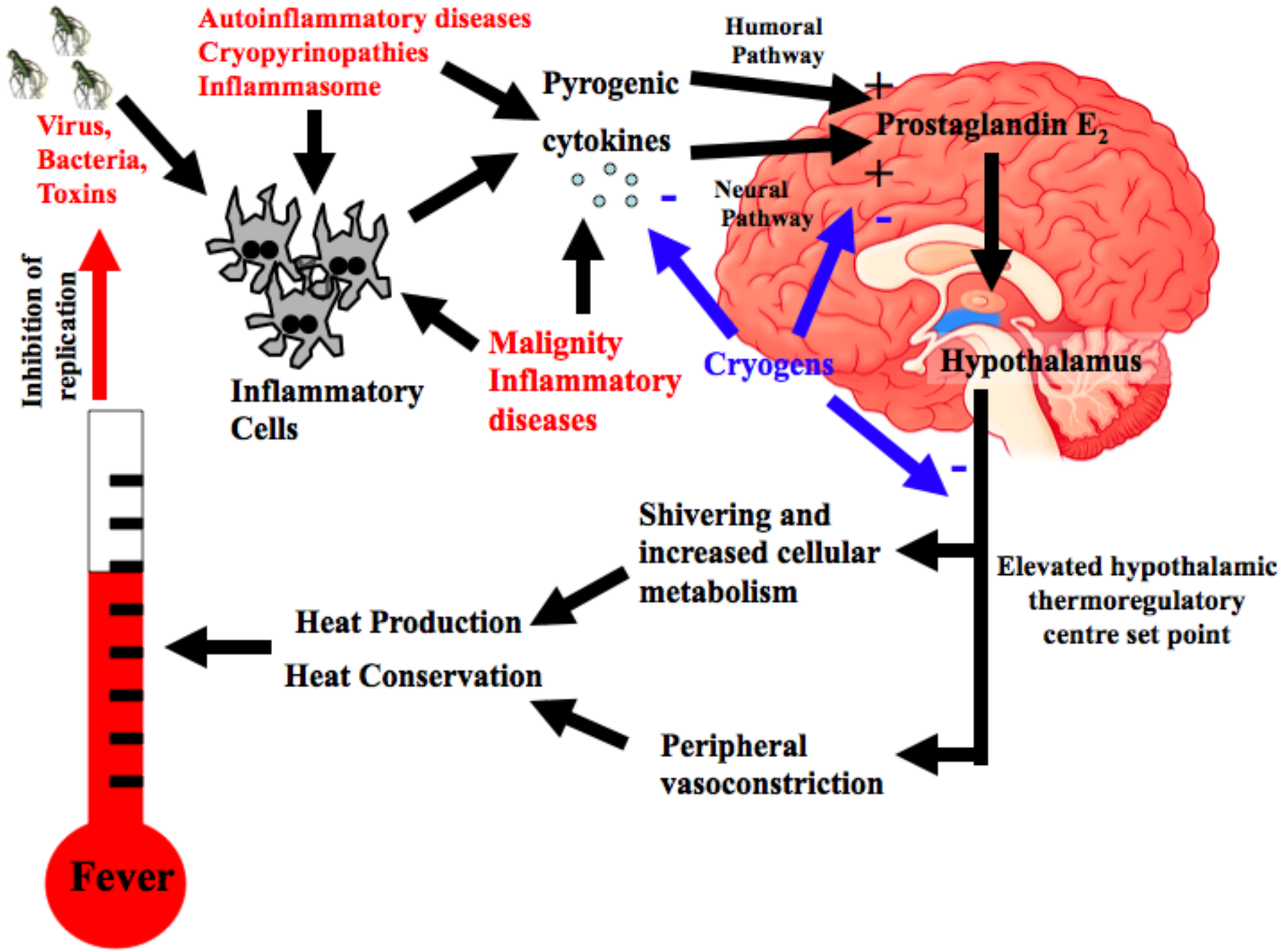

Autoinflammatory diseases
Cryopyrinopathies
Inflammasome
Virus,
Bacteria,
Toxins
Pyrogenic
cytokines
Humoral
Pathway
Prostaglandin E_2
Neural
Pathway
Inhibition of
replication
Inflammatory
Cells
Malignity
Inflammatory
diseases
Cryogens
Hypothalamus
Shivering and
increased cellular
metabolism
Elevated hypothalamic
thermoregulatory
centre set point
Heat Production
Heat Conservation
Peripheral
vasoconstriction
Fever

Humoral Pathway

Clearance

Increase

Inflammatory Cells

Danger signals

-Pathogen-associated molecular patterns: LPS, toxins, and nucleic acids

-Endogenous danger-associated molecular patterns: extracellular ATP, uric acid crystals, hyaluronan and heparan sulfate

Macrophages - Dentritic cells - Epithelial cells

Inflammosome

NLRs or ALRs

ASC

Caspase 1

Inflammation auto-activation:

-Inflammosomo-pathies: CAPS, FMF, PAPA, FCAS2, NLCR4-MAS

-Increased intracellular stress: TRAPS, MKD/HIDS

-Defective regulatory mechanisms: Majeed syndrome, DIRA, DITRA, Early-onset colitis

-Enhanced NFkB signalling: Blau syndrome, CAMPS

-Interferono-pathies: PRAAS, SAVI, Aicardi-Goutières syndrome

Recruitment and activation

IL-18

IL-1β

Pyrogenic cytokines

(i.e.; IL-6 TNF-α IFN-β)

Induction

Membrane Phospholipids

2-AG

PLA_2

MGL

Arachidonic Acid

COX-2

PGH_2

mPGES-1

PGE_2

Endotelial and perivascular cells of Blood-brain barrier

Hypothalamus

Decrease

Increase

Balance Point

Body temperature threshold for triggering cold-defence effectors

[Higher threshold leads to lower heat dispersion at higher body themperatures]

Body temperature threshold for triggering heat-defence effectors

[Lower threshold leads to higher thermogenesis (i.e.; shivering) at lower body themperatures]

Body temperature

°C 36 37 38 39 40 41

Neuronal Pathway

Kupffer Cells Cytokines production

Pyrogenic cytokines

PGE_2 formation at sites of inflammation

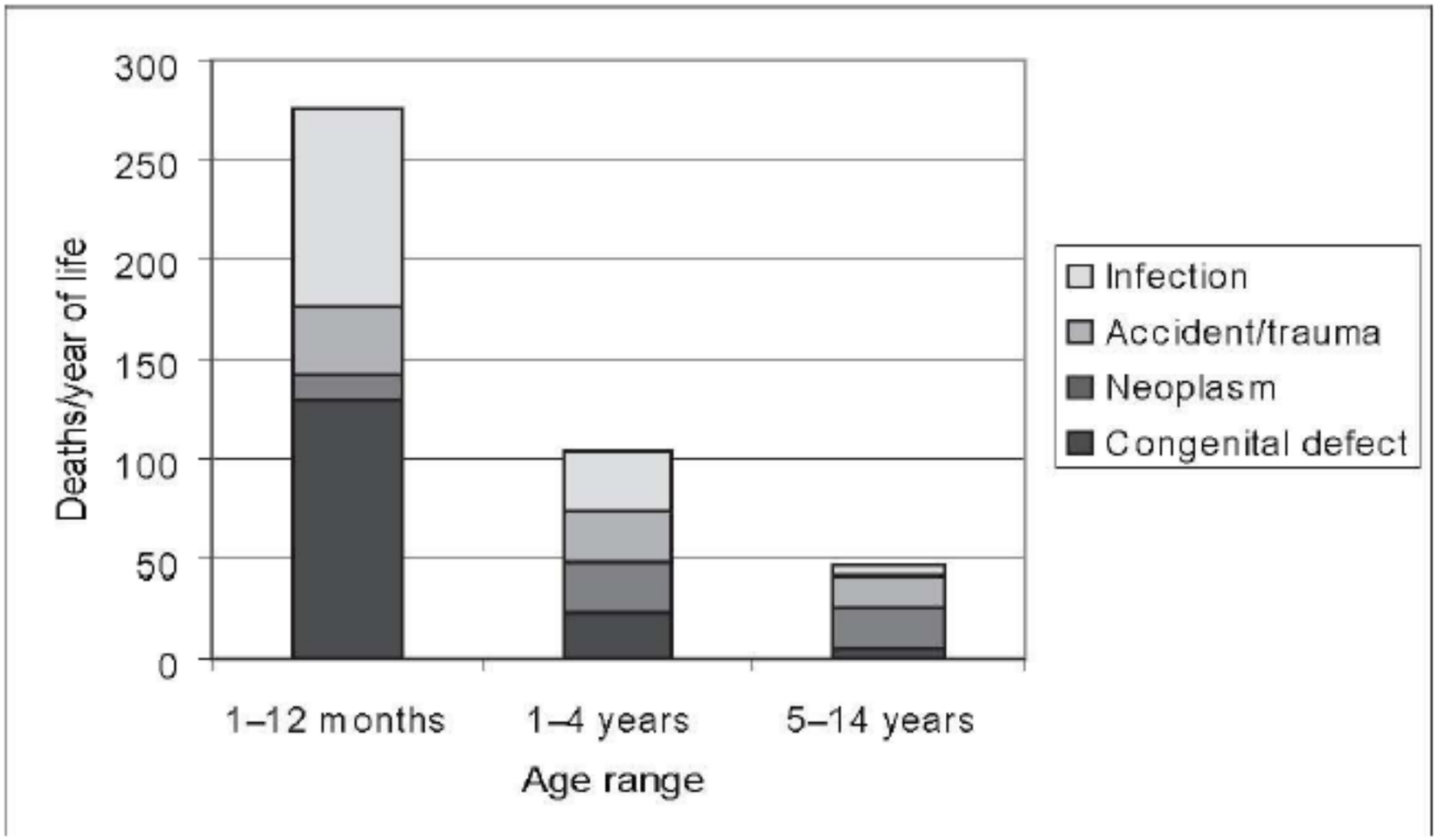
Vagus

Cold sensitives cutaneous nerves

Decrease

Increase

Figure 2.2 Contributions of the four major causative categories to childhood mortality, England and Wales, 2004; neonatal deaths and deaths due to perinatal events have been excluded; data from the Department of Health, courtesy of R MacFaul



Assessment of risk of serious illness

- In children older than 6 months, do not use height of body temperature alone to identify those with serious illness.
- Recognise that children aged 3–6 months with a temperature of 39°C or higher are in at least an intermediate-risk group for serious illness.
- Recognise that children younger than 3 months with a temperature of 38°C or higher are in a high-risk group for serious illness.

