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# Does Heat Stress Affect Immune Function in Dairy Cows?

A Knowledge Summary by

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# KNOWLEDGE SUMMARY

**Clinical bottom line**

Heat stress appears to generally suppress innate immune function in both dry and lactating dairy cows. Immune effects that are decreased include cytokine production, proliferation of immune cells, migration of lymphocytes to the udder and cell viability. This may lead to an increase in the risk of clinical diseases such as mastitis and metritis.

## Question

In dairy cows experiencing heat stress (in most papers defined as a temperature/humidity index of >65 at the lowest threshold (Bernabucci, 2014), vs. cows in environmentally cooled conditions, is innate immune functionality affected?

## The evidence

A previously published review revealed that cows experiencing high temperature humidity indices reduce milk yields beyond that expected of the reduction in dry matter intake (Baumgard, 2013) and therefore do not appear to experience ketosis. It is clear however, that cows experience some discomfort. The innate immune system is the first line of defense against invading pathogens, and any factor which suppresses the efficiency of this protection increases the risk of diseases (Kehrli, 1989).

Acronyms:

- IMI=intramammary infections;
- DIM=Days in Milk;
- Resp=respiration;
- TLR=Toll-like receptor;
- IL=interleukin;
- TNF=tumour necrosis factor;
- Temp=temperature;
- HSTF=heat shock transcription factor;
- HSP=heat shock protein;
- bST=bovine somatotropin;
- THI=temperature humidity index;
- BRS=Brown Swiss;
- HOL=Holstein;
- PMN=polymorphonuclear leukocytes;
- Th1=T-helper 1 response;
- Ig=immunoglobulin

## Summary of the evidence

| Thompson (2014) | |
|---|---|
| **Population:** | Multiparous dairy cows in the dry period |
| **Sample size:** | 15 cooled dry cows and 15 heat stressed cows. 5 from each group were induced Streptococcus uberis IMI at 5DIM |
| **Intervention details:** | THI in non-cooled conditions was 77.9-78.3. Cooling involved fans, water sprinklers and shade in this group |
| **Study design:** | Cohort Study |
| **Outcome studied:** | Rectal temperature, respiratory rate, milk yield and composition, blood parameters: Immune response genes (TLR2, IL1-β, IL6, IL8, IL10, and TNFα) |
| **Main findings: (relevant to PICO question):** | Cooled dry cows had:<br>• Lower temperature and respiratory rate,<br>• Higher milk yield (no change in composition) by 3.8L/d<br>• Higher neutrophil count after IMI<br>• Higher IL10<br>• Higher TLR2<br>• All other cytokines had no difference |
| **Limitations:** | • Very low cow numbers<br>• Measured over 0-36 hours post IMI for cytokines and to 40 weeks into lactation for physiology<br>• All cows were cooled after calving<br>• Insufficient power to conclude an effect on milk yield, however, any numerical effects seen are valid as the primiparous group were not included |

| Collier (2008) | |
|---|---|
| **Population:** | Dairy cows experiencing heat stress >35°C |
| **Sample size:** | NA |
| **Intervention details:** | NA |
| **Study design:** | Review of cohort studies |
| **Outcome studied:** | NA |
| **Main findings: (relevant to PICO question):** | Gene expression changes to heat above 35°C include:<br>• activation of heat shock transcription factor 1 HSTF1<br>• increased expression of heat shock proteins (HSP)<br>• increased glucose and amino acid oxidation and reduced fatty acid metabolism<br>• endocrine system activation of the stress response<br>• immune system activation via extracellular secretion of HSP |
| **Limitations:** | NA |

| Kamwanja (1994) | |
|---|---|
| **Population:** | Lymphocytes from 3 breeds of heifers |
| **Sample size:** | 12 heifers of Angus, Brahman and Senepol |
| **Intervention details:** | Killing lymphocytes after incubation at 45°C for 1 or 12 hours |
| **Study design:** | Cohort study on lymphocyte populations |
| **Outcome studied:** | Viability of lymphocytes and HSP production when killed after 45°C for 1 hour or 12 hours |
| **Main findings: (relevant to PICO question):** | Decrease in viability at 45°C in Brahman and Senepol |
| **Limitations:** | In vitro work with little relevance to in vivo effects |

