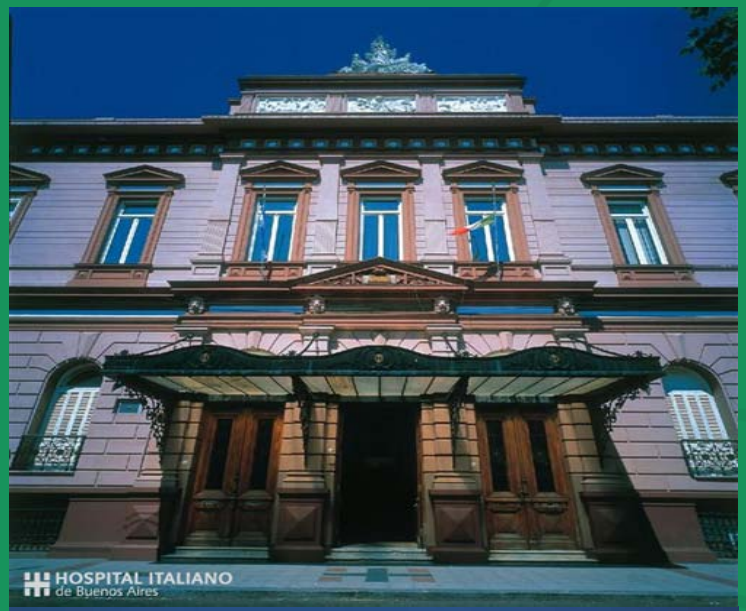

Alternar antipiréticos ¿es una alternativa?

carlos.wahren@hospitalitaliano.org.ar

Caso clínico

- Consultan por Dante de 7 meses de edad con un cuadro de fiebre de 39° de 72 hs de evolución.
- El examen físico muestra un niño eutrófico, con estado general conservado, normohidratado
- Ambos tímpanos y fauces congestivos.
- A las 24 hs de fiebre consultó en la salita del barrio y fue medicado con paracetamol 2 gotas kg cada 6 hs
- Por la persistencia de la fiebre los padres consultan muy angustiados

Ante esta situación usted decide:

A. Cambiar a ibuprofeno cada 6 hs

B. Indicar alternar ibuprofeno con paracetamol cada 3-4 hs

C. Indicar paracetamol e ibuprofeno cada 6-8hs

D. Seguir con paracetamol cada 6 hs

Importancia de la fiebre como signo o síntoma

- Manifestación muy frecuente de enfermedad
- Muchas veces el primer o único signo de enfermedad
- Marcador de mejoría o resolución de un proceso patológico
- A veces único indicador de la persistencia de una enfermedad
- Puede ser detectada con rapidez y precisión
- Es motivo de preocupación para el paciente y su familia

Fever Phobia

Misconceptions of Parents About Fevers

Barton D. Schmitt, MD

• Eighty-one parents bringing their children to a hospital-based pediatric clinic were surveyed about their understanding of fever. Most parents were unduly worried about low-grade fever, with temperatures of 38.9 °C or less. Their overconcern was designated "fever phobia." Most parents (52%) believed that moderate fever with a temperature of 40 °C or less can cause serious neurological side-effects. Hence, most parents treated fever aggressively: 85% gave antipyretic medication before the temperature reached 38.9 °C and 68% sponged the child before the temperature reached 39.5 °C. A review of the literature showed that the only serious complications of fever were febrile status epilepticus and

defenses when the amount of "phlegm" in the body increased. The doctrine stated that the heat of fever was designed to drive the excess phlegm out of the body. Fevers were encouraged and celebrated. By the middle of the 19th century, Claude Bernard had completed his experiments on the overheating of animals and had proven that death quickly occurred if the body's temperature rose 5 to 6 °C above normal.[1] Thereafter, fever gradually was looked on as injurious to health, and treatment with antipyretic medication was considered essential.

while waiting to see a physician. Many of the children were not acutely ill at the time of the visit. Eighty-one parents completed the questionnaire and returned it to a member of the clinic staff. The parents were given no assistance with answering the questions, but on completion of the questionnaire, the clinic nurse reviewed the appropriate answers with the parents as time permitted. Fifty-seven percent of all the families surveyed had one child, 32% had two, 12% had three, and 9% had four or more.

Of note is the fact that 14% of all the families had an only child younger than 6 months of age and hence their past experience with febrile illnesses may have been

Fobia a la fiebre

- **63% de los padres refieren gran preocupación por el daño que la fiebre podría producir al niño**
- **18% daño cerebral con Temp de 37° 8 A 38° 9**
- **34% daño cerebral conTemp de 38° 9 A 40º**
- **16% la temperatura seguiría subiendo hasta 43°[3] o más**

Schmit BD.Fever Phobia, Am J Dis Child 1980;134:176-181

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Jun 2001
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Fever Phobia Revisited: Have Parental Misconceptions About Fever Changed in 20 Years?

