Bovine Colostrum and Immunity in athletes: A role in reducing infection and gut permeability?

Dr Glen Davison
School of Sport & Exercise Sciences: Endurance Research Group
Are athletes at increased risk of infection?

- Yes, especially endurance athletes during periods of heavy training and competition.
- Especially infections of the upper respiratory tract (URTI)
Factors contributing to infection incidence in athletes

**Stress Responses:**
- Physiological stress of exercise
- Psychological stress of competition etc.
- Environmental stress
- Inadequate diet
- Lack of sleep

**Increased Exposure to/Entry of pathogens:**
- Increased $V_E$ & aspiration
- Skin abrasions
- Foreign travel
- Contact with other people

---

**Immunodepression**

The Open Window Theory:
*Pedersen & Ullum 1994; Nieman (1994)*

**Increased Infection RISK**
The J-Shaped Curve:


Above Average

Average

Below Average

Infection Risk

Immune function

~2-4 URTI/year

Immunodepression

Sedentary

Active Individual

Athlete
Exercise-induced immunodepression

Mechanisms:
- Acute “Open Windows” (many times in typical training week)
- Chronic effects: Cumulative acute effects; Intensified training
  - Acute effects: largely mediated by:
    - Stress Hormones, IL-6 etc.
    - Oxidative stress
    - Glucose
    - Immature Cells

Acute effects: largely mediated by:
- Gut permeability
- Immune Function
- Nutritional countermeasures???
- URTI Risk
Bovine Colostrum (Early Milk)

A nutritional countermeasure?

- Bovine colostrum:
  - The initial milk produced by cows within 48 h of calving.
  - Hyper-immune or ‘normal’
    - Hyper-immune used clinically or in animals!!!
    - Studies with athletes use **NORMAL**

- Contains bioactive (immuno-enhancing) substances
  - Provides ‘passive immunity’ to calves in 1st few days of life
  - **THIS IS NOT THE MECHANISM IN HUMANS !!!**

- **NOTE**: most products are from organic dairies and only surplus is collected.
Bovine Colostrum (Early Milk)

A nutritional countermeasure?.... What ARE the mechanisms?

Phys responses

Immune markers

URTI

1

2

3

Generally YES

Usually Not

Depends

University of Kent
Colostrum and immunity
Crooks et al. (2006). Salivary IgA
(26 g/d for 12 weeks in runners)

Figure 2—Time-dependent changes in the median absolute concentration of s-IgA and 95% confidence intervals. ** indicates significant increase in levels of s-IgA in colostrum group compared to baseline ($P = 0.0291$).
Colostrum and immunity
Davison & Diment (2010).
(20 g/d for 4 weeks)

No effects on
• Stress response markers
• salivary IgA, WBC#
• Above replicated many times
Bovine Colostrum & Infection symptoms in athletes


- N = 174
- 7-wk training period
  - 8-wk suppl.
- 60 g/d COL vs PLA
Bovine Colostrum & Infection symptoms in athletes?


- **N = 29** (highly trained ♂ road cyclists)
- 5-wk intensive training
  - pre & post testing = 9 wks total
- 10 g/d COL vs PLA

**Immune markers?**
- Blunted post-ex ↓ cytotoxic/suppressor T cells
- Prevented post-exercise ↓ in serum IgG₂
Bovine Colostrum & Infection symptoms in athletes?

Crooks et al. (2010). *Int J Sport Nut Exerc Metab*, 20, 224-235

- **N = 25**
  (elite swimmers [♂ & ♀])
- **10-wk period**
- **25 g/d COL vs PLA**

### URTI incidence

- **∼59% lower**  
  ($P = 0.062$)

### Immune markers?
- No effects on salivary or serum Ig levels
Jones et al (2013/in press), *Brain Behav Immun*

- **N = 53** endurance athletes
- **12-wk** training period
- **20 g/d** COL vs PLA
  - isocaloric/macronutrient

