Selenium in Sepsis
A new magic bullet?

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Special Interest

The following article is one of two articles offered for continuing education credit in this issue. Please see page 382 for details.

**Canadian Clinical Practice Guidelines for Nutrition Support in Mechanically Ventilated, Critically Ill Adult Patients**

Daren K. Heyland, MD, FRCPC, MSc; Rupinder Dhaliwal, RD; John W. Drover, MD, FRCSC, FACS; Leah Gramlich, MD, FRCPC; Peter Dodek, MD, MHSc; and the Canadian Critical Care Clinical Practice Guidelines Committee

*From the *Department of Medicine and the **Department of Surgery, Queen's University, Kingston, Ontario; *Department of Medicine, Division of Gastroenterology, University of Alberta, Edmonton; and **St. Paul's Hospital, Center for Health Evaluation and Outcome Sciences, Vancouver, British Columbia, Canada*

- Updated January 2007
- Summarizes 156 trials studying 15080 patients
- 34 topics ➔ 17 recommendations

www.criticalcarenutrition.com
Background

Selenium

• Essential trace element for all mammalian species
• Involved in a number of physiological processes
• Current dietary recommendations is between 55-75 ug/day
• Deficiencies lead to submaximal expression of GSH-Px and other selenoproteins compromising cell function
• In critical illness, low levels of Se associated with increased markers of oxidative stress, worse organ failure, and increased mortality
Selenium supplementation?

Glutathione Peroxidase
Rationale for Antioxidants

OFR production > OFR consumption = OXIDATIVE STRESS

Impaired
- organ function
- immune function
- mucosal barrier function

Complications and Death

Depletion of Antioxidant Enzymes
OFR Scavengers
Vitamins/Cofactors

Infection
Inflammation
Ischemia
Rationale for Antioxidants

Death

Metabolic Shutdown Survivors

• ↓ mt DNA
• ↓ ATP, ADP, NADPH
• ↓ Resp chain activity
• Ultra structural changes

Genetic down regulation

Tissue hypoxia

cytokine effect

Prolonged inflammation

Endocrine effects

↓ mitochondrial activity

Preserved ATP
• Recovery of mt DNA
• Regeneration of mito proteins

Survivors

Death

Metabolic Shutdown
mtDna/nDNA Ratio by Day 28 Survival

P=0.04

Heyland JPEN 2007;31:109
Rationale for Antioxidants

• Endogenous antioxidant defense mechanisms
  • Enzymes (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase including their cofactors Zn and Selenium)
  • Sulfhydryl group donors (glutathione)
  • Vitamins E, C, and B-carotene

Low endogenous levels

- Lipid peroxidation and inflammation
- Organ failure
- Mortality
Oxidative Stress Connected to Organ Failure

Figure 1. Correlation between plasma thiobarbituric acid reactant substances (TBARS) concentration and Sequential Organ Failure Assessment (SOFA) score at admission in systemic inflammatory response syndrome patients (n = 139).
Rationale for Antioxidants

• Non-survivors associated with:
  – Higher APACHE III scores
  – Higher degree of oxidative stress
    • ↑ LPP
    • ↓ SH
    • ↓ TAC
  – Higher levels of inflammation (NOx)
  – Higher levels of leukocyte activation (myeloperoxidase, PMN elastase)

Alonso de Vega CCM 2002; 30: 1782
Rationale for Antioxidants

21 patients with septic shock

Exposed plasma from patients to naïve human umbilical vein endothelial cells and quantified degree of oxidative stress by a fluorescent probe (2,7-dichlorodihydrofluorescein diacetate)

Figure 1. Plasma from septic shock patients on day 1 induces higher 2'-7' DCFH fluorescence in human umbilical vein endothelial cells than plasma from healthy volunteers (Mann-Whitney (p < .0001).

