0.17–0.68, p = 0.002; test for heterogeneity not applicable). In the 4 studies of mixed GI surgery, RR = 0.49 (95% CI, 0.36–0.66; p < 0.00001; test for heterogeneity p = 0.99, I² = 0%). Differences between these subgroups were not statistically significant (p = 0.06, see Fig. 4).

When the data on hospital length of stay were aggregated, arginine-supplemented diets were associated with a significant reduction in hospital length of stay in the 14 upper GI studies (WMD = −1.24, 95% CI, −3.85 to −0.39; p = 0.02; test of heterogeneity p < 0.00001, I² = 93%) and in the 5 studies of upper and lower GI studies (WMD = −2.36; 95% CI, −3.09 to −1.64; p < 0.00001, test of heterogeneity p = 0.66, I² = 0%). When the data from the 2 studies of lower GI studies were aggregated, arginine-supplemented diets had no effect on hospital length of stay (WMD = −0.74; 95% CI, −3.92 to −2.45; p = 0.65; test for heterogeneity p = 0.002, I² = 90%). There were significant differences between these subgroups (p = 0.004, Fig. 5).

We compared the data from the trials that used Impact (n = 23) with those that used other formulations (n = 12). The use of Impact was associated with a greater reduction of infectious complications in the 21 trials that reported on outcomes (RR = 0.49; 95% CI, 0.41–0.58; p < 0.00001; test of heterogeneity p = 0.74, I² = 0%) than the use of other formulations in the 7 trials (RR = 0.95; 95% CI, 0.75–1.21; p = 0.68; test of heterogeneity p = 0.98, I² = 0%). The differences between these 2 subgroups was statistically significant (p < 0.0001, see Fig. 4). When the data on hospital length of stay were aggregated and compared, the 21 studies using Impact formulas were associated with a statistically significant reduction (WMD = −2.62; 95% CI, −3.65 to −1.59; p < 0.00001; test for heterogeneity p < 0.00001; I² = 87%) compared with the 8 studies using non-Impact formulas (WMD = −0.89; 95% CI, −3.21 to −1.44; p = 0.45; test for heterogeneity p = 0.05; I² = 49%). Differences between the subgroups were significant (p < 0.00001, see Fig. 5).

Finally, patients who were fed the arginine-supplemented diets preoperatively only (7 trials), those
who received an arginine-supplemented diet both pre- and postoperatively (13 trials), and those who received the arginine-supplemented diet postoperatively (n = 18) were analyzed separately. In all subgroups, patients experienced fewer infectious complications if they were fed the arginine-supplemented diets (see Fig. 4). There was a statistically significant difference across groups, suggesting a greater treatment effect with the perioperative administration of arginine-supplemented diets (perioperative: RR = 0.46; 95% CI, 0.36–0.59; p < 0.00001, test for heterogeneity p = 0.89; I² = 0%; preoperative: RR = 0.57; 95% CI, 0.37–0.88; p = 0.01, test for heterogeneity p = 0.24; I² = 26%; and postoperative: RR = 0.78; 95% CI, 0.64–0.95; p = 0.01, test for heterogeneity p = 0.52; I² = 0%, the test of significance between subgroups, p = 0.03, see Fig. 4). Arginine-supplemented diets were associated with a significant reduction in hospital length of stay in the 11 studies of perioperative intervention (WMD = −2.38; 95% CI, −3.44 to −1.32; p < 0.0001, test for heterogeneity p < 0.00001; I² = 85%), but there was no significant effect in 6 studies of preoperative intervention (WMD = −1.38; 95% CI, −3.49 to 0.73; p = 0.20; test for heterogeneity p < 0.00001; I² = 87%). There were significant differences between the subgroups, again suggesting a greater benefit to the perioperative administration of arginine-supplemented diets (p = 0.001, see Fig. 5).

