Mythology in Medicine...

...Febrile Seizures as an Example of the Persistence of Medical Misinformation

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Sanford Children’s Hospital, University of South Dakota
Weill Cornell Medicine
June 24th, 2017
Goals

• To review the essential information about febrile seizures necessary for the care of children with a diagnosis of febrile seizures

• To provide evidence, by way of examples, of how medical (mis-) information is promulgated

• To briefly review fever and its history

• To discuss the conventional wisdom on the relationship between seizures and fever in febrile seizures

• To review the existing evidence on the use of anti-pyretics in febrile seizures
FIRST, A DISCLAIMER

• Up to 75% of what you are being taught in medical school or residency is already proven to be incorrect, will be proven incorrect, or is partially incorrect.
FIRST, A DISCLAIMER

This also applies to everything you are going to learn during this lecture.
Which of the following is not a cyclooxengase-2 inhibitor?

- Ibuprofen (Advil, Motrin)
- Acetaminophen (Tylenol)
- Celecoxib (Celebrex)
- Rofecoxib (Vioxx)
- Naproxen (Aleve)
- Diclofenac (Voltaren)
These findings reveal that acetaminophen, similar to aspirin and other non-steroidal anti-inflammatory drugs, is antipyretic by inhibiting cyclooxygenase-2, and not by inhibiting mPGES-1 or signaling cascades downstream of prostaglandin E2.
Where does the spinal cord end in newborns?

Early in utero the conus medularis is in the distal sacrum (S5), but then migrates upward such that in adulthood it is at approximately L1.

What level has the conus reached at 40 weeks gestational age? S4? S3? S1? L4? L3, L2, L1?
What is taught

• That in newborns the conus is at L3:
What is taught

• That in newborns the conus is at L3:

Lumbar Puncture: Anatomical Review of a Clinical Skill


The safe and successful performance of a lumbar puncture demands a working and specific knowledge of anatomy. Misunderstanding of anatomy may result in failure or complications.
Infants. The spinal cord ends at L3. Needle placement should therefore be at L4/5 or L5/S1. The differences between adults and children are due to differential longitudinal growth of the spinal canal and the cord. Fitzgerald (1978) and Moore and Persaud (1993) stated that the spinal cord, early in fetal life, stretches through the whole vertebral canal with the nerve roots leaving the intervertebral foramina in a horizontal fashion. Growth of the vertebral column causes the lower part of the spinal cord to ascend relative to the vertebrae as the upper end is attached to the brain. At 6 months of fetal life, the lowest limit of the spinal cord lies at the level of S1 (Moore and Persaud, 1993). At birth the conus medullaris is mostly found at the level of L3 (Fitzgerald, 1978). Up to 30
(A) 8 wks gest.  (B) 24 wks gest.  (C) Birth  (D) Normal adult

• 2011 American Academy of Neurology Annual Meeting
  – Neuroanatomy course/review (Extra cost above registration fee: $150).
  – Spinal cord lecture by Jose Biller, noted neuroanatomist, editor of many neuroanatomy review books. → L3.

• Two noon conferences during my neurology residency → L3.
Termination of the normal conus medullaris in children: a whole-spine magnetic resonance imaging study

HENRY KESLER, M.D.,¹  MARK S. DIAS, M.D.,¹  AND  PAUL KALAPOS, M.D.¹²

Departments of ¹Neurosurgery and ²Radiology, Pennsylvania State University College of Medicine, Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania
<table>
<thead>
<tr>
<th>Author(s) &amp; Year</th>
<th>Population</th>
<th>Imaging Modality</th>
<th>Average</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson et al., 1989</td>
<td>184 infants</td>
<td>MRI</td>
<td>L1/2</td>
<td>T12–L2/3</td>
</tr>
<tr>
<td>Hill &amp; Gibson, 1994</td>
<td>103 infants</td>
<td>ultrasound</td>
<td>L2U</td>
<td>T12/L1–L3M</td>
</tr>
<tr>
<td>Wolfe et al., 1992</td>
<td>114 infants</td>
<td>ultrasound</td>
<td>L1/2</td>
<td>T12–L4</td>
</tr>
<tr>
<td>Sahin et al., 1997</td>
<td>64 infants</td>
<td>ultrasound</td>
<td>L1/2</td>
<td>T12/L1–L2/3</td>
</tr>
<tr>
<td>Tane &amp; Burstal, 2003</td>
<td>45 children</td>
<td>MRI</td>
<td>L1</td>
<td>T11/12–L2/3</td>
</tr>
<tr>
<td>Demiryürek et al., 2002</td>
<td>639 adults</td>
<td>MRI</td>
<td>L1M</td>
<td>T11/12–L3U</td>
</tr>
<tr>
<td>Lee et al., 2004</td>
<td>210 adults</td>
<td>MRI</td>
<td>L1L</td>
<td>T12/L1–L2U</td>
</tr>
<tr>
<td>Saifuddin et al., 1998</td>
<td>504 adults</td>
<td>MRI</td>
<td>L1L</td>
<td>T12M–L3U</td>
</tr>
</tbody>
</table>