Huet CCM 2007; 35: 821
Figure 2. Changes in 2'-7' DCFH levels are significantly higher at day 1, day 3, and day 5 in nonsurvivors than in survivors (analysis of variance, $p = .0015$). Values are mean ± SD.
Genome level expression profiling in children with septic shock (2,482 genes)

Large number of genes that directly depend on zinc homeostasis or play a direct role in zinc homeostasis.

Hector Wong 2007
Potential genes of interest selectively upregulated in nonsurvivors

- CC chemokine ligand 4 (a.k.a. MIP-1β)
- Granzyme B
- Interleukin-8
- Metallothionein 1E
- Metallothionein 1K
- Solute carrier family 39, member 8 (zinc transporter)
- Suppressor of cytokine signaling 1
- Transferrin
- Thrombospondin
Increased survival in MT-null mice after CLP

![Bar graph showing increased survival in MT-null mice compared to wild-type mice after CLP.]
Supplementation with Antioxidants in the Critically Ill: A meta-analysis

- 14 RCTs
- Single nutrients (selenium) and combination strategies (selenium, copper, zinc, Vit A, C, & E, and NAC)
- Administered various routes (IV/parenteral, enteral and oral)
- Patients:
  - Critically ill surgical, trauma, head injured
  - SIRS, Pancreatitis, Pancreatic necrosis
  - Burns
  - Medical
  - Sepsis, Septic Shock

Heyland Int Care Med 2005:31;327;updated on www.criticalcarenutrition.com
Effect of Combined Antioxidant Strategies in the Critically Ill

Review: Antioxidants
Comparison: 01 Antioxidants (single + combined) vs standard
Outcome: 01 Mortality

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Antioxidants n/N</th>
<th>standard n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
<th>Year</th>
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<tbody>
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<td>Berger '98</td>
<td>1/10</td>
<td>0/10</td>
<td>0.26</td>
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<td>0.49</td>
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<td>0.36</td>
<td>0.85</td>
<td>[0.07, 12.00]</td>
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<td>Crimi</td>
<td>49/112</td>
<td>76/112</td>
<td>0.74</td>
<td>0.64</td>
<td>[0.50, 0.82]</td>
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<tr>
<td>Porter</td>
<td>0/9</td>
<td>0/9</td>
<td>Not estimable</td>
<td></td>
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<td>Preiser</td>
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<td>6/17</td>
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<td>1.13</td>
<td>[0.49, 2.62]</td>
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<td>0.07</td>
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<td>Zimmerman</td>
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<td>8/20</td>
<td>1.79</td>
<td>0.38</td>
<td>[0.12, 1.21]</td>
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<td>Nathens</td>
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<td>9/294</td>
<td>2.10</td>
<td>0.54</td>
<td>[0.18, 1.60]</td>
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<tr>
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<td>[0.16, 1.38]</td>
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<td>[0.31, 1.32]</td>
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<td>[0.60, 1.06]</td>
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<td>Mishra</td>
<td>8/18</td>
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<td>5.57</td>
<td>0.85</td>
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<td>Forceville</td>
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<td>13/29</td>
<td>7.84</td>
<td>1.01</td>
<td>[0.58, 1.76]</td>
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<td>Total (95% CI)</td>
<td>728</td>
<td>732</td>
<td>100.00</td>
<td>0.72</td>
<td>[0.62, 0.85]</td>
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</table>

Total events: 148 (Antioxidants), 215 (standard)
Test for heterogeneity: Ch² = 11.76, df = 13 (P = 0.55), P = 0%
Test for overall effect: Z = 4.02 (P < 0.0001)

Favours antioxidants  Favours standard
Effect of Zinc Supplementation in the Critically Ill

