

Paediatric fever guidelines – the UK experience

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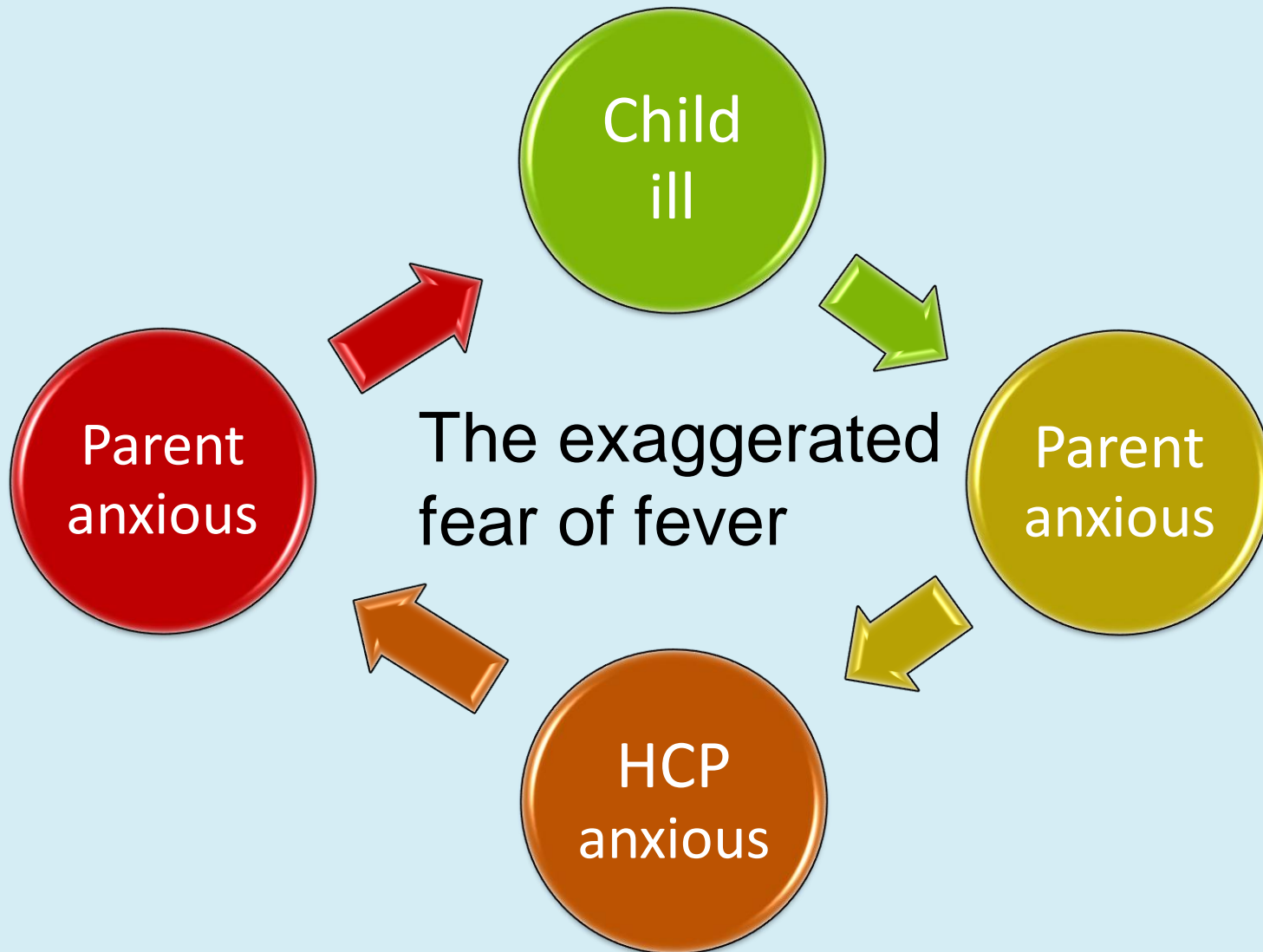
- What is fever?
- What does it mean?
- Who provides advice?
- What advice should be provided?
- Recommendations

Fever

- Differentiate from hyperthermia
- A symptom not an illness
- Worries parents and professionals alike
 - Worries are similar across time and place
 - Parents report getting most of their information from healthcare professionals

Crocetti *et al.*, (2001) *Pediatrics* 107 1241-1246
Purssell (2009) *J Clin Nurs* 18 210-218

Fever phobia



What is fever?