| Elvinger (1992) | |
|---|---|
| **Population:** | Dairy cows during lactation |
| **Sample size:** | 34 cows at parity 1-8 and DIM 30-209 given either bST or placebo (16 in control, 18 in bST treated group). On day 10 after initialising placebo or bST cows were placed in cross over heat stress and normalised environments) |
| **Intervention details:** | Heat stress (35-44°C) or normalised (26-33°C) |
| **Study design:** | Cohort study (cross-over) |
| **Outcome studied:** | Temperature, respiratory, cortisol, milk yield, lymphocyte numbers (CD4+ and 8+) |
| **Main findings: (relevant to PICO question):** | • Heat stress increased rectal temperatures, respiration rates, and plasma cortisol concentrations and decreased milk yield<br>• No discernible effects on immune function due to bST<br>• Heat stress reduced lymphocyte migration to udder |
| **Limitations:** | • Very low cow numbers<br>• Cows ranged from lactation 1-8 with no specification as to numbers in each lactation. This may affect yield results (lactation 1 cows give less milk than lactation >1). |

| Elvinger (1991) | |
|---|---|
| **Population:** | Heat stressed lactating dairy cows |
| **Sample size:** | NA |
| **Intervention details:** | Incubated lymphocytes in high or low temperatures to see viability |
| **Study design:** | Case study |
| **Outcome studied:** | Viability of leukocytes incubated at 38°C and 42°C |
| **Main findings: (relevant to PICO question):** | During spring THI was 72 and in the summer it was 79.<br>In summer: |

| | |
|---|---|
| | • DNA synthesis was lower<br>• Immunolglobulin M secretion was higher<br>• Plasma cortisol was higher (2ng vs >4ng/ml before calving, not after) |
| **Limitations:** | The cows weren't grouped<br>Variation in feed possible and other management factors (stocking etc.) |

| **Lacetera (2006)** | |
|---|---|
| **Population:** | Comparing leukocytes from BRS and HOL lactating dairy cows |
| **Sample size:** | 5 BRS and 5 HOL cows |
| **Intervention details:** | Incubation of PMNs at 39°C and 43°C |
| **Study design:** | Cohort study |
| **Outcome studied:** | PMN:<br>Proliferation<br>HSP72 synthesis |
| **Main findings: (relevant to PICO question):** | • PMNs from BRS breed appeared to have a lower tolerance to heat. BRS is supposed to be a more heat tolerant breed.<br>• Heightened temperature<br>• Lowered ROS activity<br>• Higher HSP72 synthesis in BRS but not HOL<br>• HOL appeared to have a more tolerant effect to higher temperatures than BRS |
| **Limitations:** | • Low numbers of cows, however the study is comparing cells rather than cows<br>• HSP72 synthesis may not be conclusive as it is unclear whether or not pre-or post-transcription levels on mRNA are determined. |

| **Lacetera (2005)** | |
|---|---|
| **Population:** | Transition HOL dairy cows (dry and in early lactation) |
| **Sample size:** | 34 cows. 28 calving in spring and 12 in summer. During spring THI averaged 72 and in the summer it averaged 79. |
| **Intervention details:** | Comparing cows calving in spring and summer |
| **Study design:** | Cohort study |
| **Outcome studied:** | Blood (leukocytes) taken weekly, from -4wk to +4wk around calving |
| **Main findings: (relevant to PICO question):** | In summer:<br>• DNA synthesis was lower<br>• IgM secretion was higher<br>• Plasma cortisol was higher (2ng vs >4ng/ml before calving, |

| | |
|---|---|
| | not after) |
| **Limitations:** | • Very low cow numbers<br>• Many more cows in winter group vs summer group<br>• Variation in feed possible and other management factors (stocking etc.) from spring to summer. This may have affected physiological factors |