Effect on Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Parenteral zinc n/N</th>
<th>Control n/N</th>
<th>RR (95%CI Random)</th>
<th>Weight %</th>
<th>RR (95%CI Random)</th>
<th>Year</th>
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</thead>
<tbody>
<tr>
<td>Berger</td>
<td>1/10</td>
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<td></td>
<td>9.8</td>
<td>3.00[0.14,65.91]</td>
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<tr>
<td>Berger 2001</td>
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<td>1/11</td>
<td></td>
<td>9.7</td>
<td>0.33[0.02,7.39]</td>
<td>2001</td>
</tr>
<tr>
<td>Young</td>
<td>4/33</td>
<td>9/35</td>
<td></td>
<td>60.5</td>
<td>0.47[0.16,1.38]</td>
<td>1996</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>5/54</strong></td>
<td><strong>10/56</strong></td>
<td></td>
<td><strong>100.0</strong></td>
<td><strong>0.55[0.21,1.44]</strong></td>
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</tbody>
</table>

Test for heterogeneity chi-square = 1.34, df=2, p=0.51
Test for overall effect z = -1.23, p = 0.2
## Results of Subgroup Analysis

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>Infection</th>
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<tr>
<td><strong>Selenium</strong></td>
<td>0.79 (0.64-0.99)</td>
<td>0.78 (0.49-1.25)</td>
</tr>
<tr>
<td></td>
<td>P=0.04</td>
<td>P=0.30</td>
</tr>
<tr>
<td><strong>No Selenium</strong></td>
<td>0.73 (0.41-1.29)</td>
<td>1.10 (0.6-2.04)</td>
</tr>
<tr>
<td></td>
<td>P=0.27</td>
<td>P=0.75</td>
</tr>
</tbody>
</table>
Largest Randomized Trial of Selenium in Sepsis

- Multicenter RCT in Germany
  - double-blinded
  - non-ITT analysis
- 249 patients with severe sepsis
- standard nutrition plus 1000 ug bolus followed by 1000 ug/day or placebo x14 days

Greater treatment effect observed in those patients with:

- supra normal levels vs normal levels of selenium
- Higher APACHE III
- More than 3 organ failures
Smallest Randomized Trial of Selenium in Sepsis

- Single center RCT
  - double-blinded
  - ITT analysis
- 40 patients with severe sepsis
  - Mean APACHE II 18
- Primary endpoint: need for RRT
- standard nutrition plus 474 ug x 3 days, 316 ug x 3 days; 31.6 ug thereafter vs 31.6 ug/day in control

Mishra Clinical Nutrition 2007;26:41-50
Smallest Randomized Trial of Selenium in Sepsis

• Increased selenium levels
• Increased GSH-Px activity
• No difference in
  • RRT (5 vs 7 patients)
  • mortality (44% vs 50%)
  • Other clinical outcomes

Effect on SOFA scores

Mishra Clinical Nutrition 2007;26:41-50
Most Recent Trial of Selenium Supplementation in Sepsis

- Anti-inflammatory, anti-apoptotic effects of high dose Se
- Pilot RCT, double-blind, placebo controlled
  - 60 patients with severe septic shock

4000 mcg followed by 1000mcg/day x 10 days
Placebo

No difference in pressor withdrawal, LOS, mortality

New organ failure: 32 vs 14%, p=0.09

Forceville Crit Care 2007:11:R73
Toxicity dependent on dose and type of selenium
<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Elective Surgery</th>
<th>Critically Ill</th>
<th>Population</th>
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<tr>
<td></td>
<td>General</td>
<td>Septic</td>
<td>Trauma</td>
</tr>
<tr>
<td>Arginine</td>
<td>Benefit</td>
<td>No benefit</td>
<td>Harm</td>
</tr>
<tr>
<td>Glutamine</td>
<td>Benefit</td>
<td>PN Beneficial (? receiving EN)</td>
<td>EN Possibly Beneficial</td>
</tr>
<tr>
<td>Omega 3 FFA</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>…</td>
<td>Possible Benefit</td>
<td>…</td>
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</table>

Canadian Clinical Practice Guidelines  JPEN 2003;27:355

www.criticalcarenutrition.com
REducing Deaths from Oxidative Stress:
The REDOXS study