Hospital admission rates for meningitis and septicaemia caused by *Haemophilus influenzae, Neisseria meningitidis,* and *Streptococcus pneumoniae* in children in England over five decades: a population-based observational study

Natalie G Martin, Manish Sadarangani, Andrew J Pollard, Michael J Goldacre

For children ages 3 to 36 months with fever without source in the pre-conjugate era, bacteremia rates ranged **from 2 to 3.4% vs. 0.34%** in the post-conjugate era

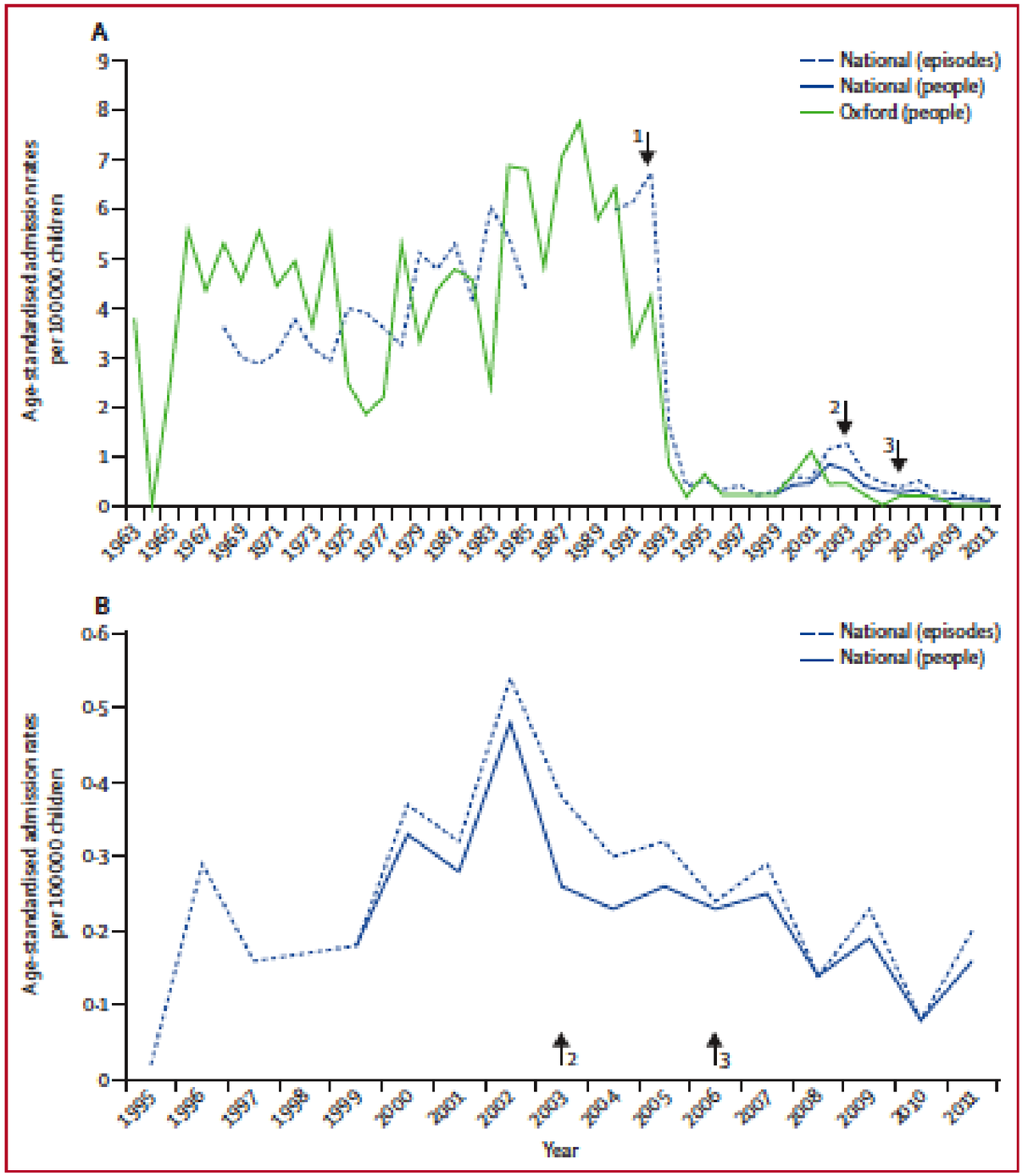


Figure 1: Hospital-admission rates for *Haemophilus influenzae* meningitis (A) or septicaemia (B) in children younger than 15 years in England

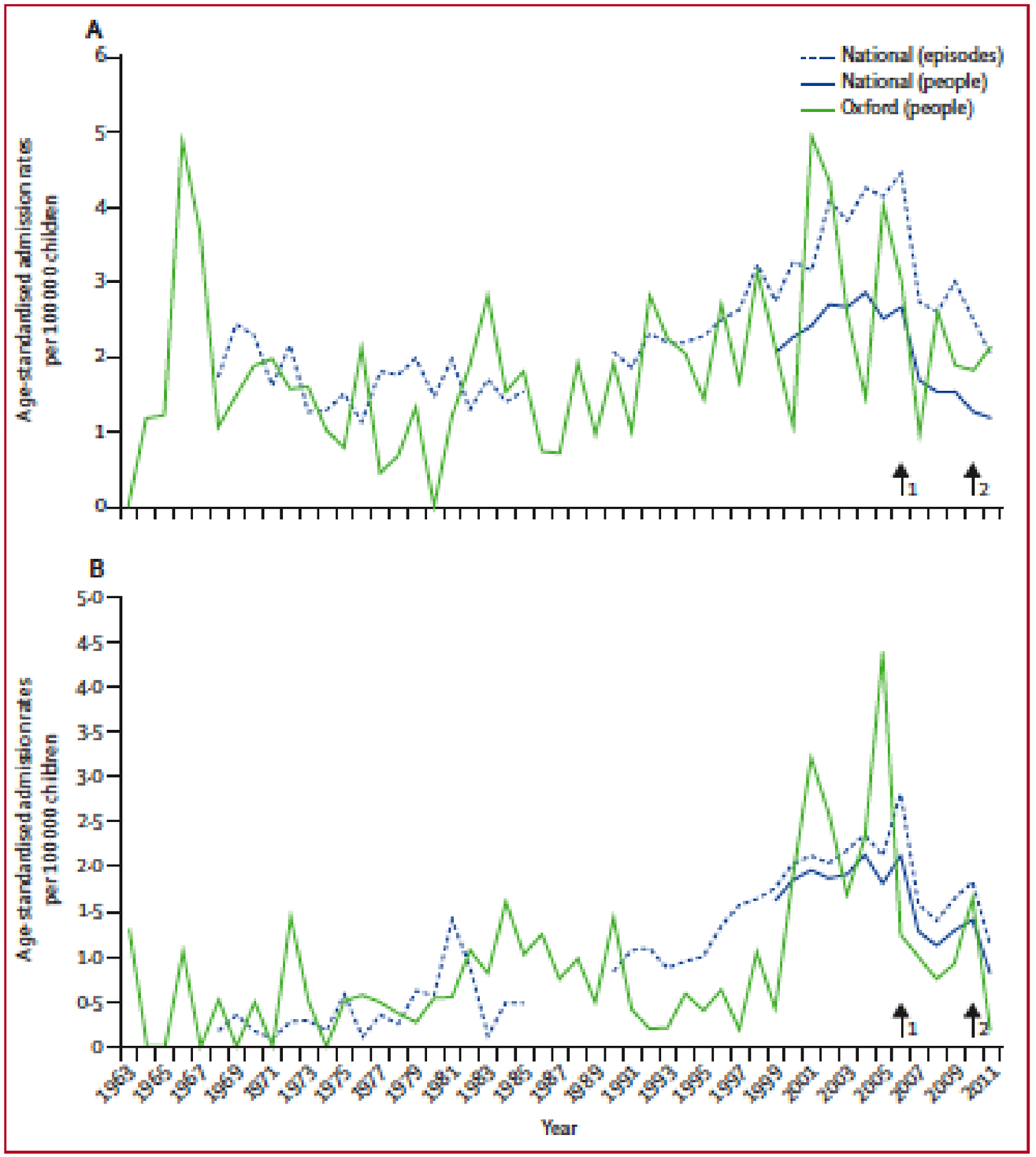


Figure 3: Hospital-admission rates for pneumococcal meningitis (A) and pneumococcal septicaemia (B) in children younger than 15 years in England

Arrow 1 is the 2006 introduction of the PCV7 vaccine. Arrow 2 is the 2010 introduction of the PCV13 vaccine.