Michael Crocetti, MD*; Nooshi Moghbeli, BA*; and Janet Serwint, MD‡

ABSTRACT. *Objectives.* Fever is one of the most common reasons that parents seek medical attention for their children. Parental concerns arise in part because of the belief that fever is a disease rather than a symptom or sign of illness. Twenty years ago, Barton Schmitt, MD, found that parents had numerous misconceptions about fever. These unrealistic concerns were termed "fever phobia." More recent concerns for occult bacteremia in febrile children have led to more aggressive laboratory testing and treatment. Our objectives for this study were to explore current parental attitudes toward fever, to compare these attitudes with those described by Schmitt in

and 7% thought that a temperature could rise to ≥43.4°C (≥110°F) if left untreated. Ninety-one percent of caregivers believed that a fever could cause harmful effects; 21% listed brain damage, and 14% listed death. Strikingly, 52% of caregivers said that they would check their child's temperature ≤1 hour when their child had a fever, 25% gave antipyretics for temperatures <37.8°C (<100°F), and 85% would awaken their child to give antipyretics. Fourteen percent of caregivers gave acetaminophen, and 44% gave ibuprofen at too frequent dosing intervals. Of the 73% of caregivers who said that they sponged their child to treat a fever, 24% sponged at temperatures ≤37.8°C

Fobia a la fiebre-2

47% consideraban fiebre muy alta 38º9

7% pensaban que la fiebre puede subir a ≥ 43,4ºc si no se trata

91% que la fiebre puede provocar algún daño

21% daño cerebral

14%muerte

25% daban antipiréticos para temperaturas menores a 37,8ºc

85% despertaban al niño para darle antitérmicos

Crocetti et al Fever phobia revisited: have parental misconceptions about fever changed in 20 years. Pediatrics. 2001;107:1241-46

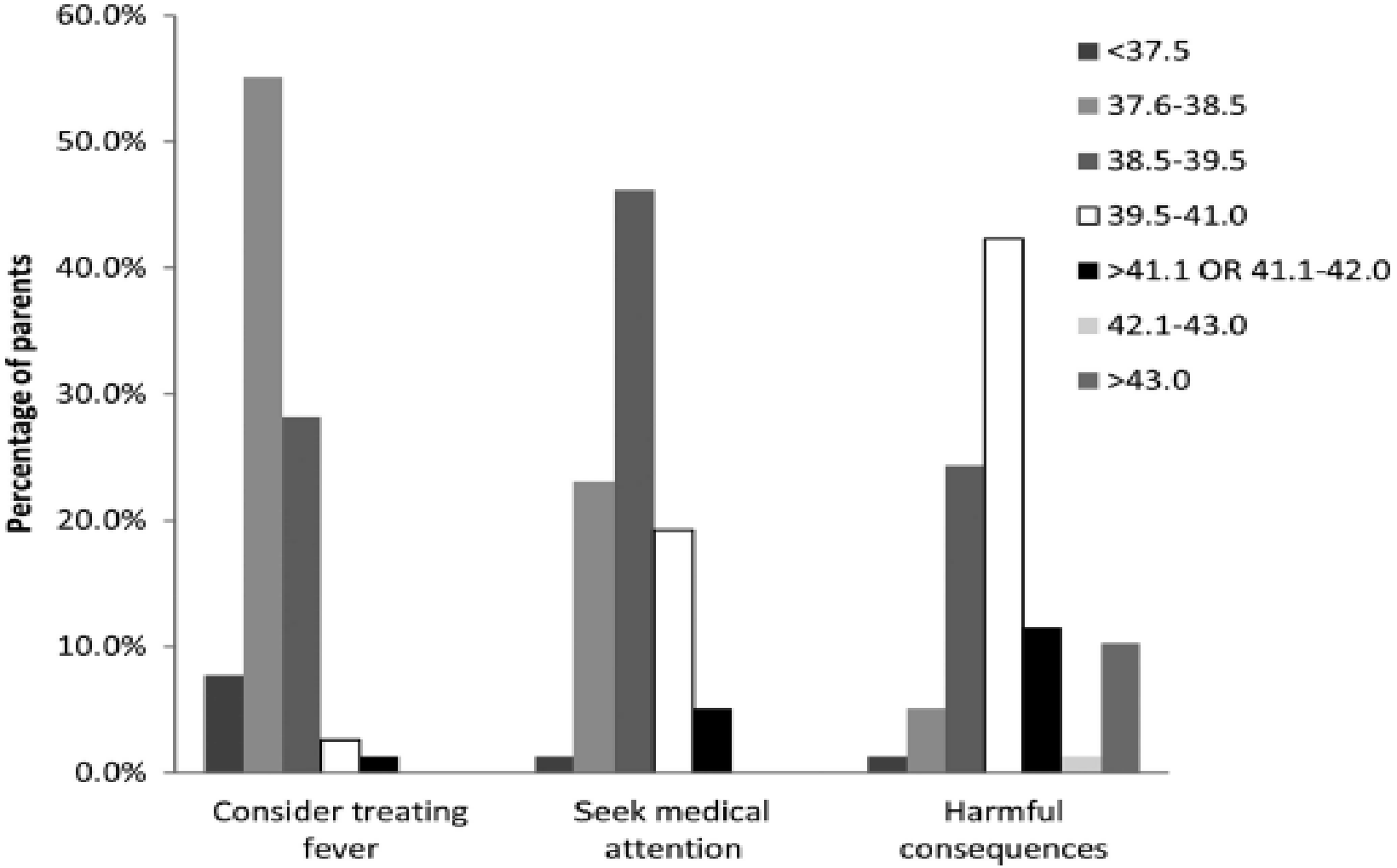


Figure 1 Temperatures above which parents would consider treating a fever, would seek medical attention and above which believe fever could have harmful consequences for their child (n=78).

