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4       Current evidence and ongoing trials on the use of glutamine in critically ill and surgical  
5       patients

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17      *Keywords*

18      Glutamine, systematic review, critical illness

19

20 *Synopsis*

21 The amino acid glutamine has numerous important roles including particularly antioxidant  
22 defence, immune function, the inflammatory response, acid-base balance and nitrogen  
23 economy. This systematic review of randomised controlled trials of nutrition support with  
24 glutamine up to August 2008 found that parenteral glutamine in critical illness is associated  
25 with a non-significant reduction in mortality (risk ratio 0.71, 95% CI 0.49 to 1.03) and may  
26 reduce infections. However, poor study quality and the possibility of publication bias mean  
27 that these results should be interpreted with caution. There is no evidence to suggest that  
28 glutamine is harmful, in terms of organ failure, and parenteral glutamine may reduce the  
29 development of organ failure in ventilated patients.

30 *Background*

31 There are many potential mechanisms by which supplementation with the amino acid  
32 glutamine could prove beneficial in critical illness. Plasma glutamine levels fall in patients  
33 with critical illness, and glutamine is released from muscle to be used by rapidly dividing  
34 cells (such as the gut and immune system) and for renal acid-base homeostasis (1). The fall  
35 in glutamine levels may suggest that glutamine becomes a 'conditionally essential' amino  
36 acid in critical illness. Glutamine supplementation improves nitrogen balance in parenteral  
37 nutrition support (2). Glutamine is particularly important as a precursor of glutathione and  
38 thus antioxidant defence.

39

40 Glutamine also plays a role in intracellular signalling, enhances heat shock protein  
41 expression (3), prevents apoptosis in injury, and attenuates hyper-inflammation (1). There is  
42 some evidence to suggest that glutamine may reduce gut injury and inflammation in critical  
43 illness, thus influencing bacterial translocation across the gut wall (4). Glutamine may also  
44 improve insulin sensitivity in critical illness (5).

45

46 With the ability now to provide glutamine in parenteral nutrition, as well as additional  
47 supplements enterally, randomised controlled trials have evaluated whether glutamine  
48 provides clinical benefits.

49

50 Guidelines for the use of glutamine in critical illness have recommended enteral glutamine  
51 for patients with burns or trauma, and parenteral glutamine, where parenteral nutrition is  
52 required (6). However, not all guidelines for critical illness have supported the use of  
53 parenteral glutamine for all patients requiring parenteral nutrition, and the quality of trials  
54 has been considered poor for guideline recommendations (7).

55

56 Heyland and Dhaliwal (8) have shown that surgery causes some cytokine activation and  
57 some depression of cellular defences, but the systemic inflammatory response of critical  
58 illness is best represented by hyper-inflammation and marked cellular immune dysfunction  
59 at the same time. Thus responses to glutamine supplementation may differ between surgical  
60 and critically ill patients. This systematic review examines the use of glutamine parenterally  
61 and enterally in critical illness and surgical groups of patients separately.

62

63 *Methods*

64 A systematic review and meta-analyses of randomised controlled trials (RCTs) were  
65 undertaken using a prespecified protocol. RCTs compared glutamine containing parenteral  
66 or enteral nutrition compared with control feeding in adult patients undergoing surgery or  
67 with critical illness. It was assumed that regimes given to intervention and control groups  
68 were isonitrogenous and isocaloric, but whether this was the case was not always clear in the  
69 reports. RCTs of immunonutrition, where glutamine was one of several nutrients, e.g. with  
70 arginine or  $\omega$ -3 fatty acids, were not included.

71  
72 RCTs were identified by searching three databases (MEDLINE, EMBASE, CINAHL), hand  
73 searching four journals (Clinical Nutrition, Journal of Parenteral and Enteral Nutrition,  
74 Intensive Care Medicine, Critical Care Medicine) and from previous reviews, including that  
75 by Novak *et al.* (9). Full published reports, conference proceedings and abstracts provided  
76 data. Details of the search strategy can be provided by contacting the author. There were no  
77 language exclusions, but the review did not include trials from China, because of continuing  
78 concerns over the authenticity of randomised trial designs from China (10). The last date for  
79 the search was August 2008.

