

# Fever, Vitamin C, antipyretics

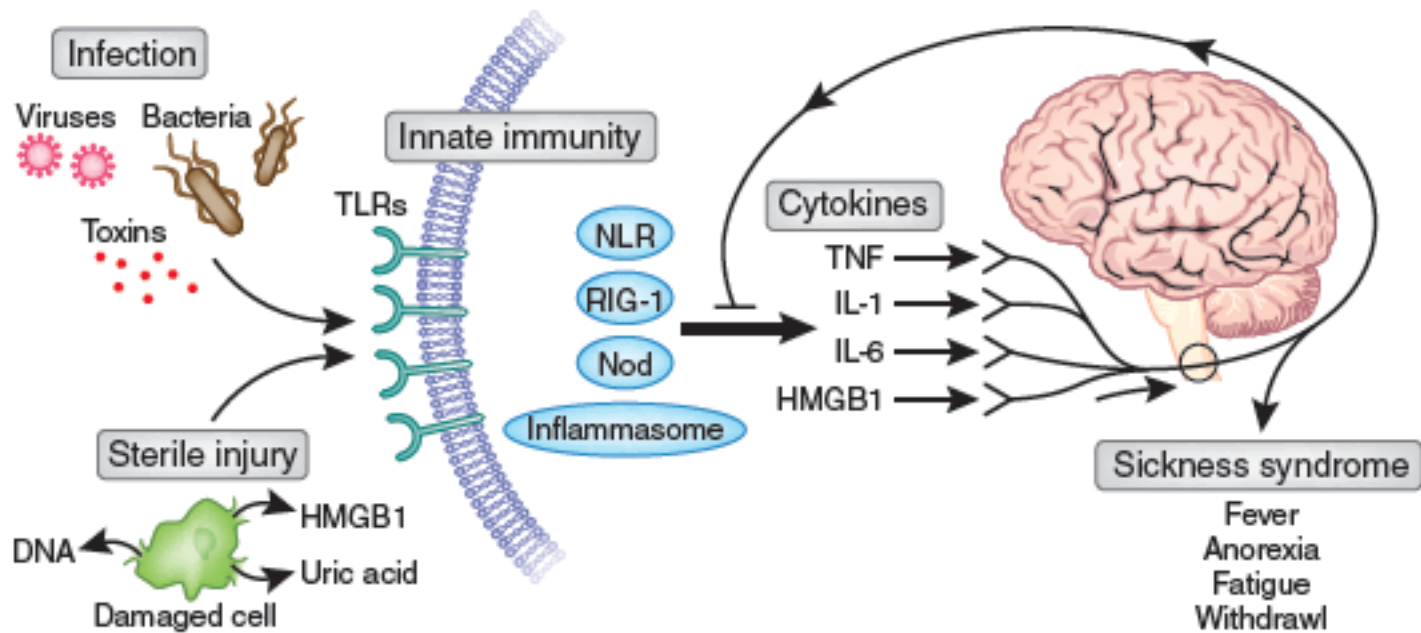
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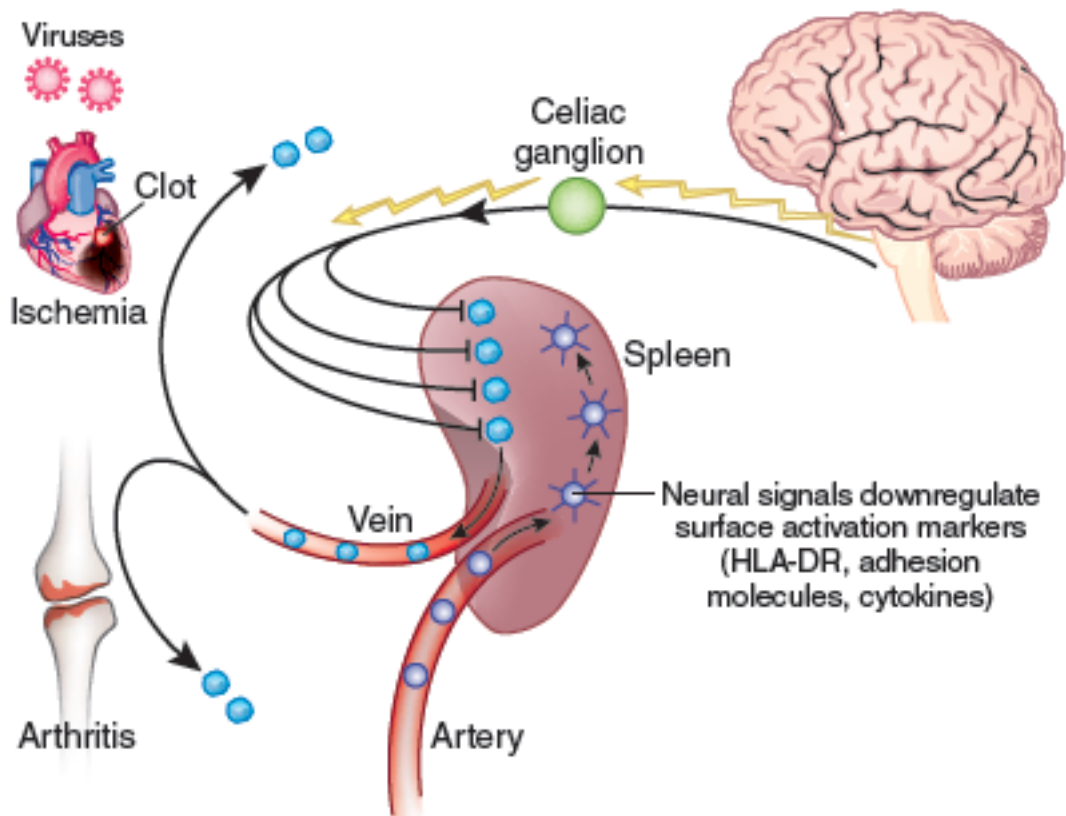
# Old Fever Interventions