* The vertebral terminology used in this paper is explained in Materials and Methods. Abbreviations: U = upper; M = middle; L = lower.
Results

One hundred children who underwent whole-spine imaging were identified during the study period. Their average age was 7.5 years (range 0.4–18 years). The

...ically represented in Fig. 4. All the CMs terminated between the lower third of T12 (T12L) and the middle of L2 (L2M). The mean corresponded to the lower third of L1 (L1L) and the mode corresponded to the L1/2 disc space. The standard deviation was 1.59 sections, yielding a 95% CI between the lower third of T12 (T12L) and the middle section of the L2 vertebra. In no child was the CM shown to be below the middle third of L2 (L2M) on the initial MR images.
Why does this misinformation continue to be propagated when we have such convincing evidence?
Why is the forehead spared in upper motor neuron facial paralysis?
Why is the forehead spared in upper motor neuron facial paralysis?
Facial paralysis: a critical review of accepted explanation.

(Med Hypotheses. 2010)

• “The classical explanations for these clinical findings are that the upper facial muscles receive bilateral innervation from the cerebral cortex and the lower facial muscles receive only unilateral innervation from the contralateral cerebral cortex....”

• “However, a review of the basic science literature indicates that commonly accepted explanations and the pattern of cortical projections are not consistent with anatomical studies.”
Dissociation of Voluntary and Emotional Innervation after Stroke

NEJM 2010
Is this figure correct?
Is this figure correct?

Does this make sense?
Warning, the following data is rated PG-13 and may not be appropriate for an immature audience.

Discretion is advised.
The Sensory Cortical Representation of the Human Penis: Revisiting Somatotopy in the Male Homunculus

Women's clitoris, vagina and cervix mapped on the sensory cortex: fMRI evidence

A Sensory homunculus

- Leg
- Hip
- Trunk
- Neck
- Head
- Shoulder
- Arm
- Elbow
- Forearm
- Wrist
- Hand
- Little
- Ring
- Middle
- Index
- Thumb
- Face
- Nose
- Upper lip
- Lower lip
- Teeth, gums, and jaw
- Tongue
- Pharynx
- Intra-abdominal

Medial       Lateral
Fevers and Febrile Seizures
Fevers and Febrile Seizures

• One can’t talk about febrile seizures without first talking about fevers
The *Gottvater* of Fever

Carl August "Pate" Wunderlich (1815-1877)

**Temperature in Diseases:**

A Manual of Medical Thermometry.

By Dr. C. A. Wunderlich,

Professor der Klinik an der Universität Leipzig, K. Sachs Geheimen Medicinalbath, Comthur und Ritter, etc.

1871
Fever – Wunderlich contributions

Based on ONE MILLION temperature readings...

Was the first to suggest 37 °C as average, and 38+ °C as ‘fever’. Correctly observed and documented:

- circadian variability (as high as 0.5 °C)*
- menstrual variation*
- Women have higher temp (~0.5 °C) than men*

Because of Wunderlich, 37 °C is still considered ‘normal’ body temp 150 years later.

But was he RIGHT?? He did not share his raw data or analysis.
Normal body temp: modern thoughts

Figure 1 The results from 20 studies with strong or fairly strong evidence of normal oral, rectal and tympanic temperature (°C) in adult men and women are presented. Temperature is obtainable as mean value (bold lines), 1st and 3rd quartiles (unfilled bars) and range (thin lines).

Normal body temp: modern thoughts

Figure 1 The results from 20 studies with strong or fairly strong evidence of normal oral, rectal and tympanic temperature (°C) in adult men and women are presented. Temperature is obtainable as mean value (bold lines), 1st and 3rd quartiles (unfilled bars) and range (thin lines).

What temp defines a fever?

Normal body temperature varies widely, and there is no universal consensus on what temperature constitutes a fever.