80  
81 Data on deaths, participants with infection and participants with organ failure are presented.  
82 A conservative method of data handling was used. Outcomes were taken from the last  
83 available time of follow-up, with a random effects model for meta-analysis (except in the  
84 case of the data used in the funnel plot). Data are presented with all participants randomised  
85 as the denominator. *Post hoc* subgroup analyses examined mortality in critical illness for  
86 glutamine dose calculated as dose/kg x days of  $\geq 4.2\text{g/kg}$  compared with  $<4.2\text{g/kg}$ , and for  
87 patients with acute pancreatitis.

88  
89 Heterogeneity amongst trials was assessed by the  $I^2$  statistic (11), where  $\geq 50\%$  was taken as  
90 indicating significant heterogeneity. Publication bias was examined by funnel plot analysis.  
91 Meta-analyses were undertaken using Review Manager version 4.2.7 software, Cochrane  
92 Collaboration, 2004. Risk ratios (RR) and 95% confidence intervals (CI) are reported.

93

94 *Results*

95 Data are presented from 31 RCTs that provided data (12-42). Twenty-two trials were  
96 identified in patients with critical illness (burns two trials, mixed intensive care unit  
97 population nine trials, trauma patients three trials, patients with pancreatitis four trials, and  
98 patients with surgical complications four trials). Eight trials were in elective gastrointestinal  
99 surgical patients, where parenteral nutrition support post-operatively would not normally be  
100 provided. One trial evaluated glutamine containing parenteral nutrition in a mixed hospital  
101 population cared for by the nutrition team (37).

102

103 Trial quality, as reported, was often limited, particularly in terms of reporting concealment of  
104 randomisation, intention to treat analysis and blinding of outcome assessment (although this  
105 is not likely to be a problem for reporting of deaths).

106

107 *Mortality (Figure 1)*

108 Parenteral glutamine in critical illness was associated with a non-significant reduction in  
109 mortality (RR 0.71, 95% CI 0.49 to 1.03, P = 0.07). For enteral glutamine in critical illness the  
110 risk ratio was 1.05 (95% CI 0.71 to 1.54, P = 0.81). Two surgical trials reported mortality and  
111 one trial reported for a mixed hospital population, in neither case was there a statistically  
112 significant reduction. Overall, if all population groups are combined the risk ratio for  
113 mortality was 0.84 (95% CI 0.66 to 1.07, P = 0.17). Thus there was a trend for a beneficial  
114 effect, most clearly for parenteral glutamine in critical illness.

115

116 *Participants with infection (Figure 2)*

117 For enteral glutamine in critical illness the risk ratio was 0.91, 95% CI 0.74 to 1.10, P = 0.33).  
118 Parenteral glutamine in critical illness was associated with a statistically significant reduction  
119 in infections (RR 0.78, 95% 0.63 to 0.97, P = 0.03). In surgical patients given parenteral  
120 nutrition containing glutamine, whether they required parenteral nutrition or not, there was  
121 a statistically significant reduction in participants with infection (RR 0.43, 95% 0.27 to 0.69, P  
122 < 0.001). Overall, for all the patient groups there was a statistically significant reduction in  
123 participants with infection (RR 0.81, 95% 0.70 to 0.93, P = 0.003).

124

125 For the outcome of participants with infection which provided the most data, a funnel plot  
126 examining for suggestion of publication bias was undertaken (Figure 3). The individual data  
127 points should be evenly distributed in an inverted V on either side of the vertical axis. The

128 plot shows fewer data points to the top right of the line, suggesting that small trials with  
129 negative results, not in favour of glutamine, were less likely to be published.

130

131 *Participants with multiorgan or renal failure (Figure 4)*

132 Few trials reported multiorgan or renal failure. Combining all parenteral glutamine trials  
133 there was a statistically significant reduction (RR 0.60, 95% 0.42 to 0.85, P = 0.004), but not for  
134 enteral glutamine (RR 1.15, 95% 0.70 to 1.87, P = 0.59). Overall there was no suggestion that  
135 glutamine was harmful in terms of multiorgan or renal failure (RR 0.75, 0.56 to 0.99, P =  
136 0.04).