- Shaving of the head
- Mercury until salivation occurred
- Venesection- blood letting
- Cupping
- Counter irritation

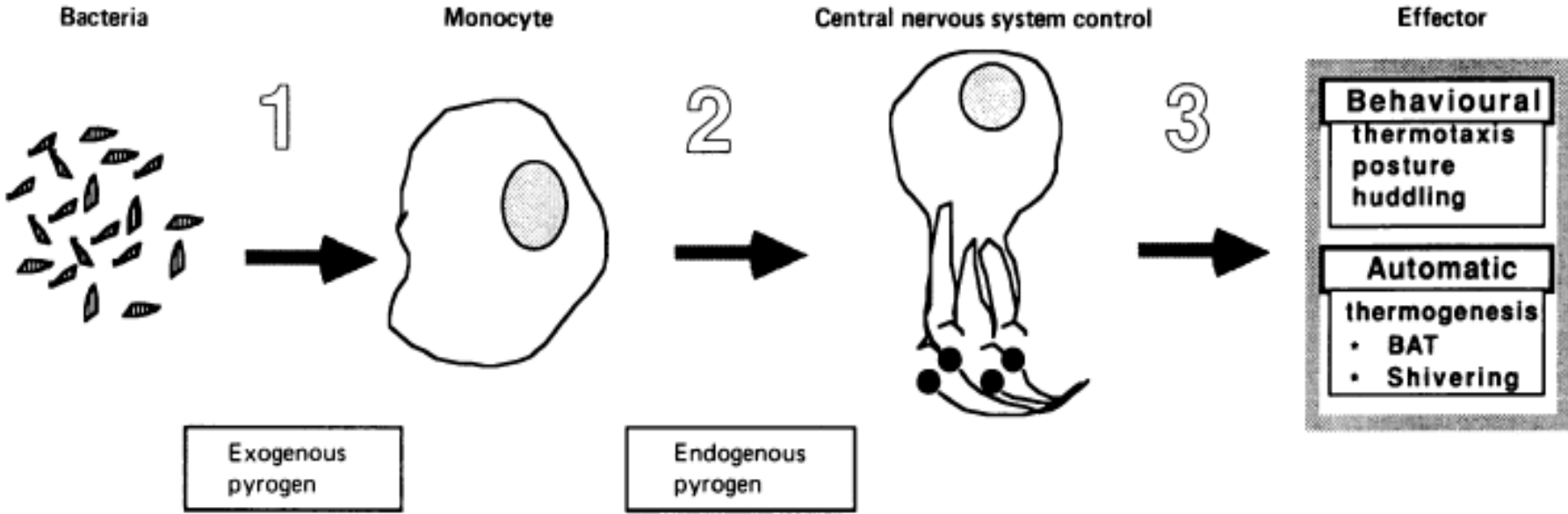
# Assumptions/Fears

- Fever is inherently dangerous and congruent with disease
  - At what level do you consider fever dangerous?
- Reducing fever and symptoms means you have helped with the infection
- The brain can melt, brain damage can occur
- The high temp will not come down
- Metabolic costs of fever exceeds its benefits