- Part of the acute phase response – early non-specific host defence mechanism
 - Immunological
 - Physiological
 - Behavioural ('sickness behaviour')
- Triggered by cytokines, most notably IL-1, IL-6, TNF- α , IFN- γ
- Results from action of PGE₂ on anterior hypothalamus
- Regulated response *'fever's glass ceiling'*

Initial assessment

NICE (2007) *Feverish Illness in children, assessment and initial management in children younger than 5 years*
London, NCCWCH

1. Temperature measurement

- Electronic or chemical dot in axilla
- Infra-red tympanic (not under 4 weeks)
- Parental report

2. Assess symptoms - 'traffic light' system

- Colour
- Activity
- Respiratory
- Hydration
- Other

Low risk	Intermediate risk	High risk
Skin normal colour	Pallor reported	Pale/mottled/ashen/blue
Responds to social cues Content/smiles Stays awake/awakens quickly Strong normal cry/not crying	Not responding to social cues Wakes only with stimulation Decreased activity No smile	No response to social cues Appears ill to HCP Unable to rouse/does not stay awake Weak, high-pitched/continuous cry
	Nasal flaring Tachypnoea Age 6-12 months >50 bpm Age >12 months >40 bpm Oxygen saturation \leq 95% in air Crackles	Grunting Tachypnoea >60 bpm Moderate/severe chest indrawing
Normal skin and eyes Moist mucous membranes	<i>Tachycardia:</i> <i>> 160 beats/minute, age < 1 year</i> <i>> 150 beats/minute, age 1–2 years</i> <i>> 140 beats/minute, age 2–5 years</i> Dry mucous membrane Poor feeding in infants CRT \geq 3 seconds Reduced urine output <i>Poor feeding in infants</i>	Reduced skin turgor
None of the amber or red symptoms or signs	<i>Age 3–6 months, temperature \geq 39°C</i> Fever for \geq 5 days <i>Rigors</i> Swelling of a limb/joint Non-weight bearing limb/not using an extremity	<i>Age <3 months temperature \geq 38°C</i> Non-blanching rash Bulging fontanelle Neck stiffness Status epilepticus Focal neurological signs Focal seizures Bile-stained vomiting

Using the 'traffic light'

All green, no amber or red	If any amber features and no diagnosis	Any red
Manage at home with advice, including when to seek help	Provide 'safety net' or refer to a paediatric specialist	Refer child urgently to a paediatric specialist

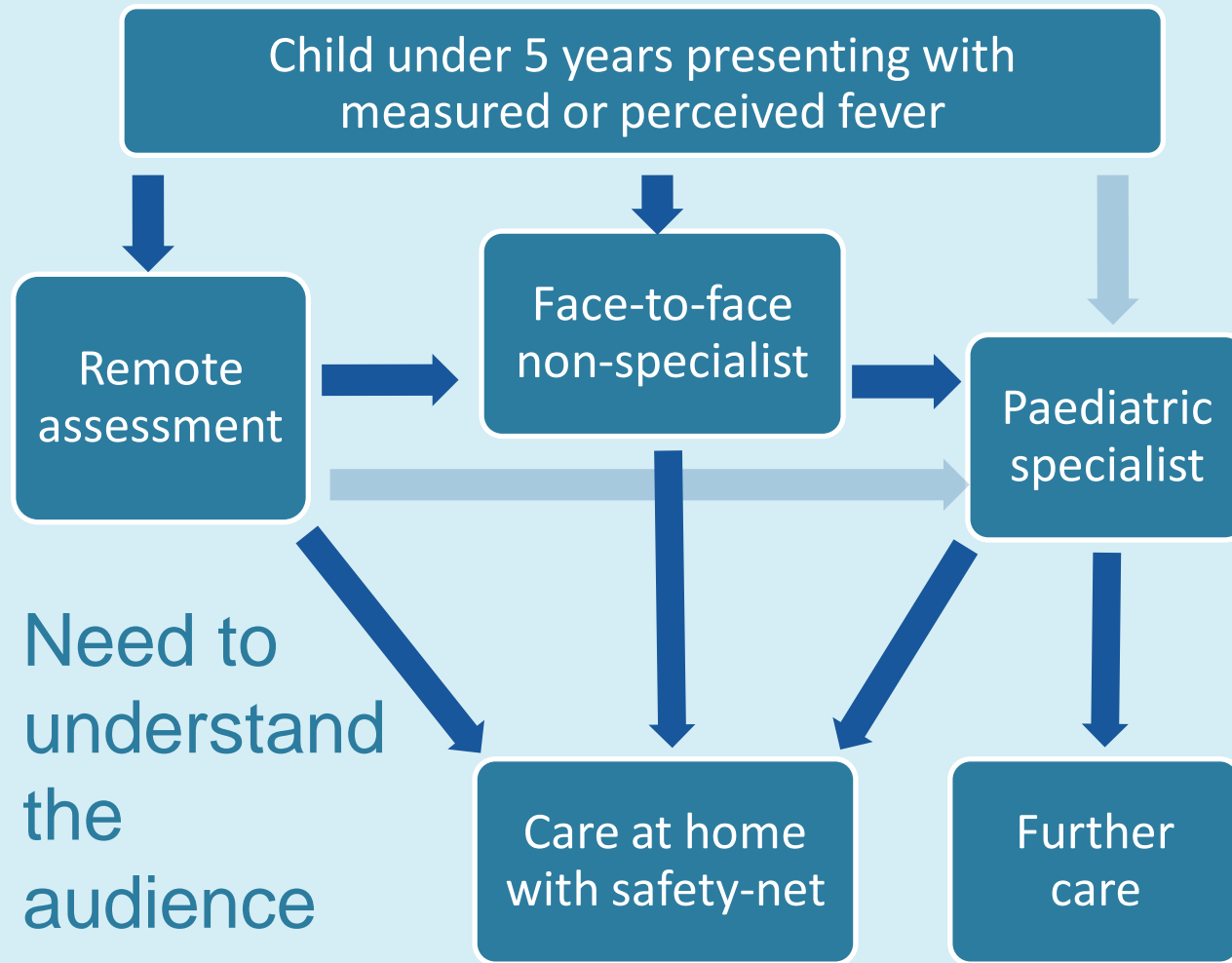
The 'safety net'

