

## MeB – Pagine Elettroniche

Volume XVI

Settembre 2013

numero 7

## APPUNTI DI TERAPIA

## La mancata risposta della febbre agli antipiretici è indicativa di una malattia severa?

Vitalia Murgia<sup>1</sup>, Federico Marchetti<sup>2</sup>

<sup>1</sup> *Pediatria di famiglia, Mogliano Veneto (Treviso)* <sup>2</sup> *UOC di Pediatria e Neonatologia, AUSL di Ravenna*

**Indirizzo per corrispondenza:** vitalia.murgia@tin.it

Il quesito che si pone l'Autore del contributo pubblicato recentemente su *Arch Dis Child*<sup>1</sup> non è banale. In presenza di un lattante febbrile (ad esempio di 9 mesi) senza segni di localizzazione e con uno stick urine negativo, se la febbre non risponde in modo convincente all'uso di un antipiretico, quanto è probabile che ci si trovi di fronte a una malattia severa? La febbre è motivo frequente di consultazione medica. Negli USA circa il 25% delle visite in un dipartimento di emergenza pediatrica sono dovute a valori di temperatura corporea elevata. La maggior parte dei bambini febbrili ha malattie virali autolimitanti ma una minoranza significativa potrebbe avere una malattia batterica grave che richiede un tempestivo trattamento antibiotico. Sulla gestione di questi bambini c'è ancora una notevole controversia. Un metodo

che viene usato comunemente dai medici e dai genitori per decidere se il bambino necessita di una valutazione approfondita è l'osservazione della risposta all'antipiretico. Infatti, è opinione comune che la febbre di eziologia benigna (virale) risponda meglio all'antipiretico rispetto a quella dovuta a una malattia batterica severa. Ma è davvero così? **Il quesito clinico** King nella sua valutazione sistematica della letteratura<sup>1</sup> ha strutturato in maniera precisa la sua domanda: *«la mancata risposta all'antipiretico (indicatore) di un gruppo di bambini febbrili (popolazione) comparata con la buona risposta di un altro gruppo di bambini febbrili (gruppo di controllo) aumenta la probabilità di malattia batterica grave nella popolazione?»* **La ricerca delle evidenze** Per dare risposta al quesito ha poi condotto, nel marzo del 2013, una accurata revisione della letteratura scientifica attraverso una ricerca su MEDLINE (1946–2013) e su EMBASE (1947–2013), con limitazione alla lingua inglese e all'età 0-18 anni, sulla Cochrane Library e BESTBETS. La revisione della letteratura ha identificato **8 studi** che hanno cercato di dare risposta a questo quesito<sup>2-9</sup>. Tutti gli studi sono risultati essere eterogenei tra loro e deboli dal punto di vista metodologico, oltre che piuttosto datati *Tabella 1*.

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

**Tabella 1.** *Da voce bibliografica 1.*

| Study                         | Study group                                                                                                  | Study type         | Outcome                                                                                                                                                                | Key result                                                                                                                                                                                | Comments                                                                                                                                                     |
|-------------------------------|--------------------------------------------------------------------------------------------------------------|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Torrey, et al. <sup>2</sup>   | 255 patients aged 3–24 months, with initial temperature $\geq 38.9$ °C, given either paracetamol or aspirin. | Prospective cohort | Rectal temperature response of children with bacteraemia compared with children without bacteraemia 60–120 min following 10 mg/kg of oral paracetamol or aspirin.      | Similar mean decrease in temperature in bacteraemic compared with non-bacteraemic children (1.32 °C vs 1.05 °C; $p=0.14$ ).                                                               | Small sample size. Use of two antipyretics. Children with prior use of antipyretic/antibiotic not excluded. Variable time period when temperature rechecked. |
| Baker, et al. <sup>3</sup>    | 1559 patients aged 8 weeks–6 years, with initial temperature $>38.4$ °C, given paracetamol.                  | Prospective cohort | Rectal temperature response of children 1 and 2 h following 15 mg/kg of oral paracetamol according to diagnosis.                                                       | Larger mean decrease in temperature in children with group A strep pharyngitis, culture positive bacterial disease or pneumonia compared with children with other diagnoses ( $p<0.01$ ). | Current use of antibiotic not noted. Little information on how diagnoses made.                                                                               |
| Weisse, et al. <sup>4</sup>   | 100 patients aged 9 days–17 years, with initial temperature $\geq 38.9$ °C, given paracetamol.               | Prospective cohort | Rectal or oral temperature response 1 h following 15 mg/kg of oral paracetamol in children with bacterial infections compared with children with viral infections.     | Similar mean decrease in temperature in children with bacterial illnesses compared with children with viral illnesses (0.82 °C vs 0.64 °C; $p=0.37$ ).                                    | Small sample size. Temperature only checked 1 h after antipyretic. Two methods of measuring temperature used (rectal and oral).                              |
| Yamamoto, et al. <sup>5</sup> | 233 patients aged 3–24 months, with initial temperature $\geq 40$ °C, given paracetamol or aspirin.          | Prospective cohort | Rectal temperature response of children with bacteraemia compared with children without bacteraemia at least 1 h following 10–15 mg/kg of oral paracetamol or aspirin. | Similar mean decrease in temperature in bacteraemic compared with non-bacteraemic children (1.61 °C vs 1.64 °C; $p=0.85$ ).                                                               | Small sample size. Two antipyretics used. Variable dose of paracetamol.                                                                                      |