Is fever phobia driving inappropriate use of antipyretics? Arch Dis Child 2014;99:701-702

Fobia a la fiebre
A qué temen los padres

- 78,2% Deshidratación
- 65,4% Convulsiones
- 29,5% Daño cerebral, coma y/o muerte

Is fever phobia driving inappropriate use of antipyretics? Arch Dis Child 2014;99:701-702

ARTICLES

Fever Phobia: The Pediatrician's Contribution

Ariane May, MD, and Howard Bauchner, MD

ABSTRACT. Fever phobia, the exaggerated fear of fever, is found among parents of all socioeconomic classes. Pediatricians may inadvertently contribute to fever phobia if their practice and educational message are incongruent. To determine how pediatricians treat fever in their practice, the authors sent a self-administered questionnaire to a sample of members of the American Academy of Pediatrics who lived in Massachusetts. Pediatricians were asked (1) how dangerous they believed fever to be, (2) how they treated fever in their practice, and (3) what types of educational information they gave families regarding fever. One-hundred seventy-two of the 234 (74%) eligible pediatricians returned the survey; 151 were completed. Sixty percent of the respondents were male, and 75% practiced some form of primary or episodic care. Ninety-eight (65%) believed that fever itself could be dangerous to a child, with 58 (60%) of the original 98 citing that a temperature of 104°F or greater could lead to complications such as seizures, brain damage, or death.

Our clinical experience suggests that pediatricians may impart mixed messages to parents about the dangers of fever. For example, although many physicians agree that treatment to reduce fever is mostly for the comfort of the child, during telephone consultations, many tend to prescribe antipyretic medication for any child with a fever.[1]

The purposes of this study were (1) to explore the beliefs and practices of pediatricians with regard to fever and to generate hypotheses on how these practices or beliefs may contribute to fever phobia and (2) to determine how and when parents are educated by pediatricians about fever.

METHODS

All physicians who were members of the Massachusetts chapter of the American Academy of Pediatrics were eligible for the study. Every fifth name was chosen from the 1989–1990 membership list

Fiebre: ¿amiga o enemiga?

USES AND ABUSES OF ANTIPYRETIC THERAPY

By Alan K. Done, M.D.

Department of Pediatrics, Stanford University School of Medicine

FEVER is undoubtedly the most common symptom confronting the physician who treats children. It is fought as though it were the patient's primary disease, and its mere presence is often accepted as being sufficient indication for the institution of antipyretic therapy. It is not surprising, therefore, that therapeutists and pharmaceutical concerns have energetically sought a number of points which deserve consideration before one elects to use an antipyretic.

DuBois[1] summarized a lifetime of study on fever and the regulation of body temperature with the statement: "Fever is only a symptom and we are not sure that it is an enemy. Perhaps it is a friend." The literature concerning the possible role of fever in body defenses is extensive and inconclusive.

IS ANTIPYRESIS INDICATED?

More critical than the *choice* of an antipyretic is the question of whether or not such therapy is indicated in the individual case, for there is little doubt that these drugs are grossly overused, at times to the detriment of the patient. Therefore, before discussing the antipyretics themselves, it seems appropriate to review briefly a number

has been postulated that, except under circumstances such as these, an "emergency regulatory mechanism" in fever operates to prevent the elevation of body temperature to levels at which fever per se is life-threatening.[3]

It is doubtful whether body temperatures in the range of 104°F (40.0°C) are harmful, even if prolonged for several days.[1] Indeed, this is the temperature level found in

Presented, in part, before the Annual Meeting of the American Academy of Pediatrics, October 20, 1958.

ADDRESS: 2351 Clay Street, San Francisco 15, California.