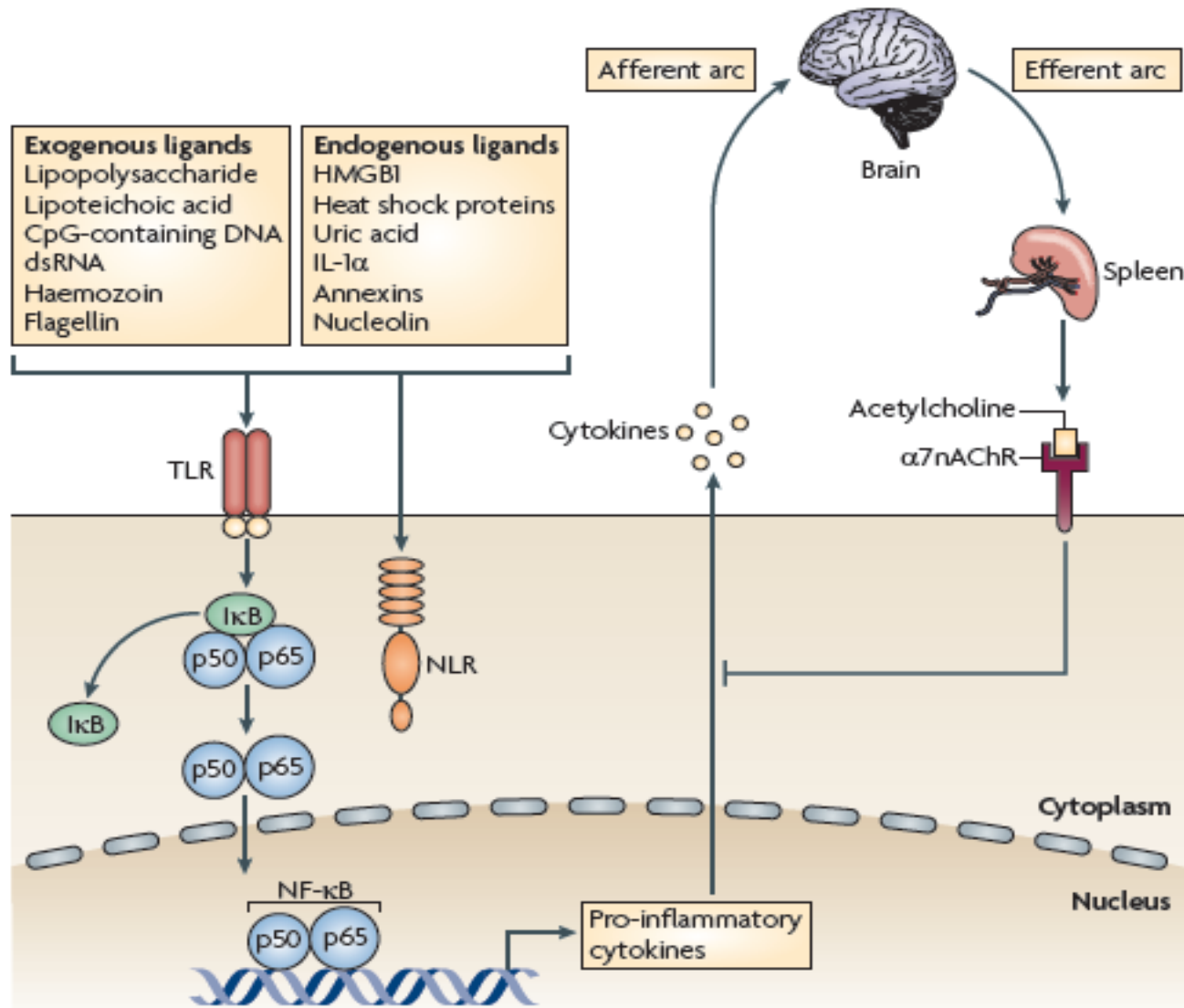


# Steps to fever



IL1 b

# Reflex neurologic control of immune responses ~ Tracey 2009



# Benefits to fever and heat of fever

- Heat shock protein released
  - Is anti-inflammatory
- Increase in phagocytosis ( junk eating cell activity)
- Bactericidal activity of neutrophils
- Enhanced cytotoxic effects of lymphocytes
- Some bacteria/ viruses become less virulent in heat of fever
- High CRP promotes phagocytic adherence to organisms and encourage tissue repair.



# Injurious effects of fever?

## Mackowiak 2000

*“Two critical assumptions are made when prescribing antipyretic therapy. One is that fever is, at least in part, noxious, and the other is that suppression of fever will reduce, if not eliminate, the noxious effects of fever. At present, neither assumption has been validated experimentally.”*