**DISCUSSION**

We have systematically reviewed all RCTs evaluating the effect of perioperative administration of arginine-supplemented diets in elective surgical patients. We found 35 eligible RCTs in elective surgery patients for consideration. When statistically aggregated, there is a substantial reduction in infectious complications and shorter hospital length of stay associated with the use of these specialty diets, with no overall effect on mortality compared with standard care. These findings are insensitive to the use of glycine in the control diets and are consistent with earlier meta-analyses on more limited samples of RCTs than were included in our comprehensive analysis.⁹,¹³
Figure 2. Effect of arginine-supplemented diets on hospital length of stay. Mean, mean hospital length of stay; SD, standard deviation; Total, total number of patients in group; IV, Random, inverse variance, random effects.

Figure 3. Effect of arginine-supplemented diets on mortality. Events, number of patients that died; Total, total number of patients in group; M+H, Random, Mantzel-Haenzel Random effects.
Admittedly, there is considerable heterogeneity in our analysis of arginine-supplemented diets, particularly in the evaluation of their effect on hospital length of stay. This heterogeneity is likely due to differences in patients, practice patterns, health care systems, study designs, treatment diets, and other methodologies across all studies. Because of the presence of heterogeneity, we pursued several hypothesis-generating subgroup analyses. We first demonstrated that the treatment effect of arginine-supplemented diets seems to be consistent across all types of GI and non-GI operations. There might be a greater reduction in hospital length of stay associated with these diets in the non-GI surgery patients compared with GI surgery (reduction of 3.7 versus 2.1 days). However, this observation should by no means diminish enthusiasm for using these products in GI surgery because they are associated with an average reduction of 2 days in hospital, which can translate into considerable cost savings for institutions and health care systems. There was no substantial reduction in hospital length of stay associated with arginine-supplemented diets in lower GI surgery. However, the risk ratio was similar to that of other GI operations, but there were only 2 studies of lower GI surgery and the findings were not statistically significant. We conclude that arginine-supplemented diets should be prescribed to all patients undergoing elective surgery with substantial risk of infectious complications.

We then explored the potential benefits of the different arginine-supplemented formulas by analyzing the RCTs that used Impact in the experimental arm and compared with RCTs that used other formulas. The treatment effect is large and statistically significant in the group of RCTs that...
used Impact, and aggregation of the data from the RCTs of other formulations showed no substantial reduction in infectious complications or hospital length of stay. Impact contains a combination of arginine, omega-3 fatty acids, and nucleotides, but it is hard to make generalizations about the formulations used in the non-Impact RCTs, except that no 2 studies used the same formulation. It is difficult to ascertain the exact amount of arginine delivered in these studies, but it was generally of a lower concentration than is found in Impact. Three of the studies supplemented with some amount of omega-3 fats, 1 study used a formula with RNA, and 2 studies also used formulas with glutamine.

The only inference from these data is that infectious complications are reduced with use of Impact and not other arginine formulations. It is possible that the specific combination of nutrients in Impact is necessary and these nutrients can interact to produce benefit. In addition, it is not possible to say what the optimal combination or dosage of specialized nutrients is from this data set. Because the clinical benefit observed relates to a substantial reduction of infections, one might postulate (at least in part) that these diets work by improving the immune response after surgery.

A causal relationship has been shown to exist between physical injury (surgery and trauma) and the predisposition for infectious complications to develop in these patients. This increased infectious risk has been hypothesized to be related to an acquired arginine-deficient state, which leads to substantial immune dysfunction. Recent investigations suggest that arginine metabolism is intimately regulated by the immune system. Soon after physical injury (surgery or trauma), an accumulation of immature cells of myeloid origin has been discovered in the
circulation and lymph tissue. These cells express arginase 1, which efficiently depletes arginine. Coupled with poor arginine intake and inadequate endogenous generation, arginase 1 serves to create a state of arginine deficiency. An increasing amount of evidence has accumulated in the last 10 years to demonstrate that suppression of T-lymphocyte function can be caused through arginine depletion by myeloid cells expressing arginase 1, giving these cells the name myeloid-derived suppressor cells (MDSC). Several clinical studies suggest that use of arginine supplementation along with omega-3 fatty acids restores T-lymphocyte function, including CD4 counts and interleukin-2 production. We speculate that arginine-supplemented diets can overcome arginine deficiency caused by MDSC through the synergistic effect of several components. First, arginine is supplemented in supraphysiologic quantities, helping increase systemic arginine availability. Second, omega-3 fatty acids can “blunt” upregulation of MDSC and arginase 1, the enzyme responsible for arginine destruction. In addition, vitamin A (and vitamin A analogues) has been shown under certain circumstances to induce maturation of MDSC and a decrease in arginase 1 expression. Additional investigation will be necessary to test these possibilities.