137

138 *Participants with pancreatitis (Figures 5 and 6)*

139 Parenteral glutamine was associated with a statistically significant reduction in mortality (RR  
140 0.36, 95% CI 0.13 to 0.99, P = 0.05) and a non-significant reduction in infection (RR 0.49, 95%  
141 0.20 to 1.16, P = 0.10) in participants with pancreatitis.

142

143 *Examination of dose effects in critical illness (Figure 7)*

144 For trials providing  $\geq 0.42$ g glutamine/kg as total dose over time the risk ratio for mortality  
145 was 0.66 (95% 0.43 to 1.01, P = 0.06), and for doses less than this RR 0.91 (0.66 to 1.27, P =  
146 0.59). Suggesting that higher doses may be more effective, but there was no statistically  
147 significant difference between the sub groups in the interaction test (P = 0.27). However, the  
148 trials with the higher dose of glutamine showed high heterogeneity ( $I^2 = 57\%$ ).

149

150 *Conclusions*

151 Compared with a previous systematic review three years before (43), there have been some  
152 changes to the results for the outcomes. The effect of glutamine on mortality is very similar  
153 to previously, with a risk ratio of 0.71 (95% CI 0.49 to 1.03) for parenteral glutamine.

154 Although this result is not statistically significant, the confidence intervals do not exclude the  
155 possibility of benefit on mortality.

156

157 Parenteral glutamine now appears to reduce infections in critical illness, but the evidence for  
158 enteral glutamine in critical illness is less strong. This is the reverse of the results from the  
159 previous review. The possibility of publication bias for this outcome remains a concern. The  
160 methodological quality of nutrition support trials in critical illness, particularly with regard  
161 to intention to treat analysis, concealment of allocation, and blinding of outcome assessment,  
162 also requires improvement (44).

163

164 Categorisation into critical illness or surgical trials was difficult. Trials where participants  
165 had pancreatitis or surgery followed by complications, e.g. peritonitis, were classified as  
166 critical illness. All the other surgical trials of parenteral glutamine gave parenteral nutrition  
167 after uncomplicated elective surgery, when it would not generally have been provided.

168 Given that parenteral nutrition itself may be associated with an increased risk of infection, it  
169 is not clear how the reduction of infection with parenteral glutamine in this group of surgical  
170 patients can be interpreted.

171

172 Large multicentre randomised trials, with rigorous methodology, are underway examining  
173 the role of glutamine in critical illness (45, 46). The REDOXS® (REducing Deaths due to  
174 OXidative Stress) trial (47) is recruiting 1200 patients in North America and Europe with  
175 organ dysfunction in critical illness. Participants are randomised to 0.35g/kg/d parenteral  
176 glutamine (independent of the need for parenteral nutrition) and 30g/d enteral glutamine  
177 and/or parenteral and enteral antioxidants or no supplements, in a factorial design. The  
178 main outcome of the trial is 28 day mortality; survival to 6 months and infections are also  
179 outcomes. The relatively high doses of glutamine and antioxidants have been established on  
180 the basis of reduction in markers of oxidative stress, and greater preservation of glutathione  
181 without affecting organ function (46).

182

183 The SIGNET (Scottish Intensive care Glutamine of selenium Evaluative Trial) is examining  
184 parenteral nutrition with 20.2g glutamine with or without 500µg parenteral selenium, also in  
185 a factorial design with isonitrogenous and isocaloric regimes, in 500 patients who require  
186 parenteral feeding in intensive care (45).

187

188 There is no suggestion from the data in this review that parenteral or enteral glutamine are  
189 harmful, and the meta-analysis suggests that parenteral glutamine may reduce organ failure  
190 (other than requiring ventilation), however, few trials reported details of organ failure.

191

192 Three small trials suggest that glutamine may reduce mortality in acute pancreatitis.

193 However, only a total of 112 patients were enrolled in these trials and not all trials had

194 patients with severe pancreatitis (33). It is not clear whether enteral nutrition support could  
195 have been achieved in these patients (48).

196

197 There is some suggestion that higher doses (equivalent to at least 0.42g/kg glutamine for 10  
198 days) may have more effect on mortality.