- Overall COL = ↓ URTI
- Only benefit during periods with ↑ incidence
- No effects on **resting** levels of salivary IgA, Lys, Lac, WBC# or WBC functions
- Overall salivary bacterial load effects
  - Marker of *in vivo* innate immune defence

---

*Graph 1*: URI reported by participants (% of group)
- ~40% lower
- ~65% lower

*Graph 2*: Total URI days (% of 4 week interval)

*Graph 3*: Log of estimated copy number of 16S rRNA genes
- g. 2. Salivary bacterial load in bovine colostrum (COL)/placebo (PLA) groups. Standard deviation as error bars. * Significant increase in salivary bacterial load from baseline to 12 weeks in PLA group (p < .001).
What causes the “Immune Effects”?  

Sugisawa et al. (2002, 2003). Neutrophil function (BC added *in vitro*)

- Priming due to lowest MW (< 10 kDa) fraction *in vitro*
  - Possibly Proteose Peptones
- LMW fraction effects inactivated by heat-treatment

So do you need to take it for up to 12 weeks?
• Potential benefits with **Acute intake**

• Blunted post-ex↓ in **some** immune markers

• Attributable to bioavailable components
  • But not as good as longer suppl. periods

• Effects on URTI **??**
What causes the “Immune Effects”?

Exercise

↑ Stress
↑ Hormones
IL-6 etc.
↓ Glucose
↑ Oxidative stress
↑ Immature Cells

↑ Gut permeability

Immune Function

URTI Risk
Summary Immune and URTI effects

- Evidence for benefit to immunity
  - But depends what you measure & when you measure it
  - Depends on load/stress (i.e. no benefit if no ↑ risk)
    - *So not for everybody, all of the time!*

- Good evidence for ↓URTI risk in athletes
  - More likely if under high load/stress
    - *Typically 30-65% lower URTI incidence*
Exercise effects on the gut

Reviewed very recently by de Oliveira et al (2014).

Gut issues

• Very common in endurance athletes
• More common in runners
  • GI problems reported in between 30–93% athletes
    • e.g. nausea, vomiting, cramping, diarrhoea, GI bleeding

• Affect performance, recovery and health?

**GI symptoms**

Some symptoms may be related to exercise-induced increases in GUT permeability (“leaky gut”).

- i.e. ↑ translocation of bacterial toxins (endotoxins, e.g. LPS)
  - Mild → diarrhoea
  - Severe → heat illness
    → sepsis, inflammatory cascade, MOF

Leon & Helwig, 2010; Lim & Mackinnon, 2006

- Not only mechanisms
- Inconclusive to what extent this is mechanistically involved in GI symptoms commonly reported by athletes
  - e.g. Jeukendrup et al (2000): no correlation between GI symptoms and LPS response
    - *but relationship may be more complex than can be explained by simple correl*
  
  e.g. Leon & Helwig, 2010; Lim & Mackinnon, 2006

- Either way…. ↑ permeability prob not a good thing!!!
Exercise effects on the gut


Causes?

- Mechanical
- Nutritional
- Physiological

GUT issues

Mechanisms?

- Gastrointestinal ischemia
- Heat stress
- Epithelial damage:
  - Barrier function/Permeability
Exercise and GUT permeability

Pals et al. (1997). Exercise-induced increase in gut permeability (60 min run)

May be related to increase in core temperature (amongst other things)!

![Graph showing lactulose/Rhamnose levels at different % Peak Oxygen Uptake](diagram1.png)

![Graph showing relationship between terminal rectal temperature and lactulose/Rhamnose levels](diagram2.png)

*Mean±SE
n=6
*p<0.05 vs. R, 40, and 60%
Increased permeability = increased endotoxaemia?

Ashton et al. (2003). Ramp test

Jeukendrup et al. (2000).
LD triathlon race
(3.8 km; 185 km; 42.2 km)
Bovine Colostrum and GUT permeability

Prosser et al. (2004).