A multicenter randomized trial of glutamine and antioxidant supplementation in critical illness
The Research Protocol

The Question(s)

In enterally fed, critically ill patients with a clinical evidence of acute multi organ dysfunction

- What is the effect of glutamine supplementation compared to placebo
- What is the effect of antioxidant supplementation compared to placebo

...on 28 day mortality?
REducing Deaths from OXidative Stress:

The REDOXS study

Factorial 2x2 design

Concealed
Stratified by
- site
- Shock

1200 ICU patients
Evidence of organ failure

glutamine

placebo

antioxidants

placebo

placebo

R

R

R

R

R
## Combined Enteral and Parenteral Nutrients

<table>
<thead>
<tr>
<th>Group</th>
<th>Enteral Supplement</th>
<th>Parenteral Supplement</th>
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<tbody>
<tr>
<td>A</td>
<td>Glutamine + AOX</td>
<td>Glutamine + Selenium</td>
</tr>
<tr>
<td>B</td>
<td>Placebo + AOX</td>
<td>Placebo + Selenium</td>
</tr>
<tr>
<td>C</td>
<td>Glutamine + Placebo</td>
<td>Glutamine + Placebo</td>
</tr>
<tr>
<td>D</td>
<td>Placebo + Placebo</td>
<td>Placebo + Placebo</td>
</tr>
</tbody>
</table>
Optimal Dose?

• High vs Low dose:
  – observations of meta-analysis
• Providing experimental nutrients in addition to standard enteral diets
Optimizing the Dose of Glutamine Dipeptides and Antioxidants in Critically Ill Patients:

A phase 1 dose finding study of glutamine and antioxidant supplementation in critical illness

JPEN 2007;31:109
The Research Protocol

The Question

In critically ill patients with a clinical evidence of hypoperfusion...

• What is the maximal tolerable dose (MTD) of glutamine dipeptides and antioxidants as judged by its effect on multiorgan dysfunction?
The Research Protocol

The Design

- Single Center
- Open-label
- Dose-ranging study
- Prospective controls

Patients

- Critically Ill patients in shock
## The Research Protocol

### Intervention

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Dose of Dipeptides (glutamine)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Parenterally* (gm/kg/day)</td>
<td>Enterally^ (gm/day)</td>
<td>AOX</td>
</tr>
<tr>
<td>1</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>.5 (.35)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>.5 (.35)</td>
<td>21 (15)</td>
<td>½ can</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>.5 (.35)</td>
<td>42 (30)</td>
<td>full can (300 mcg EN Selenium)</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>.5 (.35)</td>
<td>42 (30)</td>
<td>full can + 500ug IV Selenium</td>
</tr>
</tbody>
</table>
The Research Protocol

Outcomes

• Primary: $\triangle$SOFA
• Secondary (groups 2-5);
  • Plasma levels of Se, Zn, and vitamins
  • TBARS
  • Glutathione
  • Mitochondrial function (ratio)
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control N=30</th>
<th>Group 2 N=7</th>
<th>Group 3 N=7</th>
<th>Group 4 N=7</th>
<th>Group 5 N=7</th>
<th>All N=58</th>
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<tbody>
<tr>
<td><strong>Age (Mean)</strong></td>
<td>64.2</td>
<td>65.5</td>
<td>65.2</td>
<td>65.6</td>
<td>71.8</td>
<td>65.6</td>
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<tr>
<td><strong>Female (%)</strong></td>
<td>11 (37%)</td>
<td>2(29%)</td>
<td>1(14%)</td>
<td>2(29%)</td>
<td>3(43%)</td>
<td>19(33%)</td>
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<tr>
<td><strong>APACHE II score (Mean)</strong></td>
<td>23.2</td>
<td>25.1</td>
<td>22.1</td>
<td>21.9</td>
<td>20.6</td>
<td>22.8</td>
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<tr>
<td><strong>Etiology of shock</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Cardiogenic (%)</td>
<td>6 (86%)</td>
<td>1(14%)</td>
<td>3 (43%)</td>
<td>3 (43%)</td>
<td>1(14%)</td>
<td>13(46%)</td>
</tr>
<tr>
<td>Septic (%)</td>
<td>1(14%)</td>
<td>4 (57%)</td>
<td>4 (57%)</td>
<td>5(71%)</td>
<td>1(14%)</td>
<td>14(50%)</td>
</tr>
<tr>
<td>Hypovolemic (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1(4%)</td>
</tr>
<tr>
<td><strong>ICU days (Median)</strong></td>
<td>6.4</td>
<td>14.3</td>
<td>7.9</td>
<td>13.1</td>
<td>9.7</td>
<td>8.0</td>
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<tr>
<td><strong>28 day mortality (%)</strong></td>
<td>9(30%)</td>
<td>3(43%)</td>
<td>2(29%)</td>
<td>3(43%)</td>
<td>1(14%)</td>
<td>18(31%)</td>
</tr>
</tbody>
</table>
Effect on SOFA