199

200 Two recent Cochrane reviews (49, 50) have also examined the use of parenteral or enteral

201 glutamine in children. Tubman *et al.* (49) found that there was insufficient evidence to

202 support the use of parenteral or enteral glutamine in preterm infants to prevent morbidity

203 and mortality. Grover *et al.* (50) came to the same conclusion for parenteral and enteral

204 glutamine use in young infants with severe gastrointestinal disease.

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215

216 *Figures*

217 Figure 1 – Meta-analysis of glutamine supplemented parenteral (PN) or enteral (EN)  
218 nutrition in critical illness and surgery – risk ratios for mortality

219

220 Figure 2 – Meta-analysis of glutamine supplemented parenteral (PN) or enteral (EN)  
221 nutrition in critical illness and surgery – risk ratios for participants with infection

222

223 Figure 3 – Funnel plot examination for publication bias from infection data in figure 2

224

225 Figure 4 – Meta-analysis of glutamine supplemented parenteral (PN) or enteral (EN)  
226 nutrition in critical illness and surgery – risk ratios for participants developing organ failure  
227 (other than requiring ventilation)

228

229 Figure 5 – Meta-analysis of glutamine supplemented parenteral (PN) nutrition in pancreatitis  
230 – risk ratios for mortality

231

232 Figure 6 – Meta-analysis of glutamine supplemented parenteral (PN) nutrition in  
233 pancreatitis – risk ratios for participants with infection

234

235 Figure 7 – Meta-analysis of glutamine supplemented parenteral (PN) or enteral (EN)  
236 nutrition in critical illness and surgery – risk ratios for mortality for high ( $\geq 0.42\text{g/kg}$ ) and  
237 lower dose of glutamine ( $< 0.42\text{g/kg}$ )