Early treatment with parenteral penicillin in meningococcal disease

Keith Cartwright, Sheena Reilly, Diana White, James Stuart

360 pazienti con malattia meningococcica

340 inviati dal GP, 20 con accesso diretto in PS

TABLE V—*Effect of parenteral antibiotics given before admission on mortality in patients sent to hospital by general practitioners*

	All cases (n=340)		Cases with haemorrhagic rash (n=177)	
	No (%) survived	No (%) died	No (%) survived	No (%) died
Antibiotic:				
Given	[illegible]	5 (5)	[illegible]	4 (5)
Not given	2[illegible]	22 (9)	[illegible]	12 (12)
Not known		1		
Total	312 (92)	28 (8)	161 (91)	16 (9)
Relative risk (95% confidence interval)	0·60 (0·23 to 1·54)		0·45 (0·15 to 1·35)	

In this study the case fatality rate for meningococcal disease was reduced by 40% when general practitioners had given parenteral antibiotics before the patients were admitted to hospital; the reduction in mortality was greater than 50% when a haemorrhagic rash had been observed; these patients were most likely to

Journal of Infection (2008) 57, 449–454

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Antibiotic treatment delay and outcome in acute bacterial meningitis

Rasmus Køster-Rasmussen [a,*], André Korshin [b], Christian N. Meyer [c]

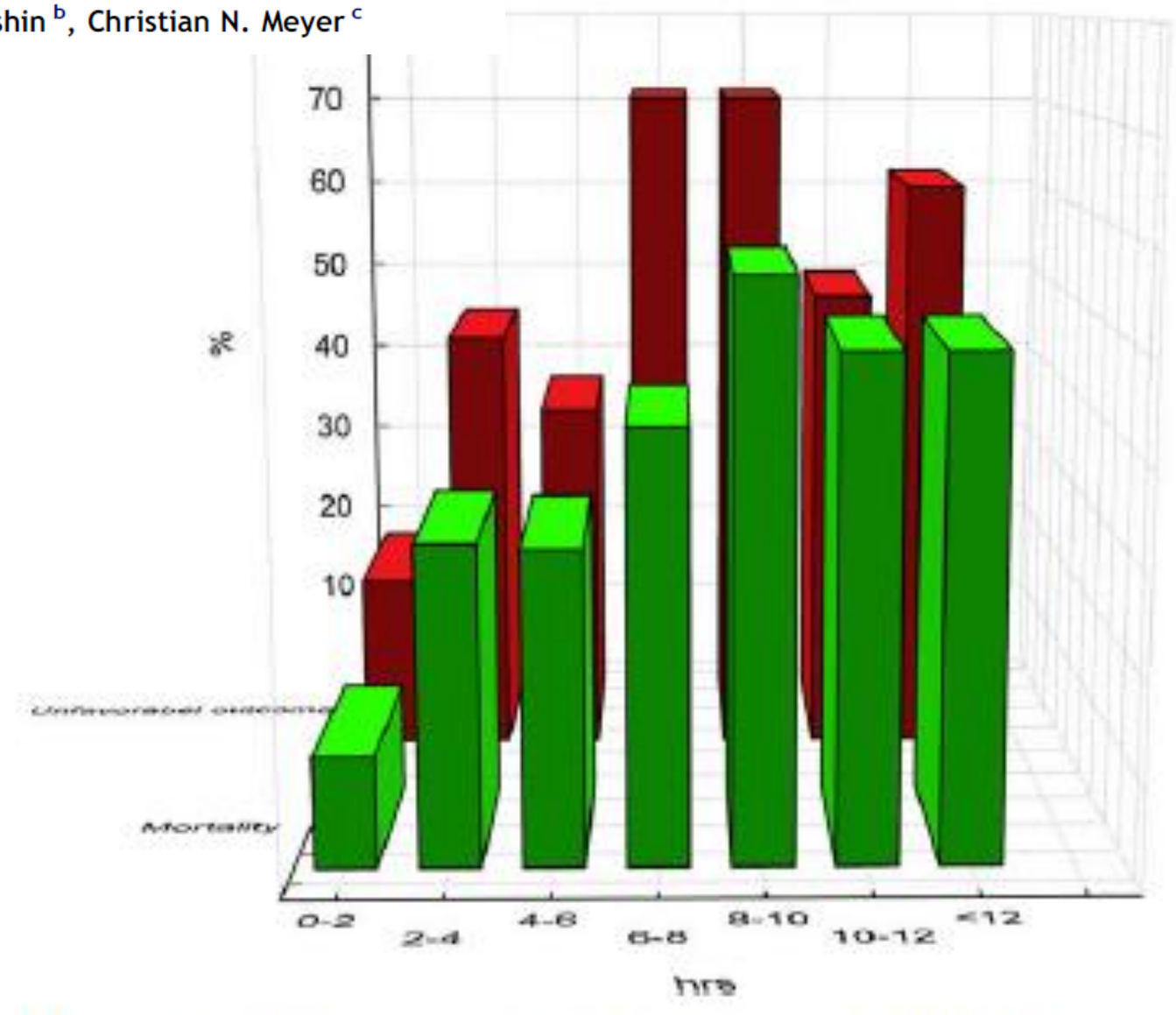


Figure 2 Rate of mortality and unfavourable outcome according to the treatment delay in time interval in acute bacterial meningitis.

Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. Pediatrics 2003.

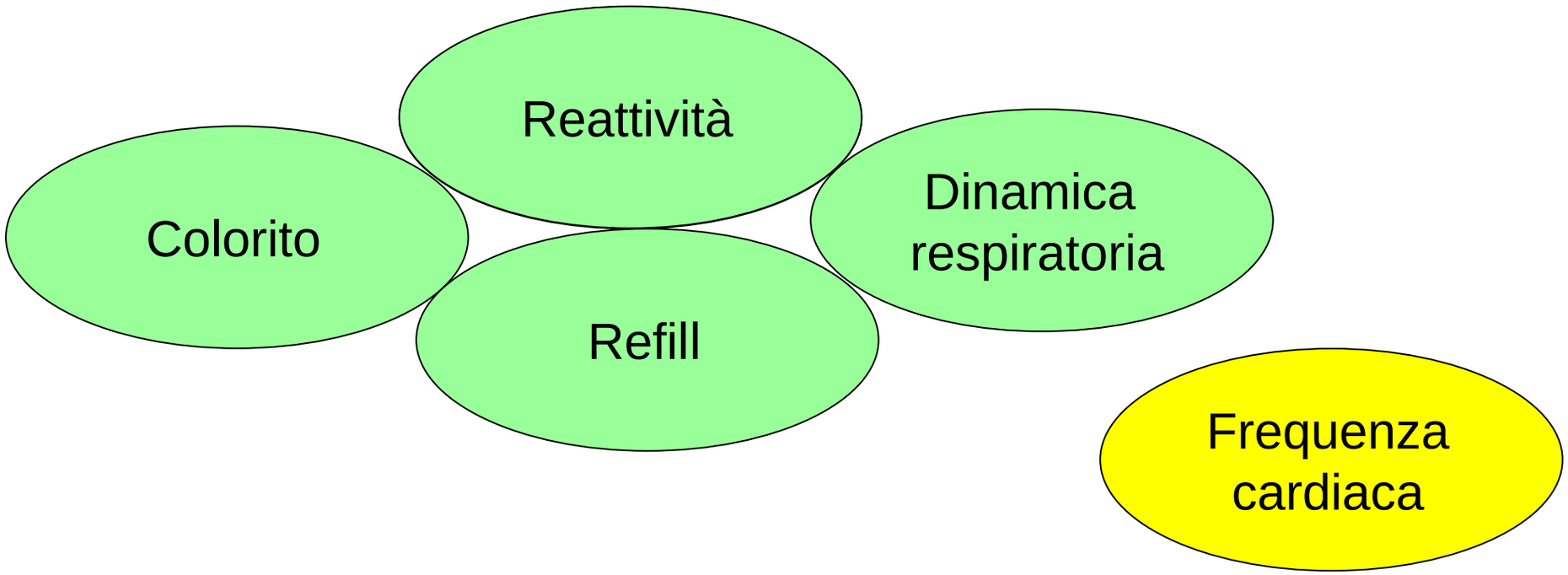
- 91 bambini, Resuscitation practice was consistent with ACCM-PALS Guidelines in only 27 (30%) patients; however, when practice was in agreement with guideline recommendations, a lower mortality was observed (8% vs 38%).

- Each additional hour of persistent shock was associated with >2-fold increased odds of mortality (2.29 [1.19-4.44]).