Naturwissenschaften (2000) 87:229–231

SHORT COMMUNICATION

Philip T. Starks · Caroline A. Blackie
Thomas D. Seeley

Fever in honeybee colonies

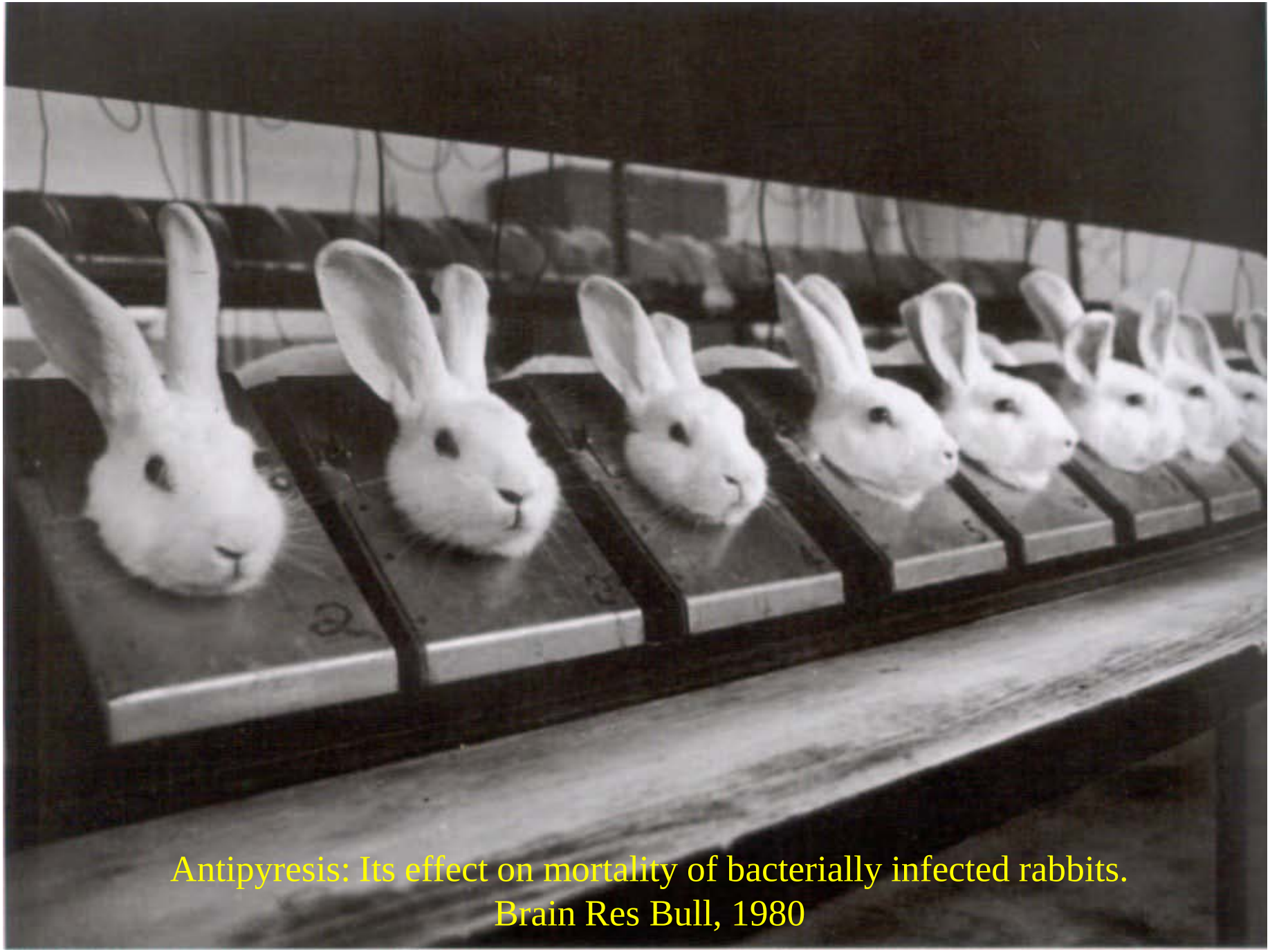
Received: 2 September 1999 / Accepted in revised form: 28 February 2000

Abstract Honeybees, *Apis* spp., maintain elevated temperatures inside their nests to accelerate brood development and to facilitate defense against predators. We present an additional defensive function of elevating nest temperature: honeybees generate a brood-comb fever in response to colonial infection by the heat-sensitive pathogen *Ascosphaera apis*. This re-

De Jong and Morse 1976; De Jong 1977; Bailey 1981). Once infected, larvae die and dry into white lumps resembling chalk (commonly called "mummies"; Maassen 1913). However, the larvae must be chilled to about 30 °C (thus just a few degrees below the normal 33–36 °C brood-comb temperature; Seeley 1985) for the disease to develop (Bailey 1981). The slightly lower

Kluger M. Fever in the lizard Dipsosaurus dorsalis. Nature;1974.


Temperature as a factor in resistance of young puppies.
J Infect Dis 120:669. 1969



Antipyresis: Its effect on mortality of bacterially infected rabbits.
Brain Res Bull, 1980

Supervivencia sube de de 0 a 50% al inducir fiebre en ratas con peritonitis por Klebsiella pneumoniae

Fever: beneficial and detrimental effects of antipyretics. Curr Opin Infect Dis. 2002 ;15:241-45

¿Y en el humano?

- **50 niños con Plasmodium Falciparum: clearance del parásito 16hs mas tarde con quinina + paracetamol que con quinina sola.**

Effect of paracetamol on parasite clearing time in Plasmodium Falciparum malaria. Lancet 1997;350:704-9

- **72 niños con varicela: evolución de costras más lenta en grupo que recibió paracetamol**

Acetaminophen: more harm than good in chickenpox? J Pediatr 1989;114:1045-8

¿Y en el humano?

- **102 niños con gastroenteritis por salmonella: correlación negativa entre la fiebre y la duración de la enfermedad.**

Association of high fever and short bacterial excretion after salmonellosis. Arch Dis Chid 1992;67:531-532

- **Uso de antipiréticos en voluntarios infectados con rinovirus suprimió respuesta de ATC séricos y prolongó síntomas y tiempo de excreción viral**

Adverse effects of aspirin, acetaminophen and ibuprofen on inmune function, viral shedding and clinical status in rhinovirus-infected volunteers. J Infect Dis 1990;162:1227-82

¿Y en el humano?