238

239 Footnote to Figure 3:

240 SE (log RR) = Standard Error of the log of the Risk Ratio

241 RR (fixed) = Risk Ratio (fixed effect model)

242

243

244 Footnotes for Figures 1, 2, 4, 5, 6 and 7:

245 n = number affected in treatment or control group

246 N = total number in treatment or control group

247 ← and → indicate that values extend beyond range of values shown

248

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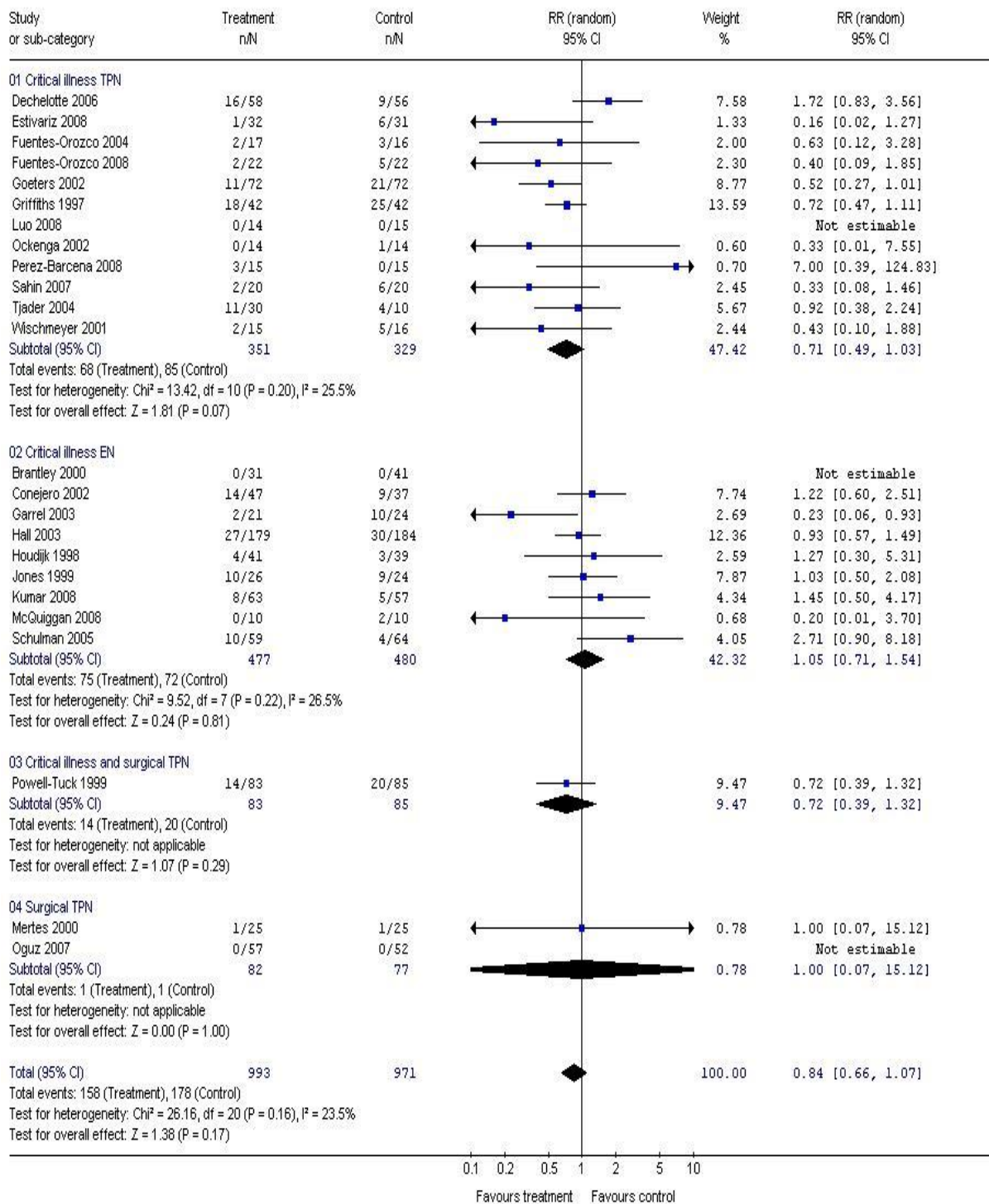
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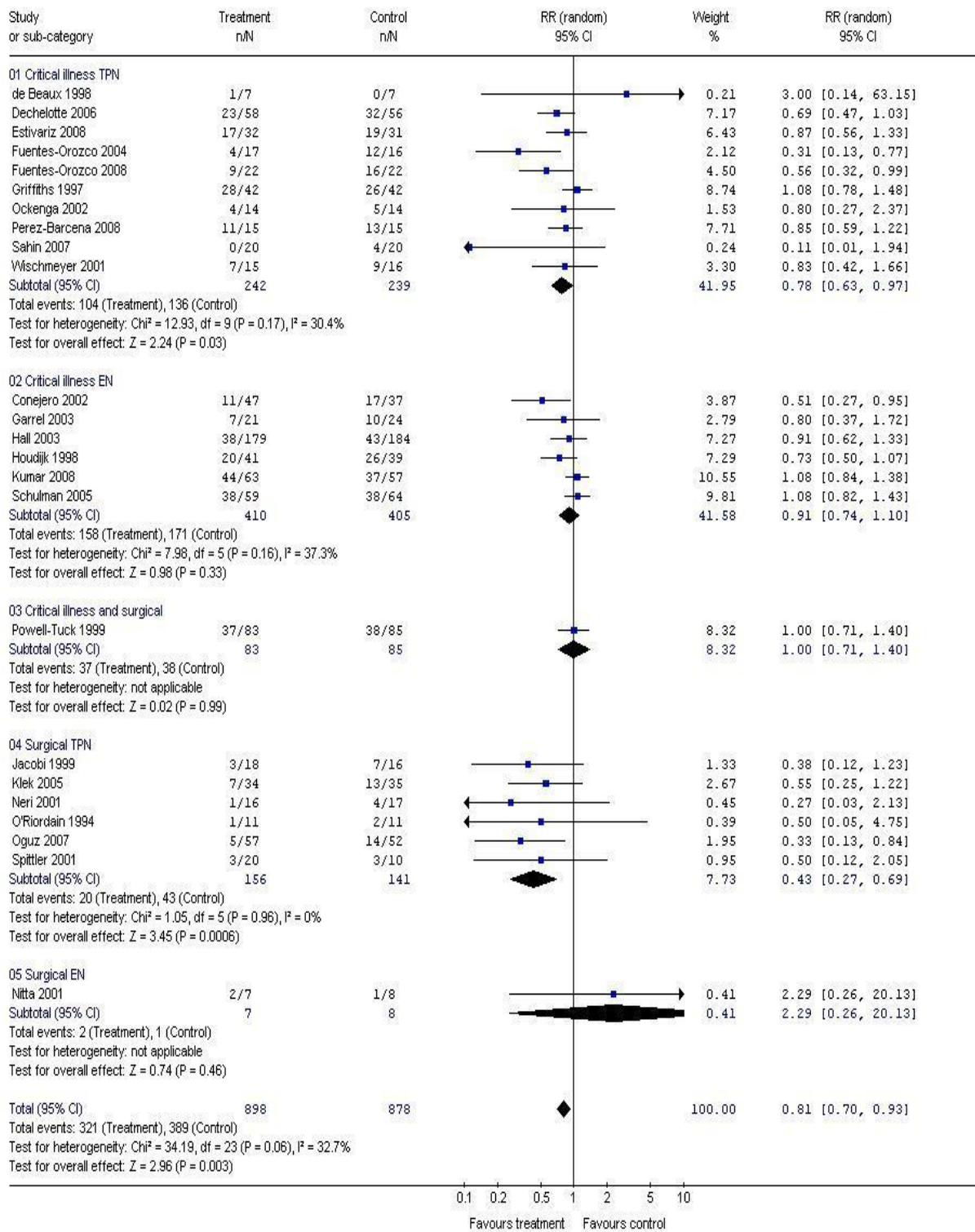
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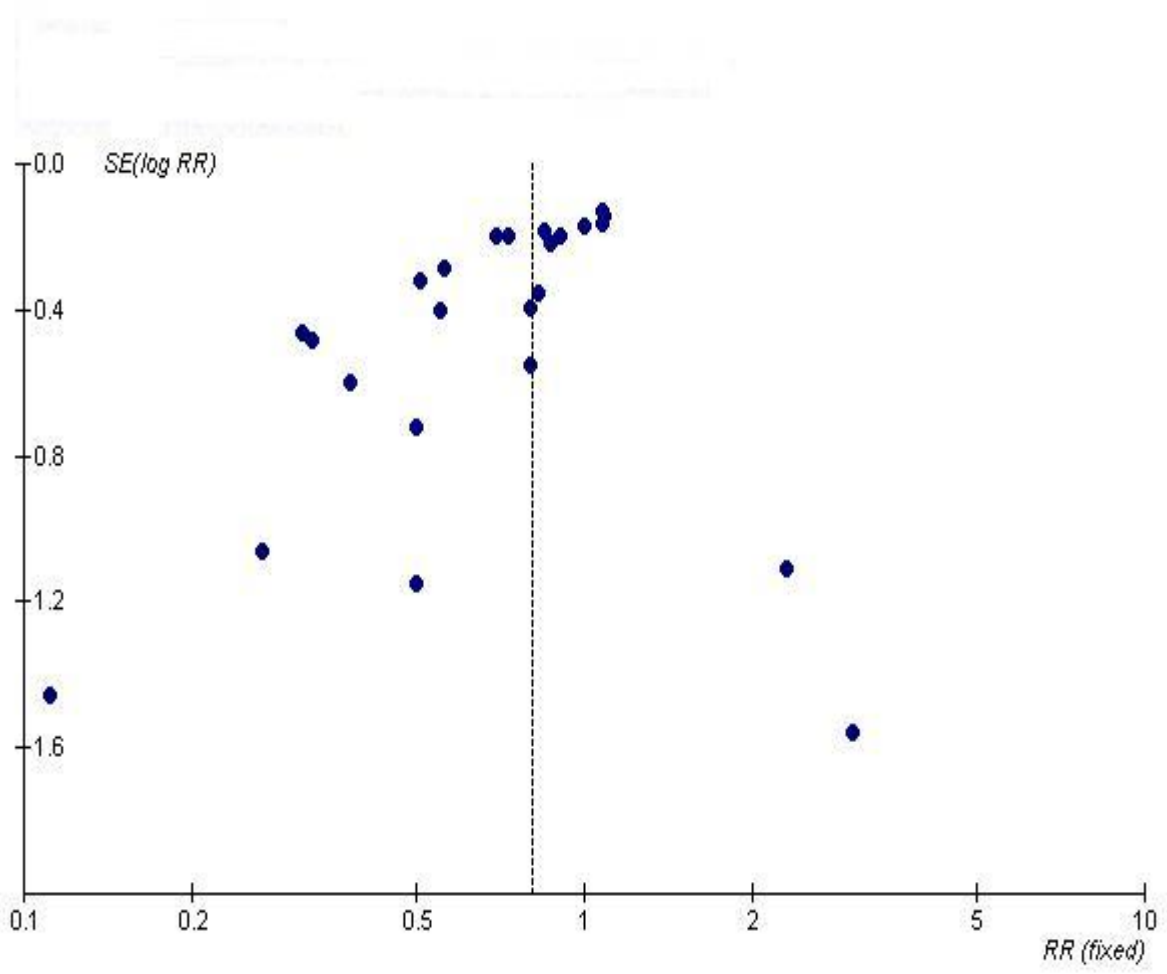