Fattori di rischio per infezione batterica severa

- 10-25% sotto i 3 mesi infezione batterica severa con febbre > 38.5
- 21 per 1000 tra 0 e 4 anni in family practice
- la misurazione a mano deve essere considerata attendibile
- apprensione/”istinto” e rivalutazione sono fattori di rischio

1. Prenditi un minuto (il primo) per guardare il bambino



NICE guideline: feverish illness in children—assessment and initial management in children younger than 5 years

	Green – low risk	Amber – intermediate risk	Red – high risk
Colour (of skin, lips or tongue)	• Normal colour	• Pallor reported by parent/carer	• Pale/mottled/ashen/blue
Activity	• Responds normally to social cues • Content/smiles • Stays awake or awakens quickly • Strong normal cry/not crying	• Not responding normally to social cues • No smile • Wakes only with prolonged stimulation • Decreased activity	• No response to social cues • Appears ill to a healthcare professional • Does not wake or if roused does not stay awake • Weak, high-pitched or continuous cry
Respiratory		• Nasal flaring • Tachypnoea: RR > 50 breaths/minute, age 6–12 months RR > 40 breaths/minute, age > 12 months • Oxygen saturation ≤ 95% in air • Crackles in the chest	• Grunting • Tachypnoea: RR > 60 breaths/minute • Moderate or severe chest indrawing
nd		• Tachycardia: > 160 beats/minute, age < 1 year > 150 beats/minute, age 1–2 years > 140 beats/minute, age 2–5 years • CRT ≥ 3 seconds • Dry mucous membranes • Poor feeding in infants • Reduced urine output	• Reduced skin turgor
		• Age 3–6 months, temperature ≥ 39°C • Fever for ≥ 5 days • Rigors • Swelling of a limb or joint • Non-weight bearing limb/not using an extremity	• Age < 3 months, temperature ≥ 38°C • Non-blanching rash • Bulging fontanelle • Neck stiffness • Status epilepticus • Focal neurological signs • Focal seizures

te

This traffic light table should be used in conjunction with the recommendations in this guideline on investigations and initial management in children with fever.

Clinical bottom line

- Be clear about how to use antipyretics in a pyrexial illness.
- Recognise the significance of temperatures in the different age groups.
- Tachycardia should not be ignored.
- The traffic light system is a helpful guide to direct investigations and management, but clinical judgement is still needed for those cases where the features are not clear-cut.

	Green – low risk	Amber – intermediate risk	Red – high risk
Colour (of skin, lips or tongue)	• Normal colour	• Pallor reported by parent/carer	• Pale/mottled/ashen/blue
Activity	• Responds normally to social cues • Content/smiles • Stays awake or awakens quickly • Strong normal cry/not crying	• Not responding normally to social cues • No smile • Wakes only with prolonged stimulation • Decreased activity	• No response to social cues • Appears ill to a healthcare professional • Does not wake or if roused does not stay awake • Weak, high-pitched or continuous cry
Respiratory		• Nasal flaring • Tachypnoea: RR > 50 breaths/ minute, age 6–12 months RR > 40 breaths/ minute, age > 12 months • Oxygen saturation ≤ 95% in air • Crackles in the chest	• Grunting • Tachypnoea: RR > 60 breaths/minute • Moderate or severe chest indrawing
Circulation and hydration	• Normal skin and eyes • Moist mucous membranes	• Tachycardia: > 160 beats/minute, age < 1 year > 150 beats/minute, age 1–2 years > 140 beats/minute, age 2–5 years • CRT ≥ 3 seconds • Dry mucous membranes • Poor feeding in infants • Reduced urine output	• Reduced skin turgor
Other	• None of the amber or red symptoms or	• Age 3–6 months, temperature ≥ 39°C • Fever for ≥ 5 days	• Age < 3 months, temperature ≥ 38°C • Non-blanching rash • Bulging fontanelle • Neck stiffness • Status epilepticus • Focal neurological signs • Focal seizures

- Recognise the significance of temperatures in the different age groups.
- Tachycardia should not be ignored.

CRT capillary refill time; RR respiratory rate

* This traffic light table should be used in conjunction with the recommendations in this guideline on investigations and initial management in children with fever.

Perfusione cutanea

Una ridotta perfusione cutanea è un segno precoce di shock

Valutare:

- Temperatura delle estremità
- Colorito cutaneo (pallido, cianotico, marezzato)
- Tempo di riempimento capillare
- Polsi centrali e periferici

Frequenza cardiaca

Situazioni ad elevato rischio

Bambini < 1 anno: FC <80/min o > 180/min

Bambini > 1 anno: FC < 60/min o >160/min

Table 5.1 The features of the Yale Observation Scale (YOS)

Observation item	Normal = 1	Moderate impairment = 3	Severe impairment = 5
Quality of cry	Strong or none	Whimper or sob	Weak or moaning, high-pitched, continuous cry or hardly responds
Reaction to parent stimulation	Cries briefly or no cry and content	Cries on and off	Persistent cry with little response
State variation	If awake, stays awake or if asleep, awakens quickly	Eyes close briefly when awake or awakens with prolonged stimulation	No arousal and falls asleep
Colour	Pink	Pale extremities or acrocyanosis	Pale or cyanotic or mottled or ashen
Hydration	Skin and eyes normal and moist mucous membranes	Skin and eyes normal and mouth slightly dry	Skin doughy or tented and dry mucous membranes and/or sunken eyes
Response to social overtures	Smiles or alerts (consistently)	Brief smile or alert	No smile, anxious, dull; no alerting to social overtures

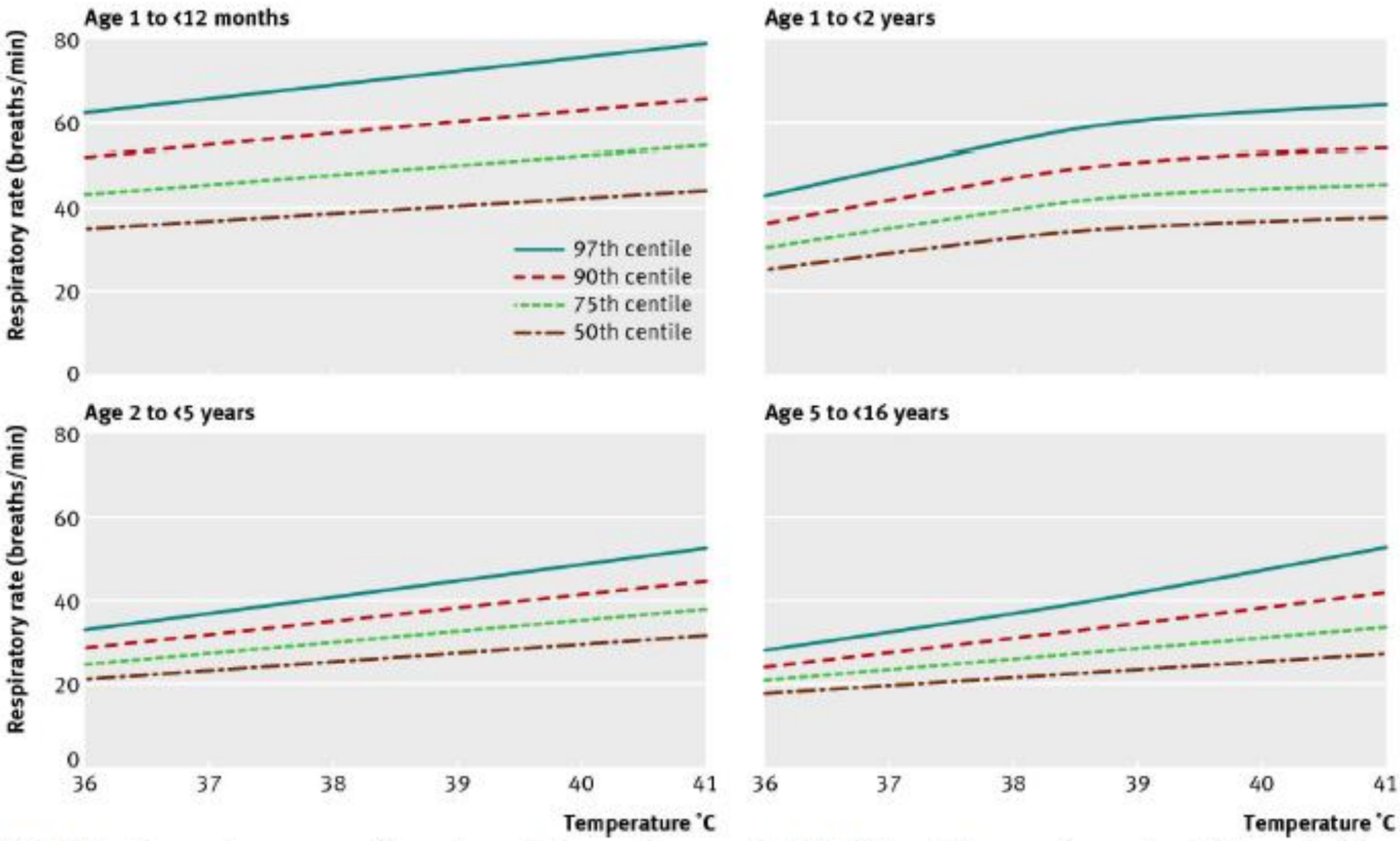
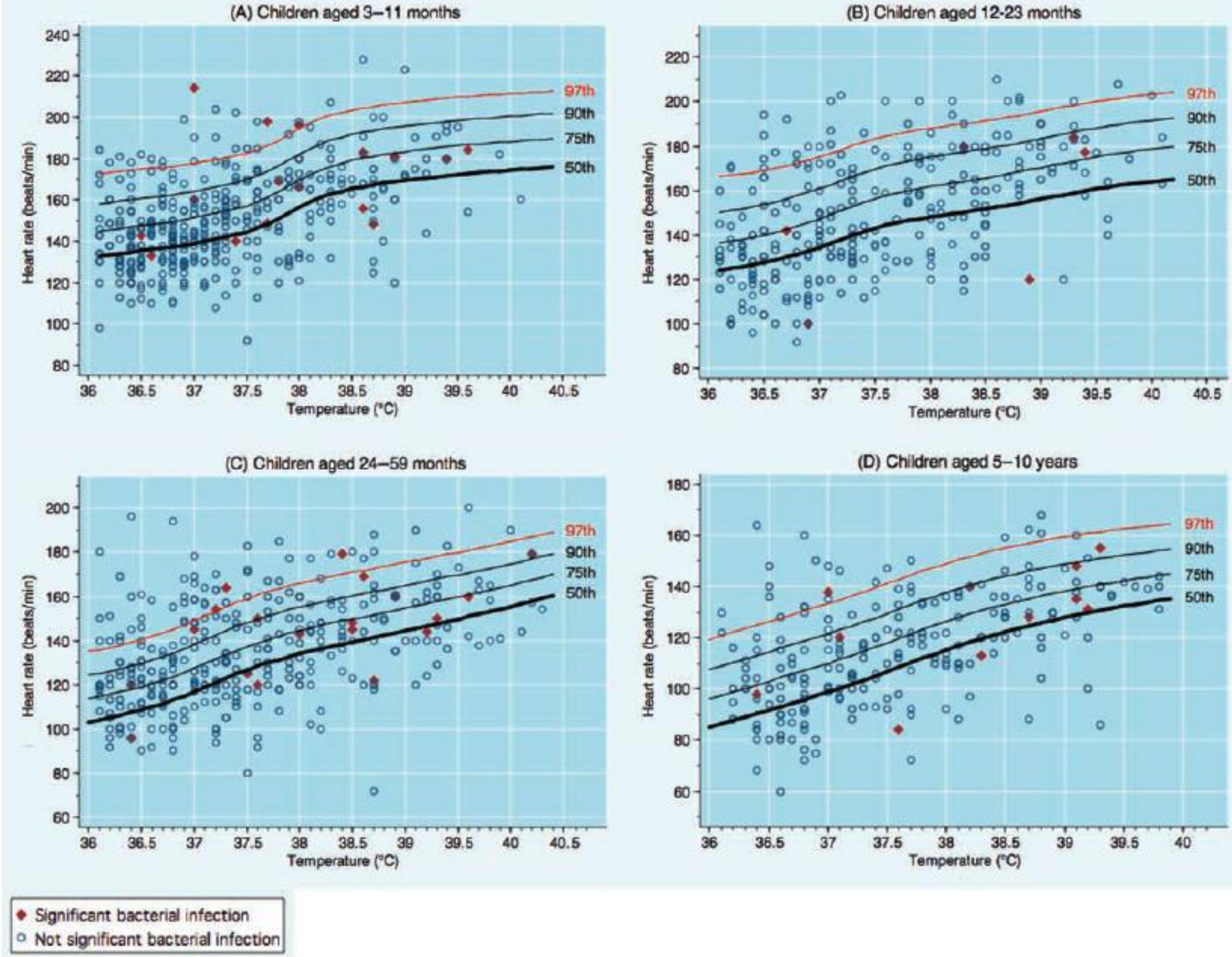