38 C is commonly used in everyday practice, based primarily on Wonderlich’s paper.

Alternately, fever is defined on a study by study basis when doing epidemiological studies, i.e. what temperature warrants an LP in a neonate?
Fever Phobia

One third of pediatrics visits are for fever. Of these 20% of children never had a temperature above 38C.

In 1980, a study found that almost all parents believed a fever can cause damage to their children (Schmitt BD. Fever phobia: misconceptions of parents about fever. *Am J Dis Child.* 1980;134:176-181)
Fever Phobia

20 years later, nothing has changed.

Fever Phobia Revisited: Have Parental Misconceptions About Fever Changed in 20 Years?
Michael Crocetti, Nooshi Moghbeli and Janet Serwint
*Pediatrics* 2001;107;1241
DOI: 10.1542/peds.107.6.1241

- 91% believed fever could cause harm, including brain damage and seizure
- 52% indicated they checked temps at least every hour during illness
- 25% gave anti-pyretics for temperatures less than 37.8 C (100F)
- 85% woke up their children to give medication
- Over 50% exceeded recommended dosages of acetaminophen and ibuprofen
- 73% also sponged their children, 24% at temps less than 100F, and 18% with alcohol
- There was indication that this “fever phobia” was higher among those who perceived their doctors to be worried about fever
Simple Febrile Seizures, Definition

• Seizure “accompanied” by temp over 38C*, in a child 6 months to 5 years of age with no prior neurologic diagnosis.
• Less than 15* minutes in duration
• Only one in a 24* hour period
• Generalized seizures only (i.e. no focal seizures)
• Quick* return to baseline with normal neurologic exam
Simple Febrile Seizures
Workup and Treatment

• No workup (in fully immunized child)
• Reassurance
• No further follow-up
• Anticipatory guidance about risk and management of further seizures
• Consider a script for an emergency medication such as rectal diazepam
Complex Febrile Seizure

This is any febrile seizure (which by definition only occurs in a previously neurologically normal child with no history of afebrile seizure) which does not meet ALL of the criteria of a “Simple” febrile seizure.
Complex Febrile Seizure

Most current guidelines state to CONSIDER:
LP, imaging, infectious workup, etc.

Note that guidelines do not MANDATE any of the above. They simply state to have a higher level of suspicion. We frequently will treat a complex febrile seizure as a simple febrile seizure “variant”. There is also no good data to support the use of EEG, although EEGs are frequently obtained.
Fast Facts about Febrile Seizures (FS)

- Occur in about 3% of all children in the US
- Peak incidence at 1.5 years of age
- About ¼ will be complex febrile seizures
- Family history of FS is risk factor
- Height of seizure is risk factor (note, this does not mean that a higher fever is more likely to cause a seizure!)
Fast Facts about Febrile Seizures (FS)

(continued)

• There is likely genetic susceptibility
• Certain infectious agents are more likely to cause FS (i.e. HHV-6)
• Associated with hippocampal sclerosis in adulthood and TLE, but NOT thought to be causative
• History of simple FS doubles or triples your risk of subsequent epilepsy
• History of complex FS → four to sixfold risk
Mythology related to febrile seizures

Correlations between fever parameters and seizures: What role for the rate of rise?

It is commonly taught that the “rate of rise” of the fever is more important in contributing to febrile seizures than absolute temperatures.
Nelson Textbook of Pediatrics, 2007: “A simple febrile convulsion is usually associated with a core temperature that increases rapidly to ≥39°C”

From Susan Markel MD, author: “Typically, the convulsions are not due to the height of the fever, but the “rate of rise” of fever, where the brain is reacting to a sudden change in temperature.

From ‘Parenting Weekly’ magazine: “A child who rapidly develops a fever of 103 degrees seems to be at greater risk of having a seizure than a child who slowly develops a fever of 104 degrees F”
Correlations between fever parameters and seizures: What role for the rate of rise?

Kittens heated rapidly are more likely to seize than ones heated slowly

<table>
<thead>
<tr>
<th>Maximum Attained Increase in Body Temperature, °C</th>
<th>Rapid Rise (20-100 min)</th>
<th>Slow Rise (&gt;100 min-8 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) of Kittens (n=42)</td>
<td>No. (%) of Kittens With Convulsions</td>
</tr>
<tr>
<td>3.0-3.4</td>
<td>4 (9.5)</td>
<td>0</td>
</tr>
<tr>
<td>3.5-3.9</td>
<td>6 (14.3)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>4.0-4.4</td>
<td>6 (14.3)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>4.5-4.9</td>
<td>6 (14.3)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>5.0-5.4</td>
<td>6 (14.3)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>5.5-5.9</td>
<td>4 (9.5)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>≥6.0</td>
<td>10 (23.8)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Total</td>
<td><strong>42 (100)</strong></td>
<td><strong>25 (60)</strong></td>
</tr>
</tbody>
</table>

Rate of Rise vs Height

Noted that animals studies investigating rate of rise were contradictory.