*With regard to the widely held perception that fever is capable of inducing thermal damage in some situations, the increases in core temperature encountered during fever, which rarely exceed a temperature of 41°C, **have never been shown** to be harmful per se*

# Effect of antipyretics

## Drug

- Aspirin
- Ibuprofen

## Effect

- Blocks production of prostaglandins and brain response to IL-1, which is released by macrophages. Leads to decreased stimulation of hypothalamus and temperature decreases, vasodilatation occurs.
- Inhibits synthesis of prostaglandin, causing less stimulation of the set point in hypothalamus.

# Effect antipyretics contin.

## Drug

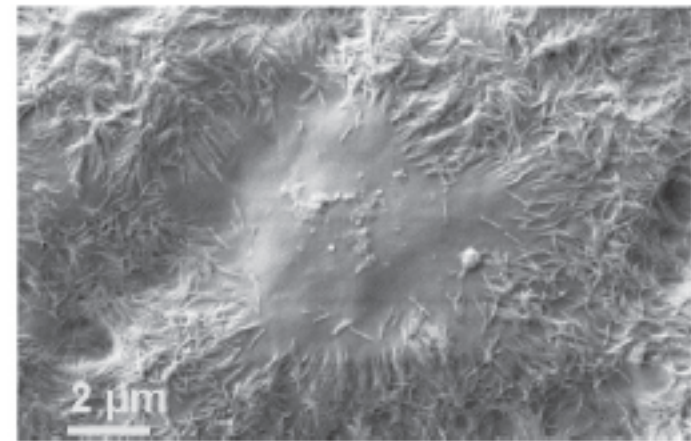
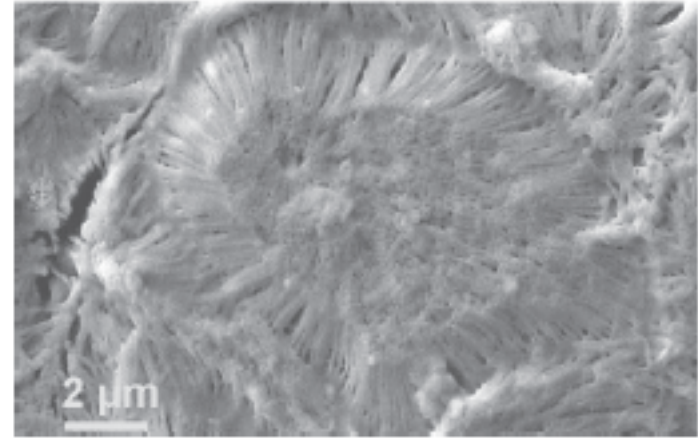
- Acetaminophen  
(paracetamol, tylenol)

## Effect

- Converted to a cyclo-oxygenase inhibitor in the brain.
- Cyclo-oxygenase stimulates prostaglandin production.
- Lowers hypothalamus set point, lowers temp.