Fig 2 Median and upper centiles of respiratory rate expected at different temperatures for children of different age groups


(A) Children aged 3–11 months
(B) Children aged 12-23 months
(C) Children aged 24–59 months
(D) Children aged 5–10 years
Heart rate (beats/min)
Temperature (°C)
97th
90th
75th
50th
Significant bacterial infection
Not significant bacterial infection

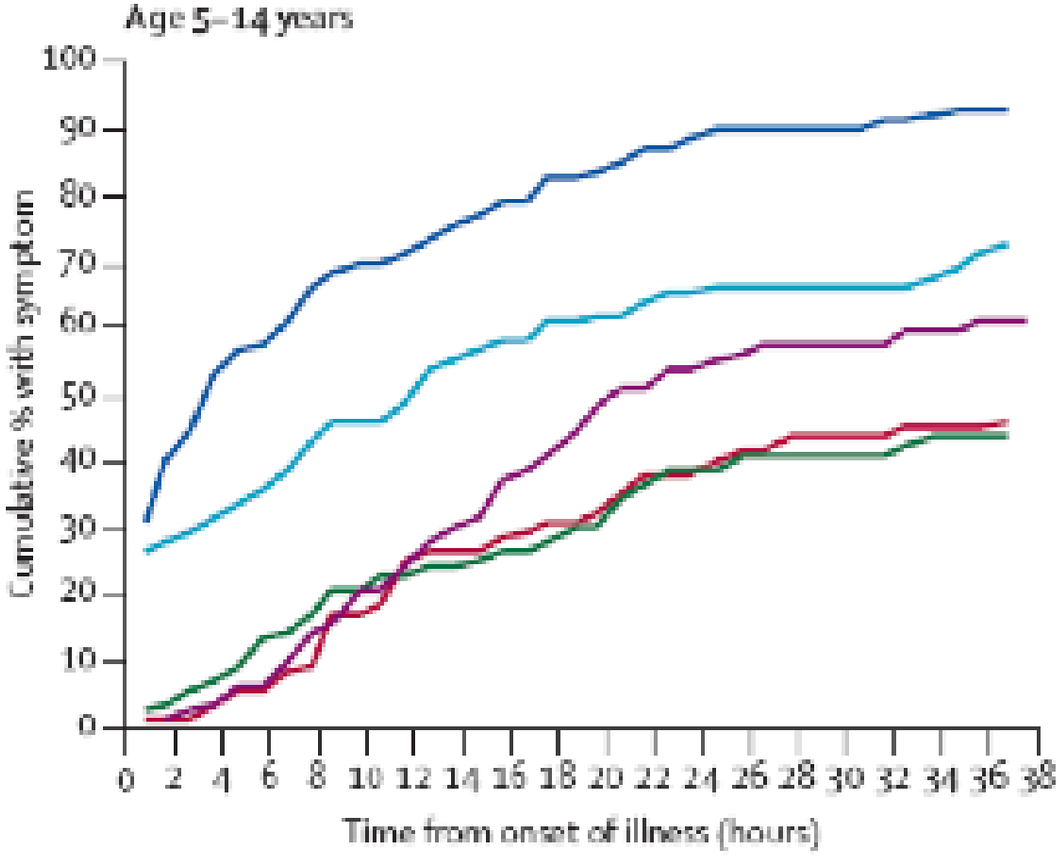
Clinical recognition of meningococcal disease in children and adolescents

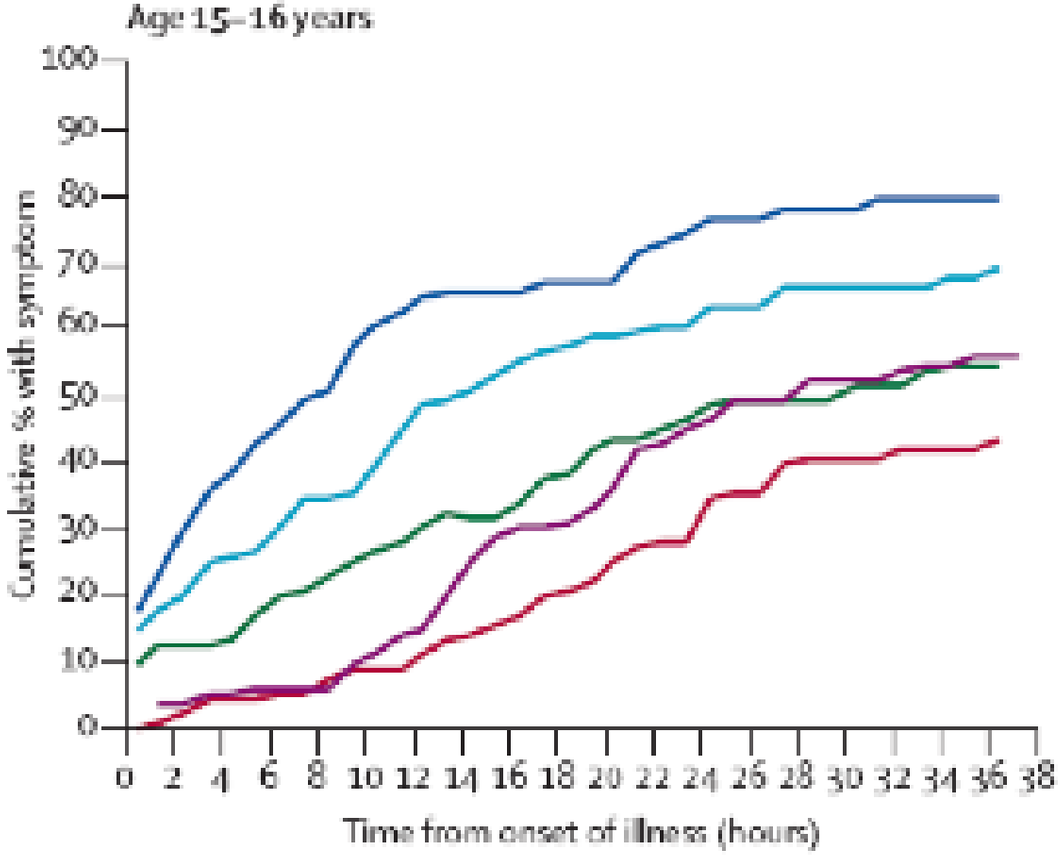
*Matthew J Thompson, *Nelly Ninis, Rafael Perera, Richard Mayon-White, Claire Phillips, Linda Bailey, Anthony Harnden, David Mant, Michael Levin