Jay Gordon Millichap. Height of Body Temperature as a Measure of the Febrile Seizure Threshold. Pediatrics 1959

Millichap used a microwave to heat mice, rats, kittens and guinea pigs at different rates until they seized.

Fig. 1 (Upper). Microwave diathermy generator used for the induction of hyperthermia in experimental animals.
Fig. 2 (Lower). Microwave heat energy director maintained at a constant distance from the animal tested.
Rate of Rise vs Height

All animals seized at same threshold regardless of rate
The notion that febrile seizures are caused by a rapid increase in temperature is deeply entrenched in the teaching of pediatrics. Yet, there are few data to substantiate this theory. Of several available and relatively recent textbooks on pediatrics that were reviewed, some contained assertions such as, “The suddenness of the rise of temperature appears to be more important than the final temperature reached.”¹ No references to empirical data were provided. The following is a review of the evidence concerning the rate of rise of temperature and height of temperature and their roles in provoking febrile seizures. It will become apparent that there are no data to support the hypothesis that the rate of rise of temperature plays a role in provoking a febrile seizure.
Why does Rate of Rise myth persist?
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Why does Rate of Rise myth persist?
Why does Rate of Rise myth persist?

Nishi Rampal, MD is a Fellow in Critical Care and Epilepsy at Columbia University, after completing neurology residency at Yale University.

Steven Karczski, MD is Assistant Clinical Professor of Neurology at the College of Physicians & Surgeons of Columbia University and Director of the Columbia Epilepsy Center at the Atlantic Neuroscience Institute.
Why does Rate of Rise myth persist?

What is a Febrile Seizure?

It’s a seizure that occurs in childhood between one month and five years of age, with a peak at 18 to 22 months. By definition, it is associated with a febrile illness. The seizure risk is associated most strongly with the rate of rise rather than the absolute temperature of the fever. In
Why does Rate of Rise myth persist?

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Relationships between seizures, illness, and fever
Do seizures CAUSE fever? Maybe.

Many times kids aren’t found to have fever until AFTER the seizure, i.e. in the ED. The above data would suggest that perhaps the seizure itself may complicate any conclusions we make about the causative effects of fevers in febrile seizures.
What DO we know about fevers in febrile seizures?

Group I: Frist seizure at high fever

Group II: Frist seizure at low fever

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Group</th>
<th>Children with Recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–18 months</td>
<td>I</td>
<td>4 (10.5)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>19 (76.0)</td>
</tr>
<tr>
<td>19–30 months</td>
<td>I</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>4 (40.0)</td>
</tr>
<tr>
<td>Over 30 months</td>
<td>—</td>
<td>7 (5:2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>94 (50:44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29 (30:9)</td>
</tr>
</tbody>
</table>

* The difference of the recurrence rate in children aged 16–18 months and 19–30 months is also significant (p < 0.01) (Mantel-Haenszel test).
In theory, the utility of antipyretics for the prevention of febrile seizure should be very easy to study.
1980 NIH meeting to discuss febrile seizures produced the ‘Consensus Statement’ (Febrile Seizures. NIH Concensus Statement Online 1980 May 19-21;3(2):1-10.), which included the following:

“As for aspirin and acetaminophen, while they do reduce fever, they have not been shown to be effective in preventing febrile seizures.”

Summing up the meeting was Hart deC. Peterson, MD, associate attending neurologist and pediatrician at New York Hospital-Cornell Medical Center. “We have tried to establish greater uniformity in the approach to the problem of febrile seizures,” he said. “We are treating fewer children and we have learned that there may be significant disadvantages to over-zealous treatment.”—by JOHN ELLIOTT

Standard of care for febrile seizures at this time was “high dose aspirin and sponge baths”
There has never been ONE study that I can find in humans that has demonstrated that antipyretics of any kind can prevent febrile seizures under any circumstances.