# Effect of 10 mM APAP on cell surface topography and microvilli using SEM

- The maximum in vivo daily dose is 4 G, which is equivalent to 17.6 mM in the in vitro model
- 10 mM APAP led to increased LDH release, oxidative stress, glutathione depletion, mitochondrial dysfunction and hepatotoxicity.
- Reduced net intestinal absorption, altered cells structure, eroded microvilli, basically tanned the surface.
- Schafer 2013



**Table 1. Adverse Effects Associated With  
Nonsteroidal Anti-inflammatory Drug Therapy**

<b>System</b>	<b>Adverse Effects</b>
Gastrointestinal	Peptic ulceration Esophagitis and strictures Small- and large-bowel erosions
Renal	Reversible acute renal failure Fluid and electrolyte disturbances Chronic renal failure Interstitial nephritis Nephrotic syndrome
Cardiovascular	Exacerbation of hypertension Exacerbation of congestive cardiac failure Exacerbation of angina
Hepatic	Elevated transaminases Fulminant hepatic failure (rare)
Central nervous system	Headache Drowsiness Confusion and behavior disturbance Aseptic meningitis
Hematologic	Thrombocytopenia Hemolytic anemia Agranulocytosis and aplastic anemia
Other	Exacerbation of asthma and nasal polyposis Rash

# Fever research reveals benefits:

- Increased mobility of leukocytes
- Enhanced leukocytes phagocytosis
- Endotoxin effects decreased
- Increased proliferation of T cells
- Trouble with real placebos
- Survival improved (Rantala 2009, Weinstein 1978, Mackowiak 1980 and 2000)
- Drug does not necessarily make a child feel better (Kramer 1991 lancet)
- Longer period of viral shedding. (Stanley 1975, Graham 1990)

# Metabolic demands of fever

- During Chill period
  - Shivering increases metabolic rate
  - Norepinephrine-mediated vasoconstriction
  - Increase in BP
- Patients with weak cardiovascular system/lungs thought to not tolerate fever as well.
- Antipyretic drugs actually lead to coronary vasoconstriction in pts w CAD
  - Oxygen demand increased after drug
  - Suppressing fever never shown to be helpful in these patients either

# Treating fever: effect on community

- Increase both the rate and duration of viral shedding
- Higher fevers shed less virus
- Antipyretic increases rhinovirus shedding in humans
- Lengthens infectious period in varicella in humans
- Number of doses positively correlates with duration of illness for Influenza A in human volunteers.
- Treating Influenza with antipyretics enhances transmission by at least 1% (Earn 2014)
  - Makes people feel better so they go back into circulation
  - Does not take into account the longer duration
- If 41,000 death per year, then 700 could be prevented by not using these drugs. (very conservative estimate of savings)



# Rantala 2009, Predictors of mortality

Table 4 First signs and symptoms predisposing to mortality during one month's follow-up in  $\beta$ -hemolytic streptococcal bacteremia.

First sign or symptom	Survivors <i>N</i> = 272 (%)	Non-survivors <i>N</i> = 42 (%)	Univariate analysis Odds ratio (95% confidence interval)	Multivariate analysis Odds ratio (95% confidence interval)
confusion	28 (10)	11 (26)	3.3 (1.4–6.8)	3.8 (1.6–9.0)
pain	120 (44)	12 (29)	0.5 (0.2–1.0)	removed
unconsciousness	6 (2)	5 (12)	6 (1.7–20.6)	6.4 (1.6–25.6)
fever	253 (93)	32 (76)	0.2 (0.1–0.6)	0.2 (0.1–0.5)
dyspnea	25 (9)	13 (31)	4.4 (2.0–9.6)	6.4 (2.8–14.8)

# Fever and Influenza

- Influenza viruses replicate in the upper respiratory tract at temperatures between 33 and 37° C, with inhibition of replication and structural damage to the virus at 38 to 41° C.
- With influenza, fever increases the proliferative response of lymphocytes and macrophages to infection, enhances cytotoxic T cell activity, and the production and activity of cytokines such as interferon.

# Influenza animal studies

- Eight studies in animals(Eyers 2010)
- Antipyretic treatment increased risk of mortality, odds ratio of 1.34.
- All three agents implicated: aspirin, paracetamol and diclofenac, suggesting a class effect of antipyretics.
- There are limitations to generalizing results to humans.
- There is insufficient evidence base to support use of antipyretics in the treatment of fever from influenza infection.