- **El uso preventivo de Paracetamol antes de la vacunación puede interferir con la respuesta de anticuerpos**

Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in chilldren: two open label, randomised controlled trials. Lancet 2009;374:1339-50

- **Efecto poblacional de suprimir la fiebre: en influenza, mayor periodo de eliminación viral, mayor interacción social**

Population-level effects off suppressing fever. Proc R Soc;281:2014 20132570

Efectos de la fiebre sobre el sistema inmune

↑ Proliferación de células T y B

↑ Producción de ATC e interleuquinas (IL1 y 2, FNT)

↑ Actividad quimiotáctica y fagocítica

↑ Producción de superóxido y otros agentes antibacterianos

↑ efecto del interferon

↑ efecto bactericida de los leucocitos

↓ niveles de Fe y zinc

Efectos negativos de la fiebre

- **Malestar general**
- **Convulsiones**
- **Deshidratación**
- **Desnutrición aguda**
- **Aumento del catabolismo**
- **Daño neurológico?**
- **Muerte?**

Convulsión febril simple

- **¿Podemos evitar una recurrencia de CF a través del tratamiento antitérmico?**

- **¿Debemos evitar una recurrencia de CF?**

Convulsión febril

- **No hay evidencia de que los antitérmicos reduzcan el riesgo de recurrencia de CF en niños predispuestos**

- **La prescripción de antitérmicos luego de una CF puede ser útil para el alivio sintomático del niño pero no debe recomendarse para prevenir futuras CF**

Antipyretic Agents for Preventing Recurrences of Febrile Seizures.Arch Pediatr Adolesc Med. 2009;163:799-804

Antitérmicos y Convulsión febril

Cita	Población	Diseño (nivel de evidencia)	Qué se midió	Resultado clave	Comentarios
Uhari et al (1995)	180 niños después de la primera convulsión en 4 grupos aleatorizados: a) placebo+placebo b) placebo+paracetamol c) diazepam+paracetamol d) diazepam+placebo	Ensayo doble ciego aleatorizado con placebo (nivel 1b)	Número de recurrencia de CF	a) 14 (25.4%) b) 9 (16.4%) c) 14 (25.5%) d) 18 (32.7%) (sin diferencia estadística)	Duración de seguimiento: dos años
Schnaiderman et al (1993)	104 niños luego de la primera convulsión febril en dos grupos aleatorizados: a) paracetamol c/ 4hs b) paracetamol según requerimientos	Ensayo controlado aleatorizado (nivel 1b)	Recurrencia temprana de CF	a) Paracetamol regular= 4 (7.5%) b) Paracetamol = 5 (9.8%) (p= no ificativa)	En hospital (sin seguimiento)
Van Stuijvenberg et al (1998)	230 niños luego de la primera convulsión aleatorizados en: a) ibuprofeno (n=111) b) placebo (n=119)	Ensayo controlado aleatorizado doble ciego con placebo (nivel 1b)	Número de recurrencia de CF	a) 31 (35.7%) b) 36 (33%) (p= no significativa)	Duración media de seguimiento 1.04
Van Esch et al (2000)	Grupo de tratamiento: a) ibuprofeno o paracetamol (n=109) b) no antipiréticos (n=103)	Ensayo no aleatorizado controlado (nivel 2a)	Número de recurrencia de CF	Risego recurrente por fiebre: a) 6.3% (grupo tratamiento) b) 12.2% (grupo control) ARR= 5.9%; (95% CI: -0.2% a 12%)	
Meremikwa et al (2002)	RCTs con paractamol comparado con placebo	Revisión sistemática (nivel 1a)	Número de recurrencia de CF	Conclusión: sin evidencia de que el paracetamol sea efectivo en la prevención de CF	

Tratamiento farmacológico de la fiebre

- **Aspirina**
- **Paracetamol**
- **Ibuprofeno**
- **Dipirona**
- **Otros AINES**
- **Alternancia de antipiréticos**
- **Combinación de antipiréticos**
- **Dosis inicial elevada de paracetamol**

Using NSAID in volume depleted children can precipitate acute renal failure

Cheri Mathews John, Rajeev Shukla, Caroline A Jones

Arch Dis Child 2007;92:524–526. doi: 10.1136/adc.2006.103564

Non-steroidal anti-inflammatory drugs (NSAID) are increasingly popular in hospital medicine and general practice and are readily available over the counter. The vast majority of healthy children who ingest therapeutic doses of NSAID for a limited duration tolerate them without any significant adverse effects. However, the risk of renal toxicity is potentially increased in situations where there is stimulation of the renin-angiotensin system such as with volume depletion or in pre-existing chronic renal disease. We describe four cases which illustrate this complication occurring in a children's hospital. We have not proven cause and effect, but further research is needed to define the true risk of the potential renal complications of NSAID in patients at risk of dehydration.

Patient 1 was a 13 year old girl with Crohn's disease of 1 year's duration. She presented to her local hospital with a relapse of Crohn's disease. She was mildly dehydrated clinically. She was treated with intravenous hydrocortisone, mesalazine, cefotaxime and metronidazole. She received four doses of 50 mg diclofenac sodium per rectum for analgesia following which she became anuric. Within 36 h of presentation to her local hospital, her serum creatinine had risen from 87 to 360 µmol/l. Her serum potassium had risen to 5.6 mmol/l. Her haemoglobin was 10.2 g/dl and platelet count was 200×10^9/l. Her blood film was normal. Her serum urea was 22 mmol/l and creatinine rose further to 629 µmol/l over the next 24 h. An ultrasound scan of her kidneys was normal.