**Randomized controlled trials which demonstrate antipyretics do not prevent seizures**

- Acetaminophen or aspirin (dose unspecified) for low temps, with cooling added for higher temps. Rate of FS recurrence with AP was similar to previous studies of untreated FS. (Pediatrics 1980; 97:16-21)

- Prophylactic acetaminophen upon admission for FS vs. PRN: Same recurrence of FS during the first 24 hours. (*European Journal of Pediatrics* 1993, 152(9):747-9)

- Acetaminophen for fever (10mg/kg q6h) was same as placebo for recurrence over 2 year period (J Pediatr. 1995 Jun;126:991-5)

- Ibuprofen (20mg/kg q6h during fever) vs placebo (*Pediatrics* 1998; v102). Noted temp was higher when there were seizures. Temp reduced by 0.7 C at 6 hours.
AAP Guidelines 1999:
“Antipyretics, although they may improve the comfort of the child, will not prevent febrile seizures”

AAP Guidelines 2008:
“Whether antipyretics are given regularly (every 4 hours) or sporadically (contingent on a specific body-temperature elevation) does not influence outcome.... Although antipyretics may improve the comfort of the child, they will not prevent febrile seizures.”
We are done, right?

Nope. Many pediatricians (including PICU and ED docs), neurologists and ‘the internets’ continue to recommend aggressive antipyretic therapy for fevers in kids with febrile seizures.
• The New York Times Health Guide states: “Focus your attention on bringing the fever down. ..apply cool washcloths to the forehead and neck”

• Wikipedia says “ A febrile seizure is the effect of a sudden rise in temperature (>39°C/102°F) rather than a fever that has been present for a prolonged length of time. Parents caring for children that may be febrile who wrap them up in warm blankets in an attempt to give comfort unknowingly increase their fever and therefore the risk”
(Insert personal anecdote here)
Antipyretic Agents for Preventing Recurrences of Febrile Seizures

Randomized Controlled Trial

Teemu Strengell, MD; Matti Uhari, MD, PhD; Rita Tarkka, MD, PhD; Johanna Uusimaa, MD, PhD; Reija Alen, MD; Pentti Lautala, MD, PhD; Heikki Rantala, MD, PhD

Arch Pediatr Adolesc Med. 2009;163(9):799-804

This is the by FAR the single best study ever done to address this issue.

Rectal diclofenac or placebo for any temp > 38 C, then 8 hours later either:

1) acetaminophen (15 mg/kg) or
2) ibuprofen (10mg/kg) or
3) placebo Q6 hours until patient was afebrile
298 Children who had had their first febrile seizure were assessed for eligibility

67 Were excluded
  30 Did not meet inclusion criteria
  37 Refused to participate

231 Were randomized

117 Received diclofenac

114 Received placebo

Randomly allocated groups for rectal medication

117 Received diclofenac

76 (41 + 35) received ibuprofen

2 Did not want to continue
  1 Was lost to follow-up
  1 Had an afebrile convulsion

31 Received diclofenac + ibuprofen

5 Did not want to continue
  1 Was lost to follow-up
  1 Received antiepileptics

34 Received placebo + ibuprofen

6 Did not want to continue
  2 Were lost to follow-up
  1 Dropped out for unknown reason

29 Received diclofenac + acetaminophen

8 Did not want to continue
  1 Had an afebrile convulsion
  4 Dropped out for unknown reason

26 Received placebo + acetaminophen

77 (39 + 38) received acetaminophen

7 Did not want to continue
  3 Dropped out for unknown reason

34 Received diclofenac + placebo

6 Did not want to continue
  1 Dropped out for unknown reason

78 (34 + 44) received placebo

27 Received placebo + placebo
Figure 2. State of cumulative nonrecurrence: comparison between the rectal diclofenac and placebo groups.

Figure 3. State of cumulative nonrecurrence: comparison between the oral medication groups.
Other interesting findings:
- All seizures happened AFTER the first med was given
- 87% of all seizures occurred after BOTH rectal and oral med
Excerpts of a letter from a family to my boss(es)

• “Dr. Keros explained to us that he does not believe that a febrile seizure is causally connected to the underlying fever, and that there is really no way to prevent the seizure from taking place once the underlying sickness is borne. He admitted to us that he was trying to educate the rest of the medical staff on his theory....Neither of us are medical experts, in any way, shape or form, but from what we understand, the illness and the fever both correlate with the febrile seizure.”

• “We were extremely thrown off and overwhelmed to hear his opinion, which seemed to greatly differ from anything that we had been told before. After leaving the emergency room we had to deal with the angst of the day, and more importantly, the words of Dr Keros on...his new research on febrile seizures...and his potential course of treatment for our daughter.”