Lancet 2006; 367: 397–403

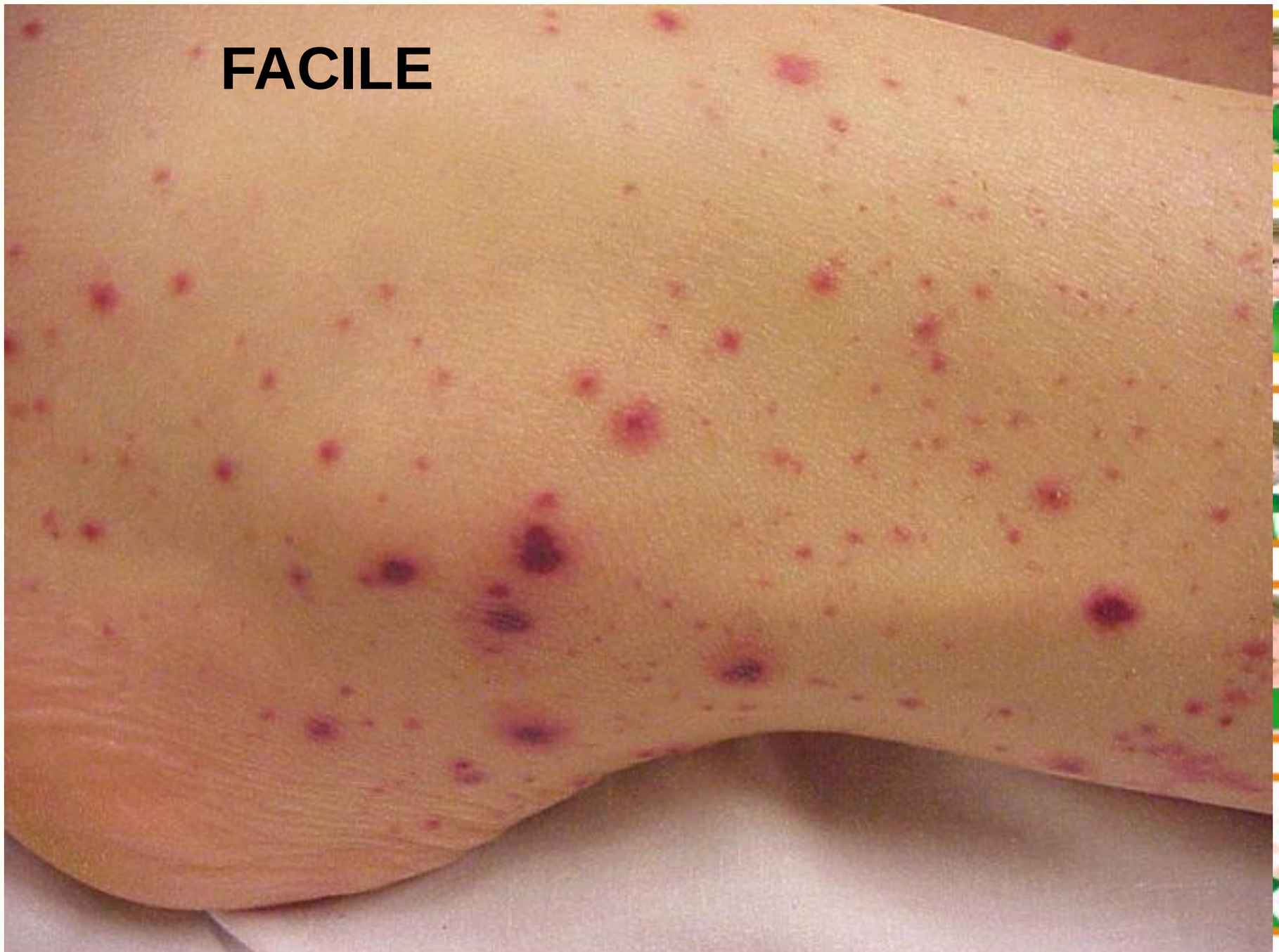
- Fever
- Sepsis features
- Impaired mental status
- Meningism
- Haemorrhagic rash

In all age groups, the first specific clinical features were signs of sepsis—leg pain, abnormal skin colour, cold hands and feet, and, in older children, thirst.





INFEZIONE → SIRS → SEPSI → SEPSI GRAVE → SHOCK SETTICO



FACILE

Incidence of Bacteremia in children with fever and petechiae

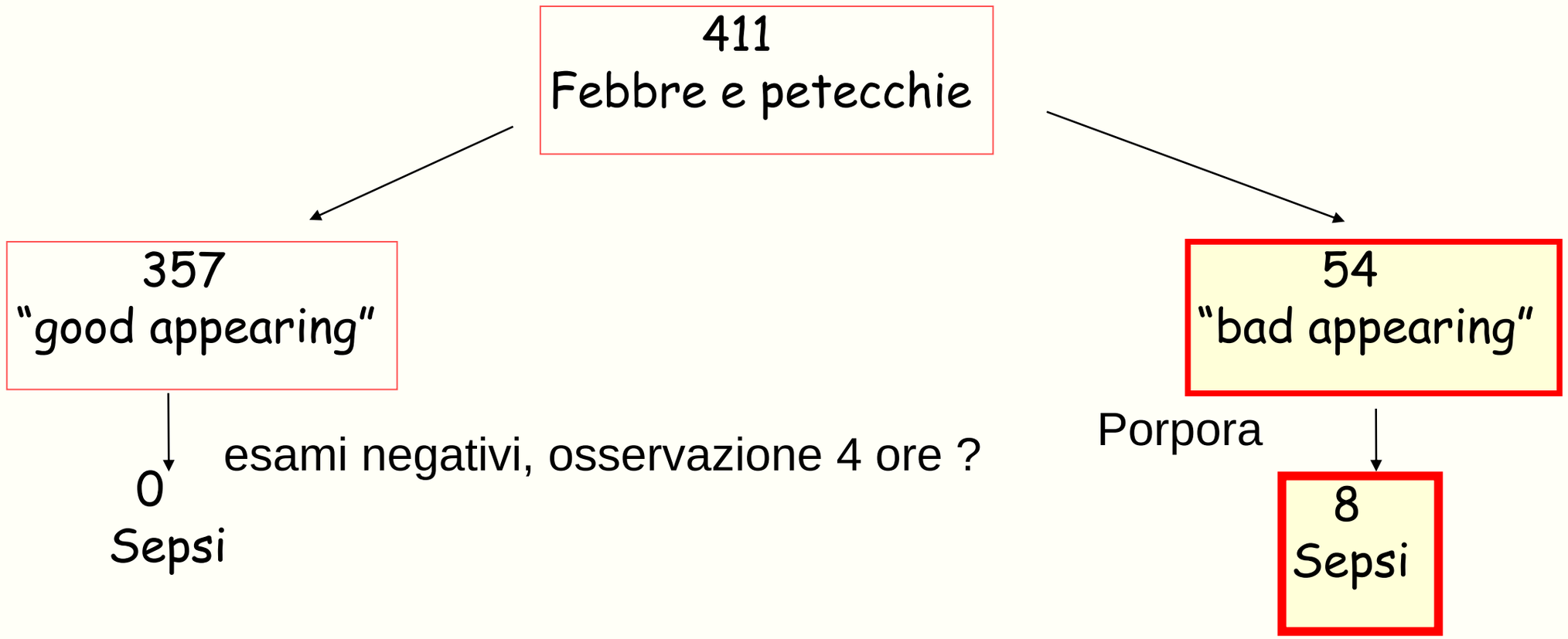
Mandl KD et al , J Pediatr. 1997;131(3):398-404

411 bambini portati in PS con febbre > 38° e petecchie

In 8 diagnosi finale di sepsi/batteriemia

Elementi maggiormente predittivi di sepsi :