1. Verbal or written information on warning symptoms and how further care can be accessed
2. Follow-up appointment at a certain time and place
3. Ensure direct access to a further assessment for their child

Specific recommendations for

- Meningococcal disease
- Meningitis
- Herpes simplex encephalitis
- Pneumonia
- Urinary tract infection
- Septic arthritis
- Kawasaki disease

Typical care pathways - UK



Antipyretics - NICE and AAP

NICE (2012)	AAP (2011)
Consider in children who appear distressed or unwell	No evidence the reduce morbidity or mortality, possible exception those unable to tolerate increased metabolic demands
<i>Do not use with the sole aim of reducing body temperature in children with fever</i>	Primary goal should be to improve the child's comfort
<i>Consider using either paracetamol or ibuprofen in children with fever who appear distressed</i>	
<i>Continue only as long as the child appears distressed</i>	
<i>Consider changing to the other agent if the child's distress is not alleviated</i>	Insufficient evidence to support or refute the routine use of combination treatment
<i>Do not give both agents simultaneously</i>	
<i>Only consider alternating these agents if the distress persists or if it recurs before the next dose is due</i>	No evidence that they decrease recurrence of febrile seizures
Antipyretic agents do not prevent febrile convulsions	No evidence that they decrease recurrence of febrile seizures

Mixed messages?

AAP (2011) Pediatrics 127 580 -587

NICE	AAP
Don't routinely use with the sole aim of reducing body temperature	Primary goal should be to improve the child's comfort

- Will remain a common practice by parents encouraged and supported by pediatricians
- They are responsible for the appropriate counselling about fever and the use of antipyretics

Modes of action of antipyretics

Simmons (2004) Parm Rev 56 387-437

Drug	Mode of action	Nature of interaction
Aspirin	Covalent modifier of COX-1 and COX-2	
Non-selective COX inhibitors Ibuprofen	Bind COX-1 and COX-2 active site	Time-independent Binds COX rapidly but washes out when removed Rapid on/off rate
Non-selective COX inhibitors Indomethacin Diclofenac	Bind COX-1 and COX-2 active site	Time-dependent Binds COX loosely becoming tighter Slow on/off-rate
Selective COX inhibitors Celebrex Vioxx	Weakly bind COX-1 Strongly bind COX-2	Time-dependent Binds COX-2 loosely then tighter Slow off-rate
Analgesic/antipyretic Paracetamol Dipyrrone	Not known, thought to be tissue specific inhibition of COX-1 and COX-2, limited evidence for COX-3	

Ibuprofen toxicity

- Linked to non-selective COX inhibition (COX-1 and COX-2)
- COX-1 constitutive
 - Maintains homeostasis
 - Inhibition of ‘housekeeping’ activities, e.g. mucosal protection and maintaining renal function in dehydration
 - Maybe important in ‘early’ inflammation
- COX-2 induced
 - Controls inflammation