• Our expectation going forward is that a divergent opinion such as Dr. Keros’....We do believe that these issues that were raised during the course of her visit to your hospital rise to the level of your attention.”
“Despite evidence to the contrary, health care professionals continue to harbor inaccurate attitudes and knowledge about fever and continue to suggest antipyretics to reduce temperature and thereby reduce the risk of febrile seizures. Clearly, continued educational interventions are needed for health care workers.”

Renee Shellhaas and Jerome Engel, noted pediatric epileptologists (http://www.medlink.com/article/febrile_seizures, on June 22 2016)
Anyone still not convinced, or is in the “what’s the harm in a little tylenol” group? 

Treating the fever prolongs the illness:

![Table 1. Duration of Illness in Subjects Receiving at Least One Dose of Antipyretic Drug and in Those Not Receiving Antipyretic Drugs](image)
Anyone still not convinced, or is in the “what’s the harm in a little tylenol” group?

Treating the fever prolongs the illness:

<table>
<thead>
<tr>
<th>Group</th>
<th>Influenza A (mean ± SD [no.])</th>
<th>S. sonnei (mean ± SD [no.])</th>
<th>R. rickettsii (mean ± SD [no.])</th>
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<tbody>
<tr>
<td>Received antipyretics</td>
<td>8.8 ± 2.3 [13]</td>
<td>4.6 ± 2.1 [21]</td>
<td>12.6 ± 5.5 [14]</td>
</tr>
<tr>
<td>Did not receive antipyretics</td>
<td>5.3 ± 3.0 [41]</td>
<td>1.9 ± 1.6 [24]</td>
<td>13.6 ± 6.5 [7]</td>
</tr>
<tr>
<td>p value (Wilcoxon test)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.50</td>
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Tylenol increases death rates in ICU patients:

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Tylenol increases death rates in ICU patients:


Acute non-oliguric kidney failure and cholestatic hepatitis induced by ibuprofen and acetaminophen: a case report

5 year old girl admitted with febrile seizures

“During hospitalization, in order to prevent a recurrence of fever peaks, she was treated with acetaminophen per os (11 mg/kg/dose, two total doses over 5 h). Thereafter, because of persistent high temperature, ibuprofen per os (5 mg/kg/dose every 8 h, three total doses) was administered for the first time (2nd day) in alternating regimen with acetaminophen.”
Feb 2013, jury award to 7 year old girl given OTC Children’s Motrin by her parents for a routine fever, who subsequently developed toxic epidermal necrolysis.

Current law: 1) Manufacturer is required to warn users of hidden dangers that may be present in a product  2) The manufacturer must instruct users how to use a product so that the users can avoid any dangers and use the product safely.

The jury determined that the label warnings on package were inadequate. The defense argued the phrase “stop taking this product immediately if you note any adverse reactions” (my paraphrase) was sufficient.
Drug-induced Stevens-Johnson syndrome: case series from tertiary care centre in Gujarat (Pharmacoepidemiol Drug Saf. 2012), 3 year prospective study:

“Individually, ibuprofen was involved in the highest number of cases (five cases, 17.2%), followed by carbamazepine (four cases, 13.8%) “

Ibuprofen Associated Acute Vanishing Bile Duct Syndrome and Toxic Epidermal Necrolysis in an Infant

Hye-young Kim,12 Hea Kyoung Yang,1 Seong Heon Kim,13 and Jae Hong Park13

Note however, that in general, ibuprofen is among the safest NSAIDs if an NSAID is to be given.
Are Anti-Pyretics Effective…

On Fever?  On Seizures?

- ILLNESS → FEVER → SEIZURE
- ILLNESS → SEIZURE → FEVER
- ILLNESS → Pathway 1 → FEVER
- ILLNESS → Pathway 2 → SEIZURE
- ILLNESS A → FEVER TYPE A → SEIZURE
- ILLNESS B → FEVER TYPE B → NO SEIZURE
Are Anti-Pyretics Effective…

On Fever?  On Seizures?

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Points for Discussion

• What should we be telling our patients (and residents and colleagues) regarding the efficacy of antipyretics for the prevention of febrile seizures?

• Are we contributing to “fever phobia”?

• Are we “doing harm”?

• Can we trust ANYTHING we are taught (or teach!) in medicine?

• Can you trust ANYTHING you just learned in this lecture?
Questions?