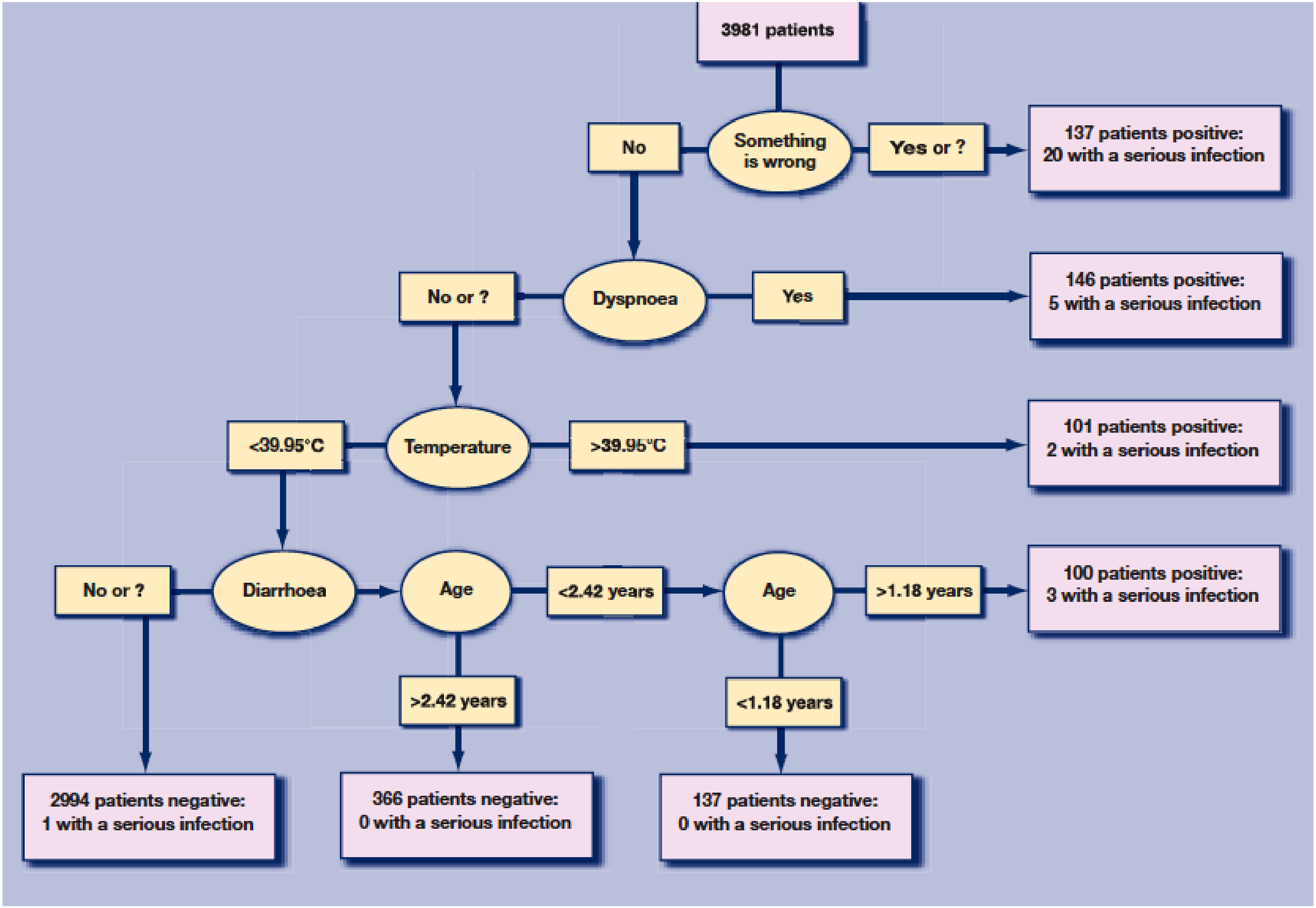
-"colpo d'occhio" (= colorito / aspetto sofferente = tempo di ricircolo)
- Leucociti : <5000 ; > 15000



Signs and symptoms for diagnosis of serious infections in children:

a prospective study in primary care

Ann Van den Bruel, Bert Aertgeerts, Rudi Bruyninckx, Marc Aerts and Frank Buntinx


3981 patients
Something is wrong
No
Yes or ?
137 patients positive:
20 with a serious infection
Dyspnoea
No or ?
Yes
146 patients positive:
5 with a serious infection
Temperature
<39.95°C
>39.95°C
101 patients positive:
2 with a serious infection
Diarrhoea
No or ?
Age
<2.42 years
Age
>1.18 years
100 patients positive:
3 with a serious infection
>2.42 years
<1.18 years
2994 patients negative:
1 with a serious infection
366 patients negative:
0 with a serious infection
137 patients negative:
0 with a serious infection

Rigors in febrile children may be associated with a higher incidence of serious bacterial infection

Report by Daniel E Lumsden, *Specialist Registrar Paediatrics*
Checked by Katherine Potier de la Morandière, *Consultant in Emergency Medicine*
Mayday University Hospital and Manchester Royal Infirmary, UK
doi: 10.1136/emj.2007.052282

Table 2

Author, date, country	Patient group	Study type	Outcomes	Key results	Study weaknesses
Tal *et al*, 1997, Israel	Children admitted to paediatric ward with febrile illness, 100 children who had experienced rigors before admission, 334 children who had not experienced rigors	Retrospective cohort study	Pr… inf… blood, urine … culture) Di… pr… infection	15% rigor group had positive culture vs. 6% of non-rigor group. Sensitivity 0.71, specificity 0.52, PPV 0.15, NPV 0.94, LR 1.47 67% of rigor group presumed bacterial infection vs 50% of non-rigor. Sensitivity 0.57, specificity 0.6, PPV 0.67, NPV 0.5, LR 1.42	All children unwell enough to require hospitalisation. Allocation to group on basis of history of rigors, not observed rigors by clinician. No blinding for either outcome. Diagnosis of presumed bacterial infection in absence of positive culture was in part subjective

LR, logistic regression; NPV, negative predictive value; PPV, positive predictive value.

Original article

Bulging fontanelle in febrile infants: is lumbar puncture mandatory?

S Shacham,[1] E Kozer,[1,2] H Bahat,[1] Y Mordish,[1] M Goldman[1,2]

What is already known on this topic

- Most infants with fever and a bulging fontanelle have benign and self-limited disease.
- It is common practice to perform a lumbar puncture in these infants to exclude bacterial meningitis, but clinical evidence for this practice is lacking.
- Another approach is that the indication for lumbar puncture should be based on signs of toxicity, but clinical evidence supporting this approach is also scarce.

Table 1 Final diagnosis in 153 febrile infants with a bulging fontanelle

Diagnosis	n (%)
Aseptic meningitis	41 (26.7)
Upper respiratory tract infection	28 (18.3)
Viral disease NOS	24 (15.6)
Roseola infantum	13 (8.5)
Acute otitis media	10 (6.5)
Pneumonia	7 (4.5)
Bronchitis	5 (3.2)
Herpangina	5 (3.2)
Tonsillitis	4 (2.6)
Pyelonephritis	4 (2.6)
Rotavirus gastroenteritis	3 (1.9)
Diarrhoea NOS	3 (1.9)
Salmonella/shigella gastroenteritis	2 (1.3)
Pneumococcal bacteraemia	2 (1.3)
Varicella	1 (0.6)
Pneumococcal meningitis	1 (0.6)
Total	153

NOS, not otherwise specified.

Prospective Longitudinal Study of Signs and Symptoms Associated With Primary Tooth Eruption

AUTHORS: Joana Ramos-Jorge, BDS, MS,[a] Isabela A. Pordeus, BDS, MS, PhD,[a] Maria L. Ramos-Jorge, BDS, MS, PhD,[b] and Saul M. Paiva, BDS, MS, PhD[a]

[a]*Department of Pediatric Dentistry and Orthodontics, Faculty of Dentistry, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; and* [b]*Department of Pediatric Dentistry and Orthodontics, Faculty of Dentistry, Universidade Federal dos Vales do Jequitinhonha e Mucuri, Diamantina, Brazil*

KEYWORDS
tooth eruption, signs and symptoms, deciduous tooth, teething

www.pediatrics.org/cgi/doi/10.1542/peds.2010-2697

doi:10.1542/peds.2010-2697

Accepted for publication May 16, 2011

TABLE 2 Descriptive Analysis and Comparison of Tympanic and Axillary Temperature Determined by Dentists on Noneruption Days, Day Before Eruption, Day of Eruption, and Day After Eruption