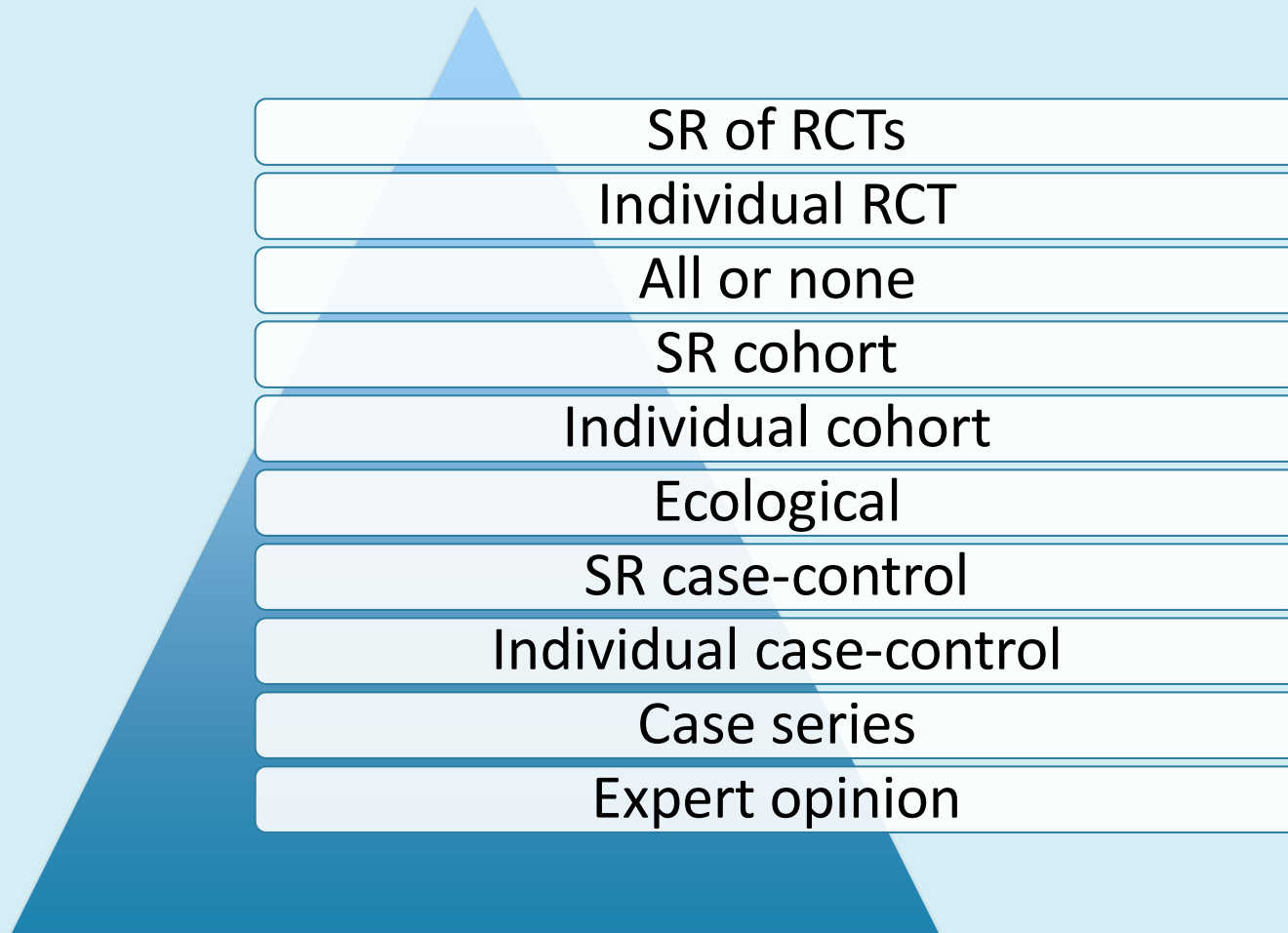
Ibuprofen and paracetamol

Hall *et al.*, (1986) *Ann Emerg Med* 15 1308-1313; Matthews *et al.*, (2007) *Arch Dis Child* 92 524–526; BNF for children (2011) London, BMA/RCPCH/NPPG

	Ibuprofen	Paracetamol
Toxic dose	400mg/kg (half-life 1.5-3 hours)	150mg/kg (75mg/kg if high risk)
Risk factors	Stimulation of the reninangiotensin system Volume depletion Pre-existing chronic renal disease	Carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes Regularly consumes ethanol Likely to be malnourished (glutathione depleted) Febrile illness
Most common symptoms	Nausea, vomiting, epigastric pain, or more rarely diarrhoea	Pallor, nausea, vomiting, anorexia and abdominal pain Liver damage, metabolic acidosis
Management	Supportive Activated charcoal if within 1 hour	Supportive Activated charcoal if within 1 hour N-acetylcysteine up to 24 hours
	Due to inhibition of COX-1, almost immediately reversible	Due to toxic metabolite NAPQI (N-acetyl-parapbenzo-quinoneimine)

Oxford Centre for EBM - levels of evidence

<http://www.cebm.net/index.aspx?o=1025>



Ibuprofen v paracetamol – pain at 2 hours

¹ Perrott *et al.*, (2004); ² Pierce and Voss (2010)

RR 50% reduction 1.14 (0.82 to 1.58) ¹
*SMD 0.28 (0.1 to 0.46) ²

Individual RCT

All or none

SR cohort

Individual cohort

Ecological

SR case-control

Individual case-control

Case series

Expert opinion

*Standardised mean
difference

0.2 small

0.5 medium

0.8 large

Ibuprofen v paracetamol – fever at 4 hours

¹ Purssell (2002); ² Perrott *et al.*, (2004); ³ Pierce and Voss (2010)

Mean difference 0.63°C (0.59 to 0.67) ¹
SMD 0.31 (0.19 to 0.44) ²
SMD 0.26 (0.1 to 0.41) ³