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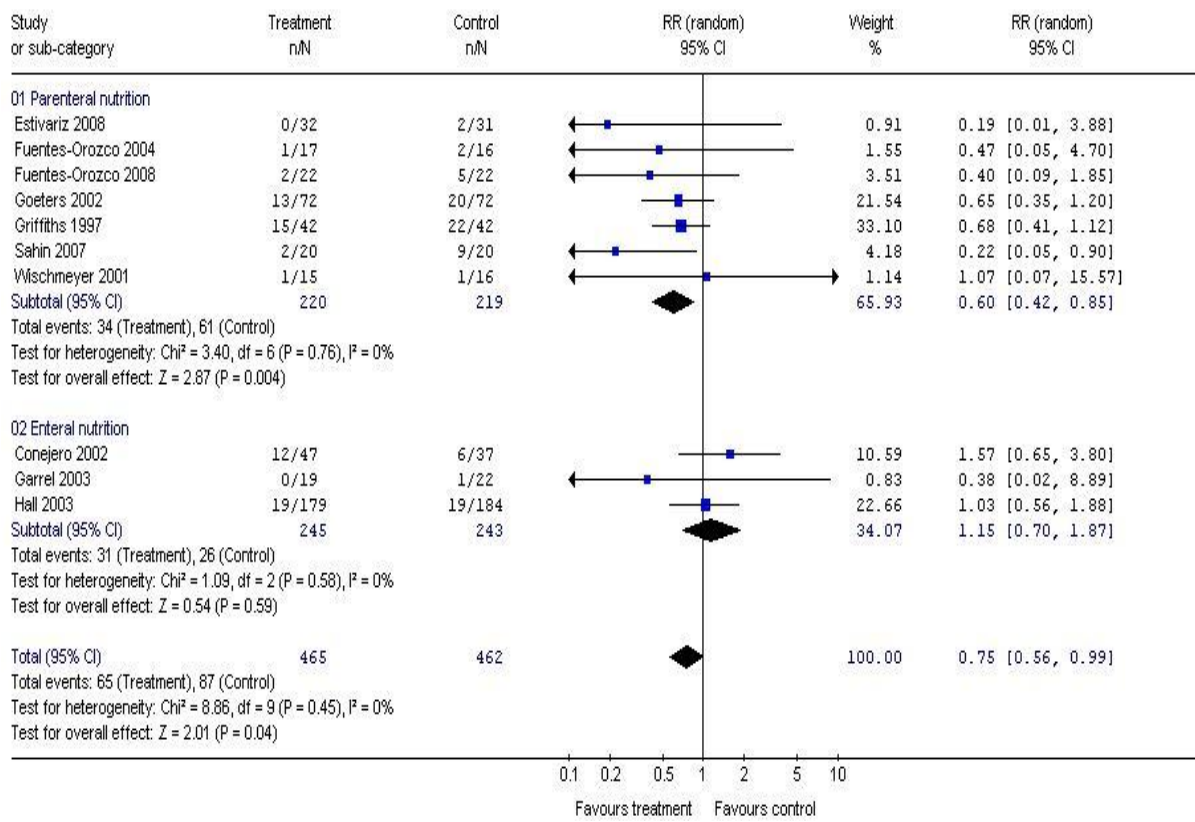