Total SOFA Score for Control Group

Total SOFA Score for Group 2

Total SOFA Score for Group 3

Total SOFA Score for Group 4

Total SOFA Score for Group 5

Total SOFA Regression Lines

Effect on SOFA
Effect on TBARS

TBARS Group 2

P = 0.82

TBARS Group 3

P = 0.90

TBARS Group 4

P = 0.11

TBARS Group 5

P = 0.03

TBARS Average Slopes

P = 0.25
Effect on Glutathione
Effect on MITO RATIO

mtDNA/nDNA Ratio Group 2
P=0.99

mtDNA/nDNA Ratio Group 3
P=<0.0001

mtDNA/nDNA Ratio Group 4
P=0.90

mtDNA/nDNA Ratio Group 5
P=0.03

mtDNA/nDNA Average Slopes
P=0.001
Effect of Antioxidants on Mitochondrial Function

![Graph showing the effect of antioxidants on mitochondrial function over time. The graph compares Group 2 and Group 3, 4, 5, with the red line representing Group 2 and the blue line representing Group 3, 4, 5. The x-axis represents day, and the y-axis represents mtDNA/nDNA ratio.]
Inferences

<table>
<thead>
<tr>
<th></th>
<th>Parenterally</th>
<th>Enterally</th>
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<tbody>
<tr>
<td>Glutamine/day</td>
<td>0.35 gms/kg</td>
<td>30 gms</td>
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<tr>
<td>Antioxidants per day</td>
<td>500 mcg Selenium</td>
<td>Vit C 1500 mg</td>
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<tr>
<td></td>
<td></td>
<td>Vit E 500 mg</td>
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<tr>
<td></td>
<td></td>
<td>B carotene 10 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zinc 20 mg</td>
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<tr>
<td></td>
<td></td>
<td>Se 300 ug</td>
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</tbody>
</table>

- High dose appears safe
- High dose associated with
  - no worsening of SOFA Scores
  - greater resolution of oxidative stress
  - greater preservation of glutathione
  - Improved mitochondrial function

Heyland JPEN Mar 2007
REDOXS: A new paradigm!

- Nutrients dissociated from nutrition
- Focus on single nutrient administration
- Rigorous, large scale, multicenter trial of nutrition related intervention powered to look at mortality
- Sick homogenous population
- Preceded by:
  - Standardization of nutrition support thru the development and implementation of CPGs
  - A dosing optimizing study
- Funded by CIHR

www.criticalcarenutrition.com
Conclusions (1)

• “Based on 1 level 1 and 9 level 2 studies, the use of IV/EN selenium supplementation alone or in combination with other antioxidants should be considered in critically ill patients.”

Optimal Dose: 500-1000 (800) mcg/day

Canadian CPGs
www.criticalcarenutrition.com
Conclusions (2)

Nutrition Therapy: Modulating the Stress Response

Adjunctive Supportive Care

Proactive Primary Therapy