Individual RCT

All or none

SR cohort

Individual cohort

Ecological

SR case-control

Individual case-control

Case series

Expert opinion

Comparing paracetamol and ibuprofen

Purssell (2002) B J Comm Nurs 7 316-320

Time	Mean diff (°C)	95% CI (°C)	n	p
1 hour	0.01	-0.04:0.02	5 studies n = 448	0.22
4 hours	0.63	0.59:0.67	6 studies n = 423	0.00003
6 hours	0.58	0.52:0.64	5 studies n = 267	0.005

Ibuprofen – benefits of combining with paracetamol

Purssell (2011)

SR - little benefit

Individual RCT

All or none

SR cohort

Individual cohort

Ecological

SR case-control

Individual case-control

Case series

Expert opinion

Ibuprofen v paracetamol – adverse events

¹ Perrott *et al.*, (2004); ² Southey *et al.*, (2009); ³ Pierce and Voss (2010)

RR 0.96 (0.68 to 1.36) ¹

RR 1.03 (0.98 to 1.1) ²

RR 0.82 (0.6 to 1.12) ³

Individual RCT

All or none

SR cohort

Individual cohort

Ecological

SR case-control

Individual case-control

Case series

Expert opinion

Ibuprofen - renal toxicity

¹ Kelley *et al.*, (1993); ² Lesko and Mitchell (1997)

General SRs no difference

RCTs no difference ^{1 2}

All or none

SR cohort

Individual cohort

Ecological

SR case-control

Individual case-control

Case reports of reversible renal failure
associated with dehydration

Expert opinion

Ibuprofen - renal toxicity

¹ Kelley *et al.*, (1993); ² Lesko and Mitchell (1997)

Many clinicians take more notice of case reports than SR and large RCT

General SRs no difference

RCTs no difference ^{1 2}

All or none

SR cohort

Individual cohort

Ecological

SR case-control

Individual case-control

Case reports of reversible renal failure associated with dehydration

Expert opinion

Ibuprofen renal toxicity

Case reports of series

- 14 case reports or series; n=51
 - Ibuprofen alone n=21
 - Other NSAID n=7
 - Mixture of NSAID n=12
 - Another mixture/drugs n=11
 - Aminoglycoside and ibuprofen n=4
 - Paracetamol alone n=2
- Most acutely ill; not all dehydrated
- Virtually all reversible; supportive care only
- Aged 5 years or less n=7

Ibuprofen - asthma

¹ Kanabar *et al.*, (2007); ² Lesko *et al.*, (2002)

SR of RCTs – low risk ¹

RR OP treatment 0.56 (0.34 to 0.95) ²

RR hospitalisation 0.63 (0.25 to 1.6)

All or none

SR cohort

Individual cohort

Ecological

SR case-control

Individual case-control

Case series

Expert opinion

Ibuprofen - asthma

¹ Kanabar *et al.*, (2007); ² Lesko *et al.*, (2002)

Ibuprofen
protective
compared to
paracetamol

SR of RCTs – low risk ¹

RR OP treatment 0.56 (0.34 to 0.95) ²

RR hospitalisation 0.63 (0.25 to 1.6)