| **Do Amaral (2010 and 2011)** | |
|---|---|
| **Population:** | Comparing lymphocyte function in heat stressed and cooled multiparous lactating cows |
| **Sample size:** | 21 heat stressed and 16 cooled lactating cows (from 42 days pre calving) |
| **Intervention details:** | Cooling system had fans and sprinklers active at greater than 21°C. |
| **Study design:** | Cohort study |
| **Outcome studied:** | mRNA expression of prolactin receptor PRL-R, Suppressor of cytokine activity proteins SOCS-1, SOCS-2, SOCS-3, cytokine-inducible SH2-containing protein, and heat shock protein 70 typed at Kilodalton A5 (or HSPA5) |
| **Main findings: (relevant to PICO question):** | Heat stress:<br>• Had greater prolactin (PRL) in plasma<br>• Had lower lymphocyte proliferation<br>• Had lower SOCS (suppressors of cytokine function) levels<br>• Had lower TNFα expression<br>• Had lower PRL receptor expression |
| **Limitations:** | • Low cow numbers<br>• Did not concentrate on many innate, Th1 parameters<br>• Did not mention the difference in temperature of cooled vs heat stressed groups |

| **Lacetera (2002)** | |
|---|---|
| **Population:** | Transition dairy cows in spring and summer |
| **Sample size:** | 20 spring calving cows and 9 summer calving cows |
| **Intervention details:** | spring THI 58<br>Summer THI 72 |
| **Study design:** | Cohort study |
| **Outcome studied:** | • Rectal temperature<br>• Respiratory rate<br>• Proliferation of PMNs<br>• Colostrum Ig levels |
| **Main findings: (relevant to PICO question):** | Summer vs spring:<br>• Increased rectal temperature |

| | |
|---|---|
| | • Increased respiratory rate<br>• No effect on proliferation or colostrum Ig levels |
| **Limitations:** | May be different management systems at different times, small cow numbers and very moderate THI for heat |

## Appraisal, application and reflection

There are relatively few papers directly addressing the effects of heat stress on immune function specifically, especially those concentrating on non-specific, innate effects that may be significant to the development of subsequent diseases. However, there are some agreements between the above papers that physiological effects are apparent as well as immune suppressive effects in temperature and humidity levels over THI levels at greater than or equal to 72.

Most papers compare cooled cows to heat stressed cows and either focus on outcomes in vivo or from leukocytes taken from the cows and subsequent functions in vitro.

Cows or leukocytes in cooled conditions appear to have:

- Lower rectal temperatures
- Lower respiratory rates
- Lower cortisol levels in plasma
- Higher milk yield (3.8L/d)
- Higher IL10,2, neutrophil count, Lower TNF α, Lower suppressors of cytokine function
- Higher viability of leukocytes
- No effect on Ig levels in colostrum
- Better migration of lymphocytes to udder
- Higher prolactin receptor expression
- Lower prolactin production
- Higher heat shock transcription factor HSTF1 and heat shock protein HSP72 expression (but(B. U. Lacetera N. 2006) states that the function of the latter molecule remains unknown) but post-transcriptive effects are not determined.

## Methodology Section

| **Search Strategy** | |
|---|---|
| Databases searched and dates covered: | Used 3 databases: PubMed, CAB Abstracts (1973-2015) accessed on the OVID platform) and Google Scholar. PubMed did not achieve many hits (5) so I tried Google Scholar. PubMed also had too many results to process when using immun*, so I had to restrict to (immune OR immunity).<br>Hit 16,400 results. Filtered to 2000-2016, After the first 4 pages, virtually none were relevant to the PICO. |
| Search terms: | ((((cow$ AND cattle AND bovi*))) AND heat stress) AND ((immune OR immunity)) – PubMed<br><br>does heat stress affect dairy cow immun* - Google Scholar<br><br>(cow$ AND cattle AND bovi* AND heat stress AND (immune OR immunity)).mp - CAB Abstracts |
| Dates searches performed: | 18th March, 2016 |

| Exclusion / Inclusion Criteria | |
|---|---|
| Exclusion: | NA |
| Inclusion: | Relevance to PICO, sufficient evidence level, answers the clinical question |

| Search Outcome | | | |
|---|---|---|---|
| Database | Number of results | Number of duplicates | Total relevant papers |
| NCBI PubMed | 17 | 12 | 5 |
| Google Scholar | 16,400 | 16,394 | 6 |
| CAB Abstracts | 53 | 47 | 6 |
| **Total relevant papers when duplicates removed** | | | **9** |

## CONFLICT OF INTEREST

The author declares no conflict of interest.

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