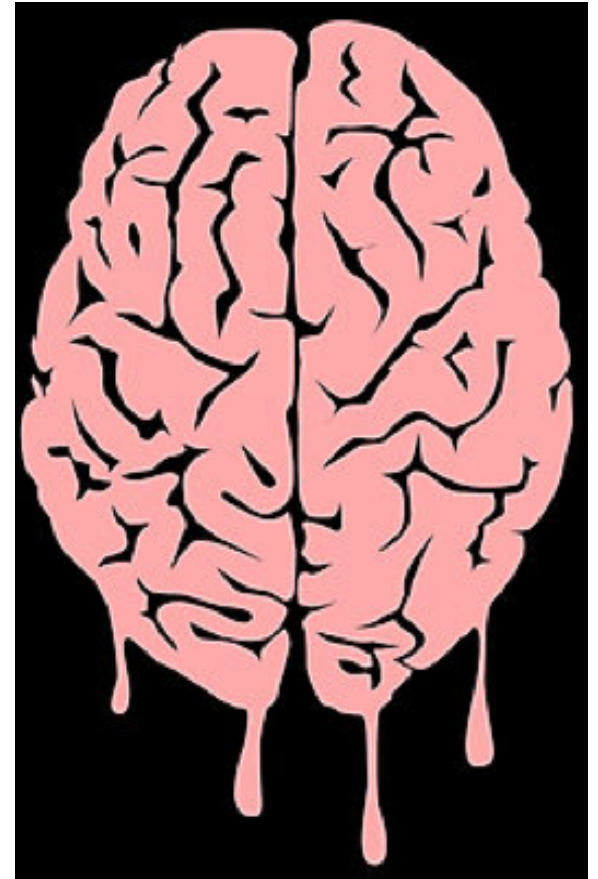
# Febrile seizure

- Most common 6 mo to 5 years
- Most children have temp  $<39$  C (102.2 F) at the time of their seizure
  - And tolerate high temp later with no sz
  - Controlled studies: fever lowering does not protect in future fevers
- 1 in 25 children will have one
- 1 in 100 of the 1 in 25 who has FS will develop epilepsy after the seizure: 4 in 10K statistically
- Vast majority of FS are short and harmless
- If a child has a fever most parents will use fever-lowering drugs such as acetaminophen or ibuprofen to make the child more comfortable, although there are no studies that prove that this will reduce the risk of a seizure. (NIH [http://www.ninds.nih.gov/disorders/febrile\\_seizures/detail\\_febrile\\_seizures.htm](http://www.ninds.nih.gov/disorders/febrile_seizures/detail_febrile_seizures.htm))
- No evidence shows that it is beneficial to treat febrile children with paracetamol. (Russell 2003 Bull. WHO)

# Temperature of concern:

*It has never been shown in humans that increases in core temperature encountered during fever, which rarely exceed 41° C (105.8° F) are harmful per se. (Plaisance 2000 Arch Int Med)*

*Fevers with infections don't cause brain damage. Only body temperatures above 108° F (42° C) can cause brain damage. (Fever myths vs facts from Johns Hopkins pediatrics [http://www.allkids.org/PediatricSymptomChecker/housecalls3tab\\_english/peds/fever\\_myths.htm](http://www.allkids.org/PediatricSymptomChecker/housecalls3tab_english/peds/fever_myths.htm))*



# Treatment of fever

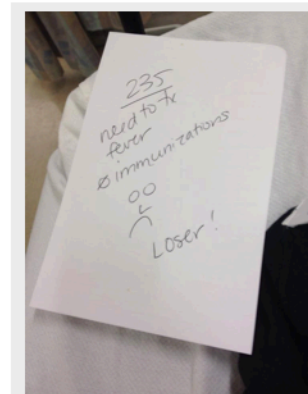
- Treat the child, not the thermometer
- Hydration
- Comfort, avoid over warming or cooling
- Vitamin C to treat underlying cause
- Omega three FA
- Avoid antipyretics
  - Worse outcome meningococcal infections (Baker 2000)
  - No evid. of any benefit besides temporary comfort (questionable placebo)
- The current WHO recommendations for the management of fever in children include the use of paracetamol for children with fever of 39° C. Insufficient data, however, support this recommendation.