All or none

SR cohort

Individual cohort

Ecological

SR case-control

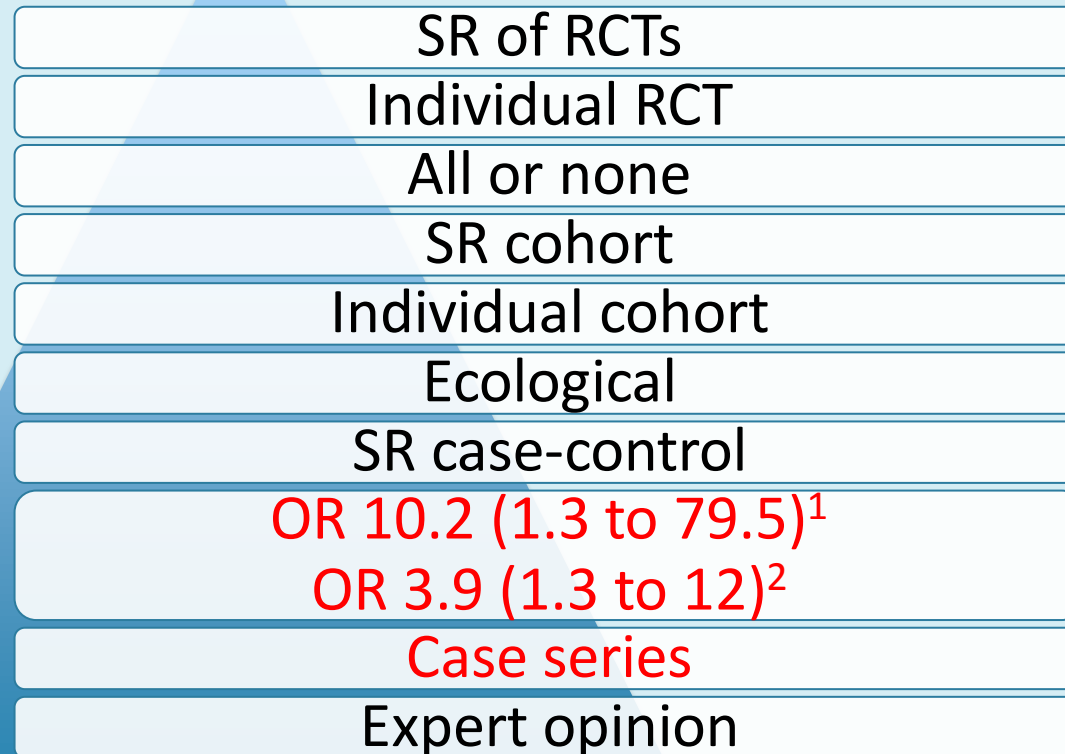
Individual case-control

Case series

Expert opinion

Ibuprofen – invasive soft tissue infections (GAS)

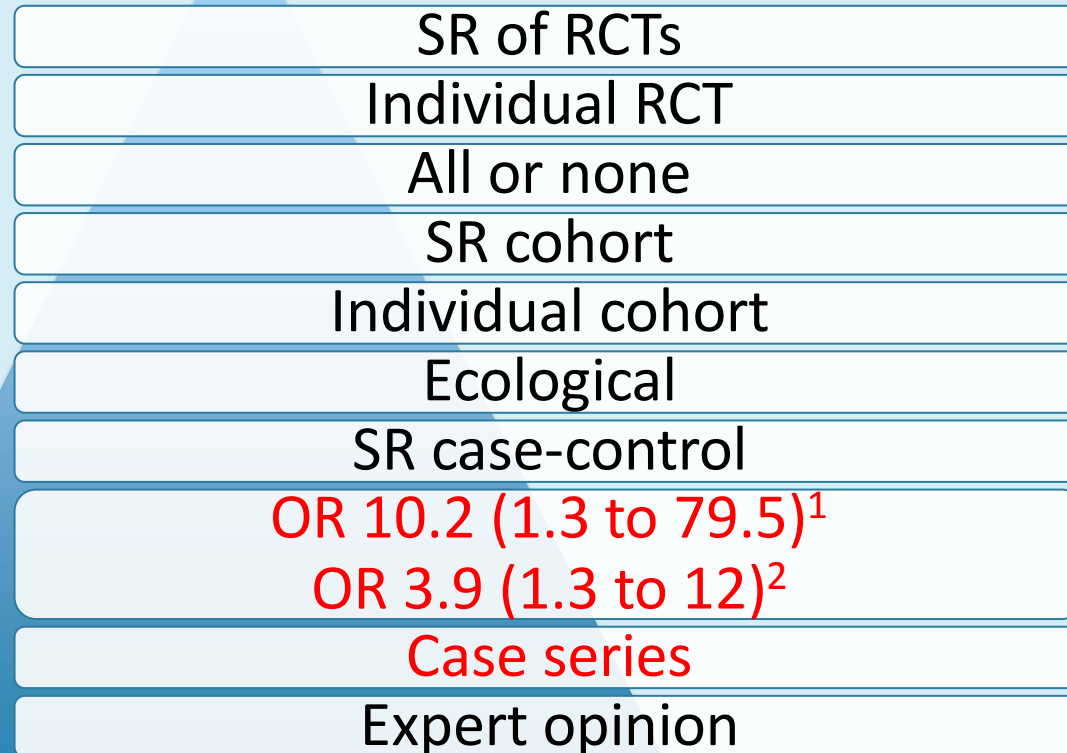
¹ Zerr *et al.*, (1999); ² Lesko *et al.*, (2001)



Ibuprofen – invasive soft tissue infections (GAS)