446 Figure 3



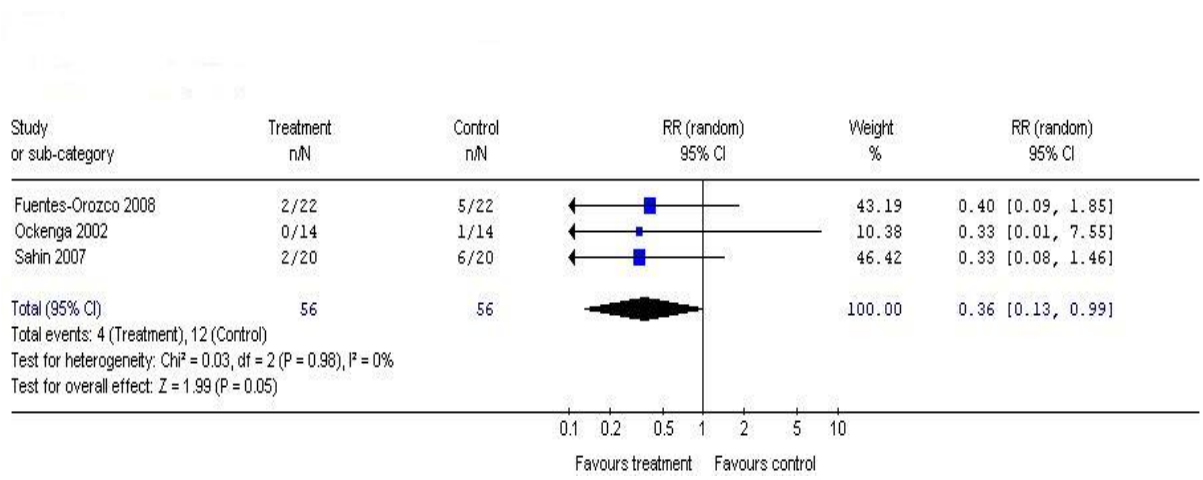
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448 Figure 4



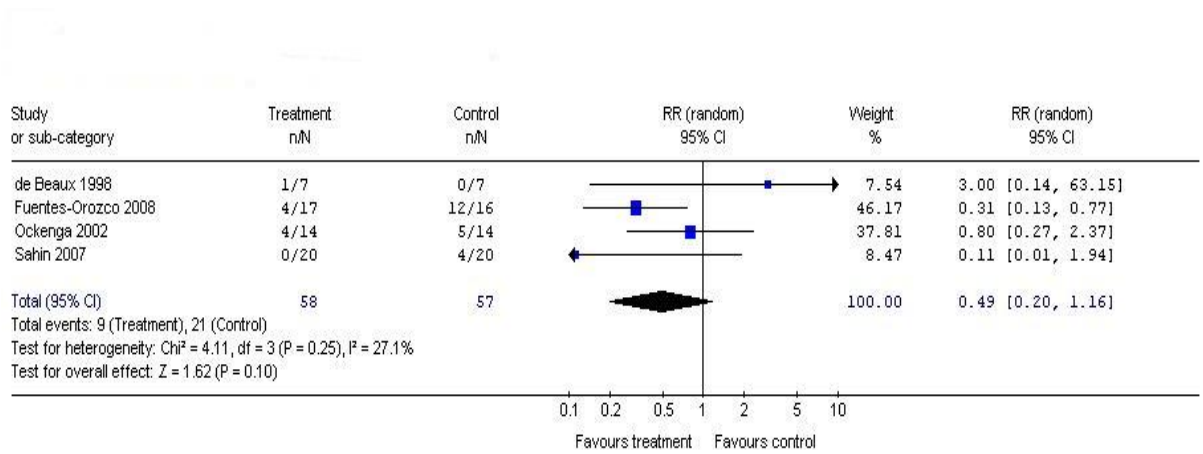
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450 Figure 5



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452 Figure 6



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