An autoimmune screen including ANA, dsDNA, p and c ANCA, anti Sm, anti GBM and anti-mitochondrial antibodies

Severe Anaphylactic Reaction to Ibuprofen in a Child With Recurrent Urticaria

Liew Woei Kang, MBBS, MRCPCH, FAMS[a], Mona Iancovici Kidon, MD[a,b], Chiang Wen Chin, BMedSci, MBBS, MRCPCH[a], Lim Siok Hoon, MBBS, MRCPCH[a], Chan Yoke Hwee, MBBS, MMed[c], Ng Kee Chong, MBBS, MMed[d]

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

An acute anaphylactic reaction after a conventional antipyretic dose of ibuprofen was diagnosed in a child with allergic rhinitis, recurrent idiopathic urticaria, and nonimmunologic cross-reactive hypersensitivity to nonsteroidal antiinflammatory drugs and acetaminophen. The patient reported several previous, mild (isolated cutaneous) hypersensitivity reactions after exposure to acetaminophen or ibuprofen. There was no evidence of an underlying inflammatory disease except as described above. Patients with chronic or recurrent idiopathic urticaria and those with atopic disease represent groups at increased risk of nonsteroidal antiinflammatory drug hypersensitivity. Mild hypersensitivity reactions to acetaminophen and/or ibuprofen may precede subsequent, more-severe adverse reactions. Risks and benefits of continued use of nonsteroidal antiinflammatory drugs in these children should be carefully considered.

Paracetamol-associated acute liver failure in Australian and New Zealand children: high rate of medication errors

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ABSTRACT

Background In children, paracetamol overdose due to deliberate self-poisoning, accidental exposure or medication errors can lead to paediatric acute liver failure and death. In Australia and New Zealand, the nature of ingestion and outcomes of paracetamol-associated paediatric acute liver failure have not been described.

Objective To describe the nature and outcomes of paracetamol-associated paediatric acute liver failure.

Design Retrospective analysis of paracetamol-associated paediatric acute liver failure cases presenting 2002–2012.

Setting New Zealand and Queensland Paediatric Liver Transplant Services.

Results 14 of 54 cases of paediatric acute liver failure were attributed to paracetamol, the majority were secondary to medication errors. 12 of the 14 children were under the age of 5 years. Seven children received doses in excess of 120 mg/kg/day. Many of the other children received either a double dose, too frequent administration, coadministration of other medicines containing paracetamol or regular paracetamol for up to 24 days. Three children underwent transplant. One of these and one other child died.

Conclusions In Australia and New Zealand, paracetamol overdose secondary to medication errors is the leading cause of paediatric acute liver failure. A review of regional safety practices surrounding paracetamol use in children is indicated.

What this study adds?

- Medication errors in relation to paracetamol are a major problem for parents and caregivers in Australia and New Zealand.
- Paracetamol overdose due to medication errors is one of the main causes for paediatric acute liver failure in Australia and New Zealand.

What is already known?

- Inappropriate paracetamol ingestion is the leading cause for contacting Poisons Information Centres in Australia and New Zealand.[1]
- In children, paracetamol overdose can lead to paediatric acute liver failure and death.
- In the UK and North America, intentional paracetamol overdose is the leading known cause of paediatric acute liver failure.

worldwide describing hepatotoxicity associated with inadvertent overdoses or prolonged dosing within the expected therapeutic range.[2–4 7–10]

Alternancia de Antipiréticos

- **2001 52%**
- **2007 67%**
- **81% por indicación médica**
- **50% dosis inadecuadas**

Alternating antipyretics: an unfounded practice passed down to parents from pediatricians.. Clin Pedatr 2007;46:146-50

EDITOR'S CHOICE

Systematic review of studies comparing combined treatment with paracetamol and ibuprofen, with either drug alone

Edward Purssell

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Accepted 21 July 2011
Published Online First 24 August 2011

ABSTRACT

Objective To evaluate the evidence surrounding the use of combinations of paracetamol and ibuprofen in the treatment of fever.

Design Systematic narrative review of randomised controlled trials using the UK Economic and Social Research Council guidance on the conduct of narrative synthesis.

Setting Inpatient, outpatient and home care.

Patients Children with fever.

Main outcome measures The effect of combination treatments of paracetamol and ibuprofen on fever and comfort, and identification of side effects.

Results Seven studies were identified, six of which provided useful data for the evaluation of the effect of treatment on temperature. Overall these studies showed limited benefit from the combined treatment until around 4 h, after which there was a statistically but only marginally clinically significant benefit. Two studies contained data directly relating to comfort; these suggest a marginal benefit from the combined treatment, but the clinical significance of this was limited. There was no evidence of greater side effects or toxicities associated with the combined treatment. However, it is important to note that these studies were small, short term, and not conducted in the normal setting in which these treatments are given.

Conclusions There is little evidence of any benefit or harm from the combined treatment compared with the use of each drug alone. In the absence of such benefit, there is little to recommend the unnecessary use of polypharmaceutical methods to treat a symptom that does not require treatment, when effective monotherapies exist.

What is known on this subject?

- Fever is a common symptom and, while it may be indicative of serious disease, is not dangerous in itself.
- Parents and professionals often treat this symptom with a combination of paracetamol and ibuprofen, despite the lack of official guidance to this effect.