|                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                            |                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                         |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Baker, et al. <sup>6</sup>   | 154 patients aged 3–24 months, with initial temperature $\geq 39.4$ °C, given paracetamol.                                                                                                                                                                                                                                                                                                                                                               | Prospective cohort         | Temperature response of children with bacteraemia or meningitis compared with children without bacteraemia 1–2 h following 15 mg/kg of oral or rectal paracetamol.                                                                                                | Similar mean decrease in temperature in children with bacteraemia compared with children without bacteraemia (1.7 °C vs 1.6 °C; $p>0.05$ ) and children with meningitis compared with children without bacteraemia (1.3 °C vs 1.6 °C; $p>0.05$ ). | Small sample size. Method of temperature measurement not specified. Children with prior use of antipyretic not excluded. Variable time period when temperature rechecked. Different preparations of paracetamol used (oral and rectal).                                                                 |
| Mazur, et al. <sup>7</sup>   | 34 children aged 2 months–6 years with occult bacteraemia and a temperature $\geq 38.9$ °C, who had been given paracetamol, compared with 68 matched controls with a temperature $\geq 38.9$ °C but no bacteraemia, who had been given paracetamol.                                                                                                                                                                                                      | Case-control study         | OR of having bacteraemia in children not responding to 10 mg/kg of oral paracetamol (defined as a drop of at least 0.8 °C within 2 h of paracetamol) compared with children responding to 10 mg/kg of oral paracetamol.                                           | OR of having bacteraemia was 9.2 in children not responding to paracetamol (95% CI 2.7 to 32.0) compared with children responding to paracetamol.                                                                                                 | Variable dose of paracetamol administered. Variable time when temperature rechecked. No record of blood cultures being obtained on all children with temperature $\geq 38.9$ °C. Method of temperature assessment not specified.                                                                        |
| Bonadio, et al. <sup>8</sup> | 59 children aged 2–24 months with a diagnosis of 'non-bacterial febrile illness' and a temperature $\geq 39$ °C, who had been given paracetamol compared with: <ul style="list-style-type: none"> <li>• 22 children with bacterial meningitis and a temperature <math>\geq 39</math> °C, who had been given paracetamol.</li> <li>• 59 children with a bacteraemia and a temperature <math>\geq 39</math> °C, who had been given paracetamol.</li> </ul> | Case-control study         | Temperature response 60–90 min following 10–15 mg/kg of oral paracetamol in <ul style="list-style-type: none"> <li>• children with non-bacterial febrile illness;</li> <li>• children with bacterial meningitis;</li> <li>• children with bacteraemia.</li> </ul> | Similar median temperature decrease in children with non-bacterial febrile illness, children with bacterial meningitis and children with bacteraemia (1.4 °C, 0.8 °C and 1.3 °C respectively; $p=0.14$ ).                                         | Retrospective study. Variable time when temperature rechecked. Variable dose of paracetamol administered. No clear description of how controls selected and if any matching occurred.                                                                                                                   |
| Mazur, et al. <sup>9</sup>   | 484 children aged 2 months–6 years with a temperature $>38.9$ °C, judged to be at risk of occult bacteraemia, who had been given paracetamol.                                                                                                                                                                                                                                                                                                            | Retrospective cohort study | Mean temperature response to 10 mg/kg of oral paracetamol in children with bacteraemia compared with children without bacteraemia.                                                                                                                                | Significantly smaller reduction in mean temperature in children with bacteraemia compared with children without bacteraemia (1.0 °C vs 1.2 °C; $p=0.01$ ).                                                                                        | Same data used as in previous study (Mazur et al 9). Variable dose of paracetamol. Consecutive patients not enrolled. Variable time when temperature rechecked. Route of temperature assessment not controlled. No record of blood cultures being obtained on all children with temperature $>38.9$ °C. |

## Bibliografia

- King D. Question 2: Does a failure to respond to antipyretics predict serious illness in children with a fever? Arch Dis Child. 2013;98(8):644–6.
- Torrey SB, Henretig F, Fleisher G, et al. Temperature response to antipyretic therapy in children: relationship to occult bacteremia. Am J Emerg Med 1985;3:190–2.
- Baker MD, Fosarelli PD, Carpenter RO. Childhood fever: correlation of diagnosis with temperature response to acetaminophen. Pediatrics 1987;80:315–18.
- Weisse ME, Miller G, Brien JH. Fever response to acetaminophen in viral vs bacterial infections. Pediatr Infect Dis J 1987;6:1091–4.
- Yamamoto LT, Wigder HN, Fligner DJ, Rauen M, Dershewitz RA. Relationship of bacteremia to antipyretic therapy in febrile children. Pediatr Emerg Care 1987;3:223–7.
- Baker RC, Tiller T, Bausher JC, et al. Severity of disease correlated with fever reduction in febrile infants. Pediatrics 1989;83:1016–19.
- Mazur LJ, Jones TM, Kozinetz CA. Temperature response to acetaminophen and risk of occult bacteremia: a case-control study. J Pediatr 1989;115:888–91.
- Bonadio WA, Bellomo T, Brady W, Smith D. Correlating changes in body temperature with infectious outcome in febrile children who receive acetaminophen. Clin Pediatr 1993;32:343–6.
- Mazur LJ, Kozinetz CA. Diagnostic tests for occult bacteremia: temperature response to acetaminophen versus WBC count. Am J Emerg Med 1994;12:403–6.
- Marchetti F, Torenese G, Panizon F. Valutazione e gestione iniziale della malattia febbrile nei bambini di età inferiore ai 5 anni secondo un sistema a semaforo. Medico e Bambino 2008;27(2):95–102.