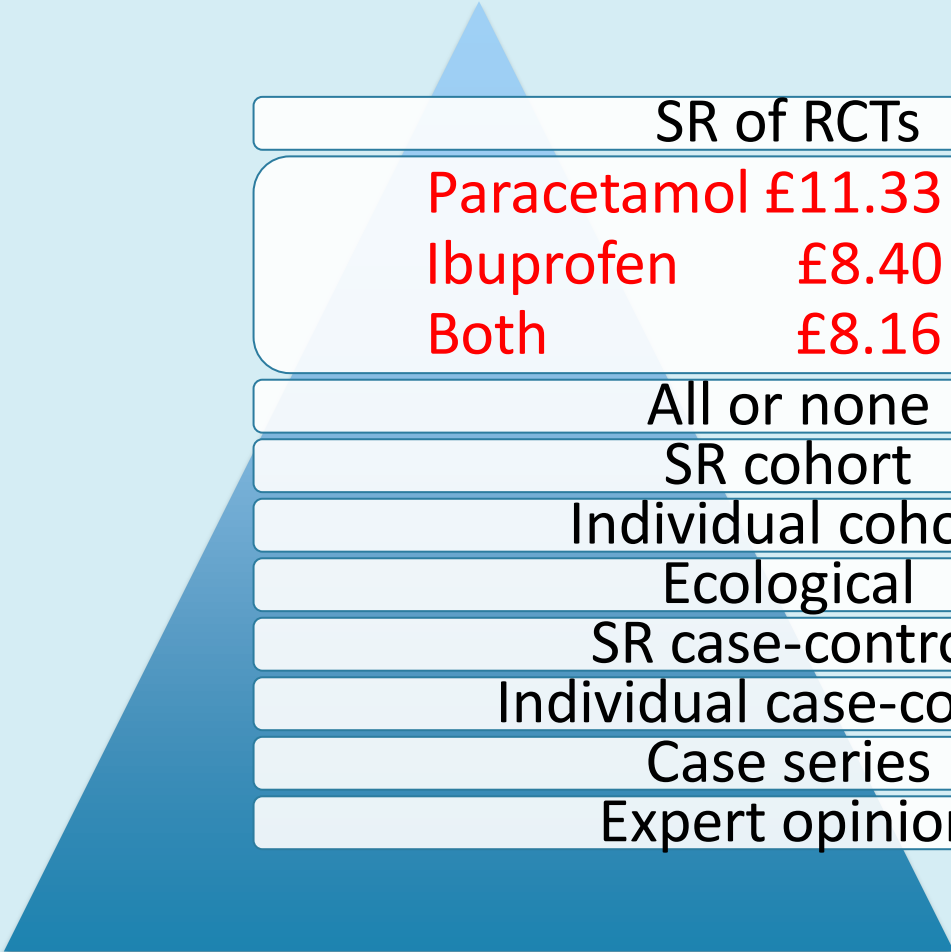
¹ Zerr *et al.*, (1999); ² Lesko *et al.*, (2001)

Ibuprofen often commenced after onset of infection, and no dose relationship



Cost at 48 hours to health services and parents (UK)

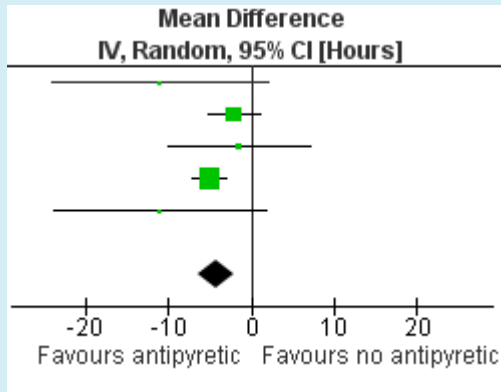
Hollinghurst *et al.*, (2008) *BMJ* 337 1490



SR of RCTs		
Paracetamol	£11.33	£23.86
Ibuprofen	£8.40	£20.60
Both	£8.16	£25.07
All or none		
SR cohort		
Individual cohort		
Ecological		
SR case-control		
Individual case-control		
Case series		
Expert opinion		

Do antipyretics slow recovery? time to fever resolution

Purssell et al (in preparation)



Mean diff -3.94 (-6.3 to -1.6)

Individual RCT

All or none

SR cohort

Individual cohort

Ecological

SR case-control

Individual case-control

Case series

Expert opinion

Antipyretics – effect on immunity

Prymula *et al.*, (2008) Lancet 374 1339-1350

- Prophylactic paracetamol reduced antibody response to primary and booster vaccination in infants
 - Initial antigen specific response enhanced by raised temperature and/or COX-2
 - Does not affect viability of activated B-cells
 - Many vaccination guidelines now reflect this
“it is not recommended that these drugs are used routinely to prevent fever following vaccination”

Advice to parents -general

AAP (2011) Pediatrics 127 580-587

- Fever is not dangerous to healthy children
- Aim is not to normalise temperature but to improve the comfort and well-being
- Minimize fever phobia and emphasize that antipyretic use does not prevent febrile seizures
- Focus on monitoring for signs/symptoms of serious illness
- Other products that contain acetaminophen and ibuprofen should not be given to children

Advice to parents - antipyretics

- Check appropriate usage of drugs (formulation, dose, and dosing interval)
- Clear labelling, simplified dosing, standardise drug concentrations and delivery devices
- Use one formulation
- Check proper handling and storage of drugs
- Antipyretics are safe and effective but minimise the risk of adverse effects and toxicity
- Combining drugs may increase risk of dosing errors and adverse outcomes

GRADE summary

Quality of evidence	Study design
High	Randomised trial
Moderate	
Low	Observational study
Very low	Any other

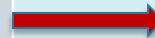
Lower if there are...
Study limitations (bias)
Inconsistency
Indirectedness
Imprecision
Publication bias