What this study adds

- A systematic review of randomised controlled trials comparing combinations of paracetamol and ibuprofen to each drug alone, combined with expert opinion in the form of official guidelines.
- Only marginal benefit was shown for the combined treatments compared with each drug individually, which taken alongside the risk of overdose and further increasing the fear of fever, suggests that there is little to recommend this practice.

reduce temperature.[4] This narrative systematic review aims to collate and critique the evidence surrounding the practice of combining paracetamol and ibuprofen, using the principles underlying the UK Economic and Social Research Council guidance on the conduct of narrative synthesis[5] and the Preferred Reporting Items

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Combined and alternating paracetamol and ibuprofen therapy for febrile children (Review)

Wong T, Stang AS, Ganshorn H, Hartling L, Maconochie IK, Thomsen AM, Johnson DW

A COCHRANE REVIEW JOURNAL
EVIDENCE-BASED CHILD HEALTH
Official Journal of the European Paediatric Association (EPA/UNEPSA)
COCHRANE CHILD HEALTH FIELD
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Table 1 Study characteristics

Study	Interventions	Temperature	Age	Follow-up time
Lal *et al*[9*]	G1: paracetamol 10 mg/kg 8 hourly, n=33 G3: paracetamol 10 mg/kg and ibuprofen 10 mg/kg 8 hourly, n=18	≥38.5°C axilla	Mean (95% CI) 2.85 years (1.75 to 3.95) and 3.02 (2.34 to 3.7)	5 days
Erlewyn-Lajeunesse *et al*[14]	G1: paracetamol 15 mg/kg single dose, n=37 G2: ibuprofen 5 mg/kg single dose, n=35 G3: paracetamol 15 mg/kg and ibuprofen 5 mg/kg single dose, n=36	≥38°C tympanic	6 months–10 years	2 h
Nabulsi *et al*[13]	G2: ibuprofen 10 mg/kg, followed by placebo at 4 h, n=33 G3: ibuprofen 10 mg/kg, followed by paracetamol 15 mg/kg at 4 h, n=36	≥38.8°C rectal	6 months–14 years	8 h
Sarrell *et al*[11†]	G1: paracetamol 12.5 mg/kg 6 hourly, n=154 G2: ibuprofen 5 mg/kg 8 hourly, n=155 G3: paracetamol 12.5 mg/kg alternately with ibuprofen 5 mg/kg 4 hourly, n=155	≥38.4°C rectal	6 months–3 years	10 days
Hay *et al*[10]	G1: paracetamol 15 mg/kg 4–6 hourly, n=52 G2: ibuprofen 10 mg/kg 6–8 hourly, n=52 G3: paracetamol 15 mg/kg 4–6 hourly and ibuprofen 10 mg/kg 6–8 hourly, n=52	37.8–41°C axilla	6 months–6 years	5 days
Kramer *et al*[12]	G1: paracetamol 15 mg/kg followed by placebo at 3 h and paracetamol 15 mg/kg at 4 h, n=19 G3: paracetamol 15 mg/kg followed by ibuprofen 10 mg/kg at 3 h and placebo at 4 h, n=19	>38°C oral (rectal <2 years)	6 months–6 years	24 h
Paul *et al*[15]	G1: ibuprofen 10 mg/kg followed by paracetamol 15 mg/kg at 3 h, n=20 G2: ibuprofen 10 mg/kg G3: ibuprofen 10 mg/kg and paracetamol 15 mg/kg	>38°C temporal artery	6 months–6 years	6 h

*This study also included a nimesulide arm not analysed here.
†Half of each group were initially loaded with paracetamol and ibuprofen; because there was no difference these were analysed together.

Table 3 Summary of outcome measures

Study	Temperature	Side effects	Comfort
Lal *et al*[9]	Insufficient data	Slightly raised SGPT, SGOT, urea and creatinine in mixed group. No clinical significance	No data
Erlewyn-Lajeunesse *et al*[14]	**Mean fall over 1 h °C (t)** No clinically or statistically significant difference P 0.95, I 0.92, PI 1.22	No data	No data
Nabulsi *et al*[13]	**% Afebrile at 6–8 h (r)** greater in mixed group 6 h: I 57.6, PI 83.3, p=0.018 7 h: I 45.2, PI 86.1, p<0.001 8 h: I 35.5, PI 80.6, p<0.001 **Max temperature decline** no difference	No serious adverse reactions. No sign of GI, hepatic, renal toxicity	No data
Sarrell *et al*[11]	**Mean max temperature on days 1–3 °C (r)** lowest in mixed group, highest in paracetamol 1 day: P 40.6, I 40.6, PI 39.6 p<0.001 2 day: P 39.7, I 39.7, PI 38.8 p<0.001 3 day: P 39.3, I 39.6, PI 38.5 p<0.001	No differences in renal and liver values and no abnormalities at 14 days	NCCPC score and repeat dosages on days 1–3 lower in mixed group, highest in paracetamol group
Hay *et al*[10]	**Minutes without feverfirst 4 h (a):** greatest in mixed group, shortest in paracetamol group P 116.2, I 156, PI 171.1 **Pairwise comparison**mixed vs paracetamol p<0.001, ibuprofen vs paracetamol p=0.001 **First 24 h:** same pattern P 940.3, PI 1055.2, PI 1217.4	Diarrhoea, vomiting, rash, cough, cold to touch, admitted to hospital no differences and none considered to be related to study	No discomfort at 48 h, pairwise comparisons no difference
Kramer *et al*[12]	**Mean temperature at 3–6 h °C (o/r)**no difference at 3 or 6 h, at 4 and 5 h lower in mixed group 4 h: P 38, PI 37.4, p=0.05 5 h: P 37.9, PI 37.1, p=0.003	No side effects prevented administration and did not differ between groups	Repeat dosages needed at 3 and 4 h no difference
Paul *et al*[15]	**Mean temperature at 1–6 h °C (ta)** no difference at 1–3 h, at 4–6 h lower in mixed (PI) and alternating (IP) than ibuprofen (note order of groups) 4 h: IP 36.9, I 37.5, PI 36.9, p=0.002 5 h: IP 36.8, I 38, PI 36.9, p<0.001 6 h: IP 36.9, I 38.5, PI 37.2, p<0.001	Did not evaluate effect of multiple doses or adverse events that could occur from this	No data

a, axilla; I, ibuprofen; GI, gastrointestinal; NCCPC, non-communicating children's pain checklist; o, oral; P, paracetamol; PI/IP paracetamol and ibuprofen; r, rectal; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; t, tympanic; ta, temporal artery.