Playford et al. (2001). NSAID-induced ‘gut damage’
Bovine Colostrum and Exercise-induced gut permeability

Marchbank et al. (2011), *Am J Physiol Gastrointest Liver Physiol*, 300, G477-G484

- **N = 12**
  - (healthy, active males)
- 2 weeks supplementation
  - Double-blind, counterbalanced-crossover design
- **20 g/d COL vs PLA**
  - isocaloric/macronutrient
- Treadmill running: 20 min at 80% VO\textsubscript{2}max.
Bovine Colostrum and Exercise-induced gut permeability

**Mechanisms?**
- ↓ heat-induced Apoptosis in Gut epithelial cells
- ↑ HSP induction (esp. under heat stress).
- ↓ *damage* and/or ↑ *repair*??
GUT damage

March et al (2014)

Replicated Marchbank et al. (2011) design.... extending in vitro work to identify mechanisms.
↓ GUT damage

March et al (2014)

Replicated Marchbank et al. (2011) design…

… extending in vitro work to identify mechanisms

Marker of intestinal epithelial damage

March et al (in prep)
Acute effects?? March et al (2014)

Replicated Marchbank et al. (2011) design…plus 2d suppl.

Prolonged/repeated exposure may be required?
Gut permeability summary

• COL limits exercise-induced ↑ gut permeability

  • Likely contributes to immune effects

  • May have role in GI complaints???
    • But this needs further work as the relationship between permeability, LPS and GI symptoms is still not fully understood
Controversy ???

Colostrum is not prohibited *per se*, however it contains certain quantities of IGF-1 and other growth factors which are prohibited and can influence the outcome of anti-doping tests. Therefore WADA does not recommend the ingestion of this product.
Controversy ???

IGF-1 ???

- Actually- no credible evidence that it would influence a doping test.
- Proteins digested and broken down
- Meat intake = more likely to increase IGF-1 levels
  - e.g. Giovannucci et al. (2003), *Cancer Epidemiol Biomarkers Prev*, 12, 84-9.
- Can consume same amount with very high milk intake
  - See Playford et al. (2000), *Am J Clin Nutr* 72, 5-14
- COL part of natural diet of some pastoral communities

- But the WADA statement puts us in a difficult position
- *What should we advise our athletes???
IGF-1

Kuipers et al (2002), *Nutrition*, 18, 566-7

- **60 g/day for 4 weeks**
- **Plus acute dose (2 h pre-sample)**

![Graph showing IGF-1 levels over time](image)

**Other studies on IGF**

- **Buckley et al. (2003), J Sports Sci, 21, 577-88**
  - 60 g/d 8 wks = **NO EFFECT**

- **Mero et al. (2002), J Appl Physiol, 93, 732-9.**
  - 20 g/d 2 wks = ~17% **INCREASE**
  - Tracer method confirming breakdown during digestion
  - So could be due to PRO vs CHO in Placebo
  & Similar ↑ seen just from **PROTEIN** (e.g. Willoughby et al., 2007, *Amino Acids*, 32: 467–477- 40 g protein/day = 25% ↑)

- **Duff et al. (2013), Int J Sport Nutr Exerc Metab, in press.**
  - 60 g/d 8 wks = **NO EFFECT**

![Graph showing IGFBP-3 levels over time](image)
Side-effects???

- Most research: no serious side-effects
- Some minor side-effects noted occasionally (for 1-2 days):
  - **Herxheimer reaction**
    (note: this is sometimes seen with antibiotics)
    - minor rashes
    - bowel changes
    - flu-like symptoms
Summary

• Daily COL supplementation may:
  • Maintain immunity during heavy training/stressors
  • Decrease URTI risk

• Can limit exercise-induced gut permeability
  • May contribute to immune effects?
  • … and GI complaints??? (needs further work)

• Dose-response & duration/dose response???
  • not yet studied (well)
Thanks for your attention

Endurance Research Group
Acknowledgements

**Funding**

The Golden Dairy Ltd

**Collaborators**

Prof. Ray Playford
Dr. Tania Marchbank
Bethany Diment
Jemma Oakes
Prof. Luis Mur
Simon Cameron

**PhD students**

Arwel Jones
Daniel March