# Visits to doctor/hospital for fever

- Harassment for not vaccinating
- Blood drawing 53% (Crocetti 2001 Pediatrics)
- Oral antibiotics 60%
- IV antibiotics 20%
- No intervention 12%

*“At the ER my 9 month old is learning to pull up and when he fell to his butt he twisted his ankle. Anyways he was exposed to hand foot & mouth on Halloween and has a fever. Of course I told the ER we don’t vaccinate so when she came to give him meds for his fever she put this next to me.”*

## Ignorant Nurse Calls Parent “Loser” for Not Vaccinating Her Child



A nurse working for Palmetto Health Children's Hospital left this note calling the mother a "loser" for choosing to not vaccinate her child.

A recent post on the [Great Mothers \(and others\) Questioning Vaccines](#) Facebook page is starting to gain a lot of attention.

According to the post, a mother who made a trip to the emergency room at Palmetto Health Children's Hospital was left a nasty note from a nurse calling her a "loser."

The nurse apparently disagreed with the mother's choice not to have her child injected with neurotoxic chemicals and dangerous biological agents.

The Facebook post from the brave mother read,

- **Williams 2005** the degree of temperature increase was negatively associated with later allergy and asthma outcomes. These relationships again appeared to be time dependent because higher temperatures between 7 and 12 months of age appeared protective for both allergic sensitization and asthma with allergic sensitization at age 6 to 7 years, and higher temperatures between 13 and 18 months of age appeared to protect against asthma without allergic sensitization.
- **Kramer 1991**: Parents had a low success rate in guessing which agent their child had received--correct guesses were obtained in only 45% of the paracetamol group and 52% of the placebo group.



# Acetaminophen

- Glutathione depletion
- ASD? Synergy, depleted antioxidants, aluminum
- Administered with and after vaccines
- Fever suppression
- Lowers vaccine antibody response so is also affecting the immune system.
- Inhibits polymorphonuclear leukocyte activity. ~Shalabi 1992 Effect worsened by high temperatures ~ Shalabi 1996
- Increased risk of asthma and other allergic diseases.(Cohet 2004 among others)

# CDC's current advice

- Evidence does not support use of antipyretics before or at the time of vaccination; **however, they can be used for the treatment of fever and local discomfort that might occur following vaccination.** <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm>

# Vit C in toxic systems

- Attenuates expression of iNOS
- Controls excessive activity of NF-KB
- Maintains intracellular GSH levels
- directly quenches ROS and RNS produced in phagocytes.
- supports liver cytochrome function
- maintains liver GSH levels
- Protects liver from endogenous radicals
- blunts LPS signaling
- in general maintains liver function

*One of the things that frequently astounded me about vitamin C is its rapidity of action. Literally a child could go from screaming, unconscious, a full-blown 'meningitis' presentation to normal in the space of 20-30 Minutes. Sometimes it took a few hours. It was always fast.*

~ Dr Archie Kalokerinos, *Endotoxin and Vitamin C*

*Part 2 - SIDS and the Shaken Baby Syndrome, J. Aust. Coli. Nutr. & Env. Med. Vol. 24 No. 2  
(August 2005) pages 3 - 8*

# Vit C administration

- Maintain hydration
- Alkalize system and urine
- Take anemia history
- Life and death situations, administer the vitamin and ask questions later. In scurvy, vit C is used rapidly.
- Learn about dosing crystalline SA, liposomal Vitamin C, and IV vit C.

# SAFETY

## Vitamin C

- No reports of healthy people overdosing/dying.
- 227 G ingestion in adult would survive.

## Common OTC drugs

- 3-28% hosp/year ADE. Fatal ADE 0.31% of hosp pts.(Classen 1997)
- 380 people die per day in USA from prescription or OTC drugs.
- Paracetamol: liver damage.
  - USA 56K ER visits
  - 26K hospitalizations
    - (Nourjah 2006)
  - 458 deaths/yr unintentional OD
- NSAIDS:ulcers in older people.
  - 41K hospitalizations
  - 350K days in hosp(NCHS 1987)
  - 3300 deaths per year(Ray 1990)



# LD-50's

## Substance

## Dose mg/kg weight

- |               |          |
|---------------|----------|
| ○ Vitamin C   | ○ 11,900 |
| ○ Table salt  | ○ 3000   |
| ○ Paracetamol | ○ 1944   |
| ○ Coumarin    | ○ 293    |
| ○ Aspirin     | ○ 200    |
| ○ Caffeine    | ○ 192    |