Finally, we explored a priori the question of whether providing the specialized formula is better done before surgical insult, after the surgical insult, or both. We observed that all 3 strategies are associated with a substantial reduction in infectious complications. Both perioperative and postoperative use of these diets were associated with a reduction in hospital length of stay and, used in the preoperative setting, were not associated with a substantial reduction in hospital length of stay (WMD = −1.38, 95%, CI, −3.49 to 0.73; p = 0.20). Additionally, when we compared the estimates of treatment effect across these 3 subgroups, we observed that the largest treatment effect was associated with the perioperative administration of the arginine-supplemented diets. We are cautious not to overstate these findings, as this comparison is an indirect comparison of studies—we are comparing RRAs across 3 subgroups. There is only 1 head-to-head study that compares perioperative administration of arginine-supplemented diets with postoperative use only. In this study of 46 patients with stomach or pancreas cancer, use of perioperative arginine diets was associated with a reduction in infection (RR = 0.34; 95% CI, 0.16–0.71; p = 0.004) and a reduction in hospital length of stay (WMD = −9.18; 95% CI, −11 to −7.26; p < 0.00001) compared with the group that just received arginine-supplemented diets in the postoperative phase. Although this hypothesis warrants additional investigation, it appears, based on these results, that use of arginine-supplemented diets in both the pre- and postoperative phase are superior to either phase alone. That is not to say that use in the preoperative only or postoperative phase only is not worthwhile. It means that we can expect a greater treatment effect if we use them both before and after surgery.

We would like to acknowledge some of the limitations of this review. The studies included in this review, although RCTs and of reasonable methodological quality (as evidenced by an average scoring of 8.2 of a maximum of 14), cover a span of almost 2 decades. Recent advances in discharge management (affecting hospital length of stay), glucose and antibiotic therapy (affecting infection control), and surgery (eg, minimally invasive surgery) could affect results from later studies. Some of the included studies had small sample sizes (n < 100) with more than 1 intervention and/or control group, and in other studies the same intervention was used in varying settings, ie, pre-, post-, and/or perioperatively. Although we have separated these varying interventions into the various subgroups, the appropriateness of the study design in some cases is questionable. Lastly, many studies, despite reporting a reduction in infectious morbidity, failed to report data related to infections in a clear, meaningful way, and these studies had to be deleted from our analyses. Despite these limitations, the strong signals for a reduction in infections from our analyses cannot be ignored.

In conclusion, in this review we have demonstrated some clinical evidence that use of nutrition therapy containing arginine and omega-3 fatty acids used both pre- and postoperatively in high-risk elective surgical patients is associated with a substantial reduction in infection and shorter length of hospital stay. Efforts to implement the use of these diets in the perioperative setting are worthwhile. These efforts will result in considerable reduction in morbidity for our patients and substantial reductions in costs for the health care system.

**Author Contributions**

Study conception and design: Drover, Dhaliwal, Weitzel, Wischmeyer, Ochoa, Heyland
Acquisition of data: Wischmeyer, Drover, Heyland, Dhaliwal
Analysis and interpretation of data: Dhaliwal, Heyland
Drafting of manuscript: Drover, Heyland
Critical revision: Wischmeyer, Dhaliwal, Ochoa

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REFERENCES