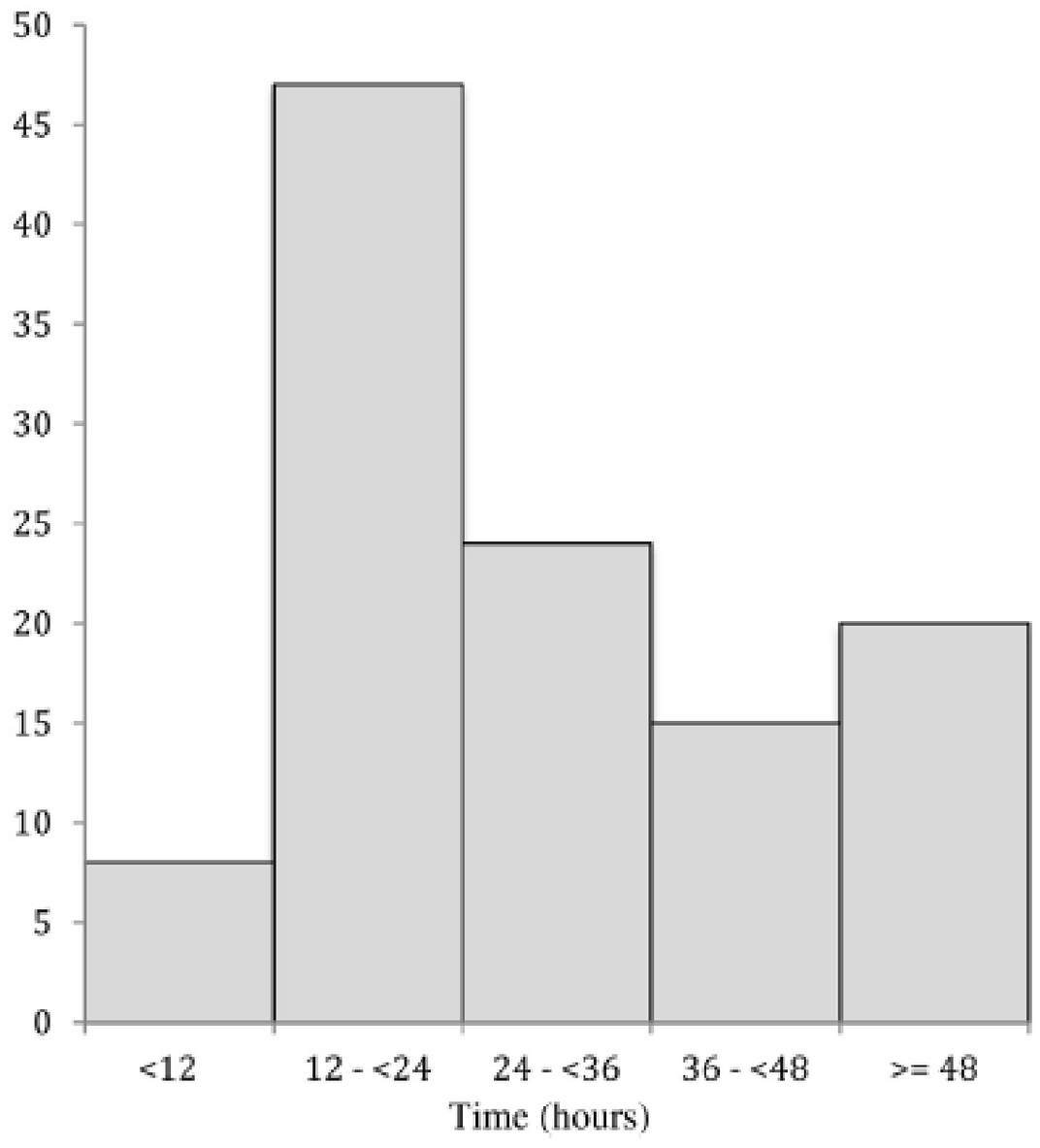
Temperature	Mean (SD)	Median	Minimum	Maximum	Wilcoxon Rank Test[a]
Tympanic					
Noneruption	36.39 (0.26)	36.46	35.8	36.8	Noneruption vs previous day, $P = .004$
Previous day	36.47 (0.23)	36.60	36.0	36.7	Noneruption vs eruption, $P = .012$
Eruption	36.51 (0.20)	36.60	36.0	36.8	Noneruption vs following day, $P < .001$
Following day	36.49 (0.22)	36.60	36.0	36.7	
Axillary					
Noneruption	35.98 (0.36)	36.04	35.4	36.6	Noneruption vs previous day, $P < .001$
Previous day	35.99 (0.26)	35.93	35.7	36.6	Noneruption vs eruption, $P = .516$
Eruption	35.99 (0.46)	36.06	35.2	36.5	Noneruption vs following day, $P = .007$
Following day	35.80 (0.37)	35.90	35.0	36.4	

[a] Bonferroni correction, $P < .016$.

Repeated Emergency Department Visits Among Children Admitted With Meningitis or Septicemia: A Population-Based Study

Samuel Vaillancourt, MDCM, MPH*; Astrid Guttmann, MDCM, MSc; Qi Li, MSc; Ian Y. M. Chan, BHSc, MPH; Marian J. Vermeulen, MHSc; Michael J. Schull, MD, MSc

*Corresponding Author. E-mail: Sam.Vaillancourt@utoronto.ca, Twitter: @VaillancourtSam.



What this study adds to our knowledge

In this database of all Ontario ED visits during a 5-year period, 1 in 5 children with meningitis or septicemia had a previous ED visit. Children who return to the ED and receive a diagnosis of meningitis and septicemia have clinical outcomes similar to those who receive a diagnosis at the initial visit.

Sick Kids Look Sick

Steven M. Green, MD*; Lise E. Nigrovic, MD, MPH; Baruch S. Krauss, MD, EdM

*Corresponding Author. E-mail: steve@stevegreenmd.com.

www.jpeds.com • THE JOURNAL OF PEDIATRICS

Does the Use of Antipyretics in Children Who Have Acute Infections Prolong Febrile Illness? A Systematic Review and Meta-Analysis

Edward Purssell, PhD, and Alison E. While, PhD

Conclusion There is no evidence from these studies that the use of antipyretics slows the resolution of fever in children. *(J Pediatr 2013;163:822-7)*.

Archimedes

Arch Dis Child August 2013

Does a failure to respond to antipyretics predict serious illness in children with a fever?

Clinical bottom line

Response to antipyretics should not be used to predict serious illness in febrile children (grade C)

Non lo sfebbramento ma il miglioramento dell'aspetto del bambino aiutano ad orientarsi verso una malattia più o meno severa…

Se hai un dubbio prenditi un'altro minuto

Antipyretic interventions

- Antipyretic agents do not prevent febrile convulsions and should not be used specifically for this purpose.
- Tepid sponging is not recommended for the treatment of fever.
- Children with fever should not be underdressed or overwrapped.
- Do not use antipyretic agents with the sole aim of reducing body temperature in children with fever.

le ragioni del no

- sepsi : aumento mortalità 28 gg
- vaccinazioni : ridotta risposta anticorpale
- prolunga durata infezione da rhinovirus, varicella e malaria
- prolungata escrezione salmonella
- non migliora outcome meningite

Trattare sempre se

- malattia mitocondriale/metabolica
- cuore polmonare
- febbre post-arresto
- febbre alta e danno neurologico acuto

BMC Pediatrics

BioMed Central

Research article

Open Access

Equal antipyretic effectiveness of oral and rectal acetaminophen: a randomized controlled trial [ISRCTN11886401]

Mona Nabulsi*[1], Hala Tamim[2], Ramzi Sabra[3], Ziyad Mahfoud[2], Shadi Malaeb[1], Hadi Fadlh[4] and Mohammad Mikati[1]

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* Corresponding author

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Accepted: 06 September 2005

This article is available from: http://www.biomedcentral.com/1471-2431/5/35

Abstract

Background: The antipyretic effectiveness of rectal versus oral acetaminophen is not well established. This study is designed to compare the antipyretic effectiveness of two rectal acetaminophen doses (15 mg/kg) and (35 mg/kg), to the standard oral dose of 15 mg/kg.

Methods: This is a randomized, double-dummy, double-blind study of 51 febrile children, receiving one of the three single doses: 15 mg/kg oral, 15 mg/kg rectal, or 35 mg/kg rectally. Rectal temperature was monitored at baseline and hourly for a total of six hours. The primary outcome of the study, time to maximum antipyresis, and the secondary outcome of time to temperature reduction by at least 1°C were analyzed by one-way ANOVA. Two-way ANOVA with repeated measures over time was used to compare the secondary outcome: change in temperature from baseline at times 1, 2, 3, 4, 5, and 6 hours among the three groups. Intent-to-treat analysis was planned.

Results: No significant differences were found among the three groups in the time to maximum antipyresis (overall mean = 3.6 hours; 95% CI: 3.2—4.0), time to fever reduction by 1°C or the mean hourly temperatures from baseline to 6 hours following dose administration. Hypothermia (temperature ≤ 36.5°C) occurred in 11 (21.6%) subjects, with the highest proportion being in the rectal high-dose group.

Conclusion: Standard (15 mg/kg) oral, (15 mg/kg) rectal, and high-dose (35 mg/kg) rectal acetaminophen have similar antipyretic effectiveness.

Background

Parents of febrile children often conceive fever as a disease that requires treatment, rather than being a symptom or a sign of illness. In their anxious quest to treat fever, parents suffering from "fever phobia" may end up unintentionally overdosing their children with different antipyretics, or with different preparations of the same antipyretic [1-3]. Acetaminophen, in its various preparations, is a widely

Vale per la febbre non per il dolore

Assorbimento rettale lento ed erratico

Servono dosi teoriche di 50 mg/kg carico

e 30 mg/kg dose (tossiche)

Table 1 Conditions and situations that may increase the risk of paracetamol toxicity also with therapeutic dosing

Conditions and situations
Diabetes mellitus [106]
Obesity [81]
Chronic undernutrition [123]
Prolonged fasting [118]
Family history of hepatotoxic reaction [7]
Myopathies [25]
Inherited or acquired higher activity of CYP2E1 [111]

Table 2 Drugs that can stimulate higher activity of CYP2E1 with increased conversion of paracetamol to NAPQI

Drugs
Carbamazepine [7]
Ethanol [99, 118]
Isoniazid [26, 75, 99]
Phenobarbital [7]
Rifampin [7]

fattori di rischio gastrotossicità fans

Ministero della Salute

- ulcera pre-esistente
- alte dosi o associazioni di diversi FANS
- uso concomitante di steroidi
- uso concomitante di anticoagulanti
- presenza di infezione da Helicobacter Pylori

fattori di rischio nefrotossicita fans

Ministero della Salute

- alta dose
- storia di deplezione di volume
- contrazione diuresi
- uso concomitante di diuretici, ace inibitori, sartanici

- Consider using either paracetamol or ibuprofen in children with fever who appear distressed.
- When using paracetamol or ibuprofen in children with fever:
  - continue only as long as the child appears distressed
  - consider changing to the other agent if the child's distress is not alleviated
  - do not give both agents simultaneously
  - only consider alternating these agents if the distress persists or recurs before the next dose is due.