Alternancia de Antipiréticos Ventajas

- **Mayor disminución de la temperatura a las 6hs (0,5°C)**
- **Disminución inicial de la temperatura más rápida**
- **«Calma» la ansiedad de los padres**

Alternating ibuprofen and acetaminophen in the treatment of febrile children: a pilot study. BMC Medicine 2006;4:4

Antipyretic Treatment in Young Children with Fever. Acetaminophen, Ibuprofen or both Alternating in a Randomized, Double-blind Study. Arch Pediatr Adoles Med.2006;160:197-202

Combined and alternating paracetamol and ibuprofen therapy for febrile children. Evid-Based Child Health 9:3:675-729.2014 (Cochrane Review Journal)

Alternancia de Antipiréticos Desventajas

- **Toxicidad renal por efecto sumativo y sinergístico en niños deshidratados**
- **Ibuprofeno inhibe producción de glutation**
- **Posibilidad de sobredosis**
- **Efecto sobre la preocupación de los padres respecto a la fiebre**
- **No se observa efecto positivo sobre el bienestar del niño**

Systematic review of studies comparing combined treatment with paracetamol and ibuprofen, with either drug alone. Arch Dis Child 2011;96:1175-79

Alternancia de Antipiréticos

Revisión sistemática de estudios aleatorizados controlados comparando la alternancia o combinaciones de paracetamol e ibuprofeno a cada droga sola.

Se demostró sólo un beneficio marginal de la combinación comparada con las drogas individuales, lo que al lado del riesgo de sobredosis y el fomento del miedo a la fiebre lo hace poco recomendable.

Systematic review of studies comparing combined treatment with paracetamol and ibuprofen, with either drug alone. Arch Dis Child 2011;96:1175-79

Combined and alternating paracetamol and ibuprofen therapy for febrile children. Evid-Based Child Health 9:3:675-729.2014 (Cochrane Review Journal)

Alternancia de Antipiréticos

- **NICE: no dar paracetamol e ibuprofeno simultáneamente. Si considera alternar hágalo bajo supervisión médica**

NICE Guideline 2013

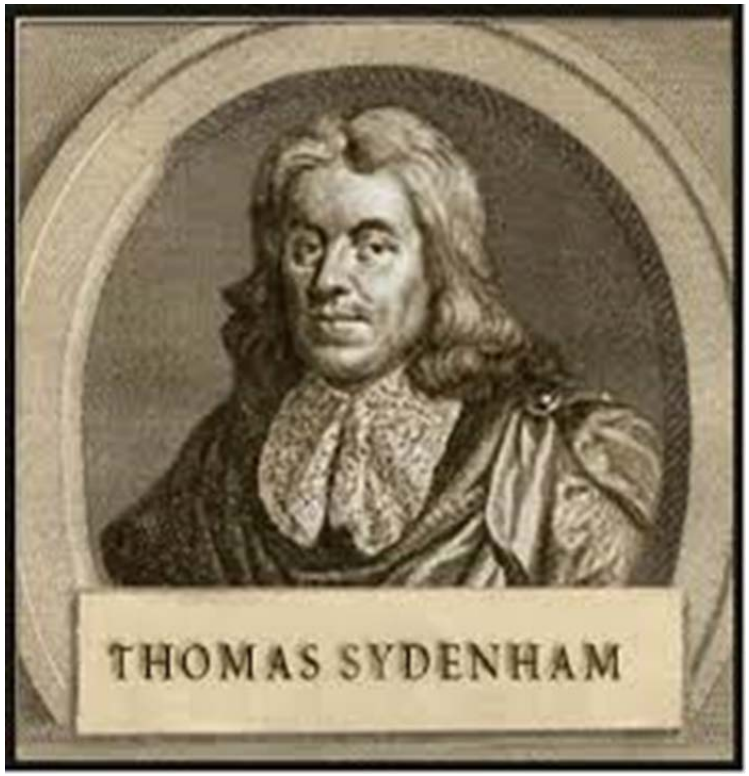
- **AAP: el uso combinado de paracetamol con ibuprofeno puede aumentar la posibilidad de error en la dosificación y contribuir a la «fobia a la fiebre»**

Fever and antipyretic use in children. Pediatrics 2011,127:580-587

- **CPS: No alterne paracetamol con ibuprofeno ya que puede poner a su niño en riesgo de falla hepática.**

Caring for kids: fever and temperature taking. Canadian Pediatric Society 2013

Observé que método podría elegir la Naturaleza, con la intención de dominar el síntoma siguiendo sus huellas.



«La fiebre es una máquina poderosa que la Naturaleza trae al mundo para combatir la enfermedad»