Higher if...
Strong evidence of association (e.g. $RR > 2$; < 0.5)
Very strong evidence of association (e.g. $RR > 5$; < 0.2)
Evidence of dose-response gradient
All plausible confounding would reduce a demonstrated effect

Recommendations	Most well informed people...
Do it	would do it
Probably do it	would do it but some would not
Probably don't do it	would not do it but some would
Don't do it	would not do it
No recommendation	Insufficient evidence

Grading evidence

Study design	Quality
Randomised trial	Starts high
Observational study	Starts low
Any other	Starts very low



Look for evidence to bring this down

Study limitations (bias)

Inconsistency

Indirectness

Imprecision

Publication bias



Look for evidence to bring this up

Strong evidence of association
(e.g. $RR > 2$; < 0.5)

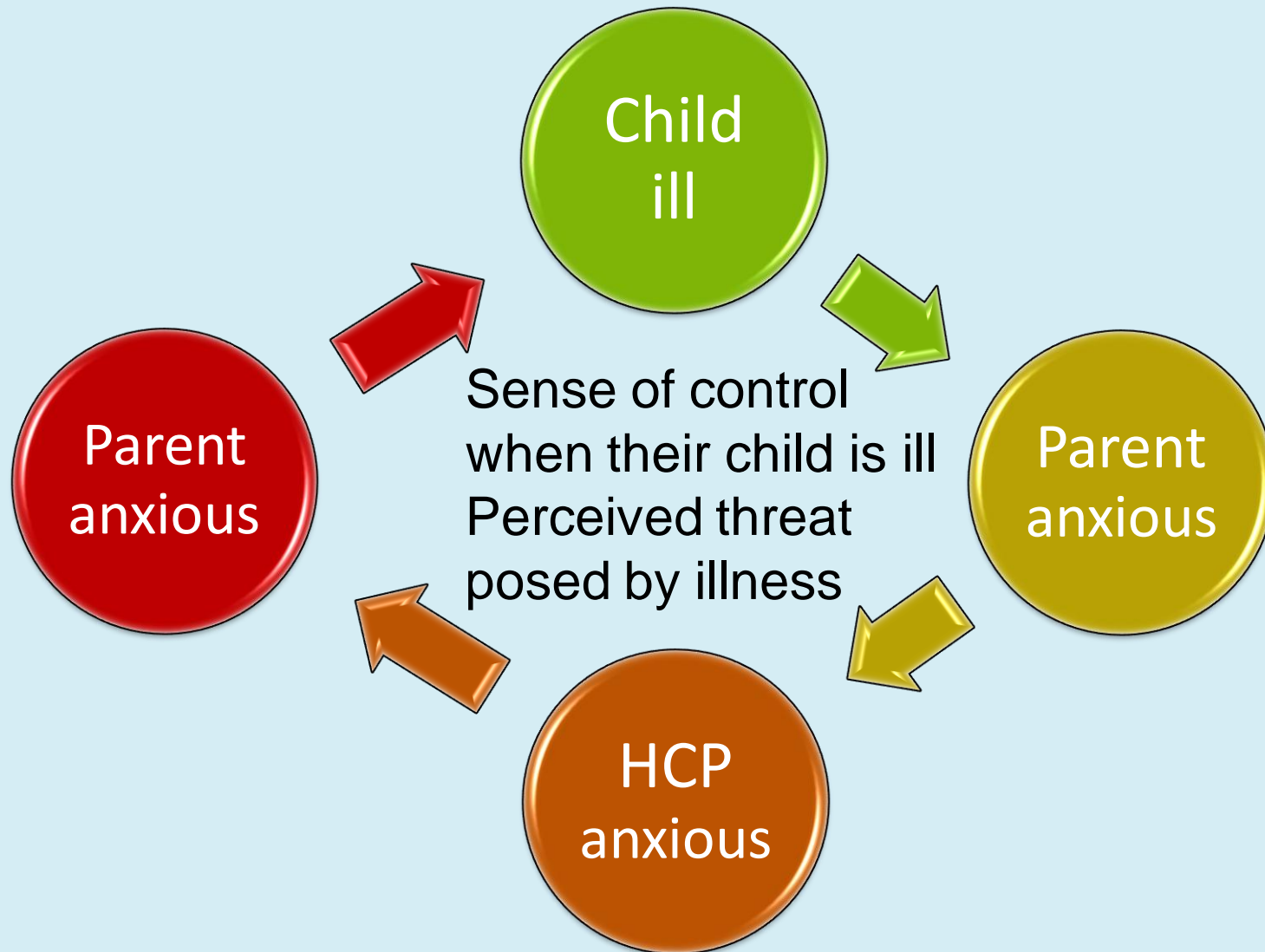
Very strong evidence of association
(e.g. $RR > 5$; < 0.2)

Evidence of dose-response gradient

All plausible confounding would reduce a demonstrated effect

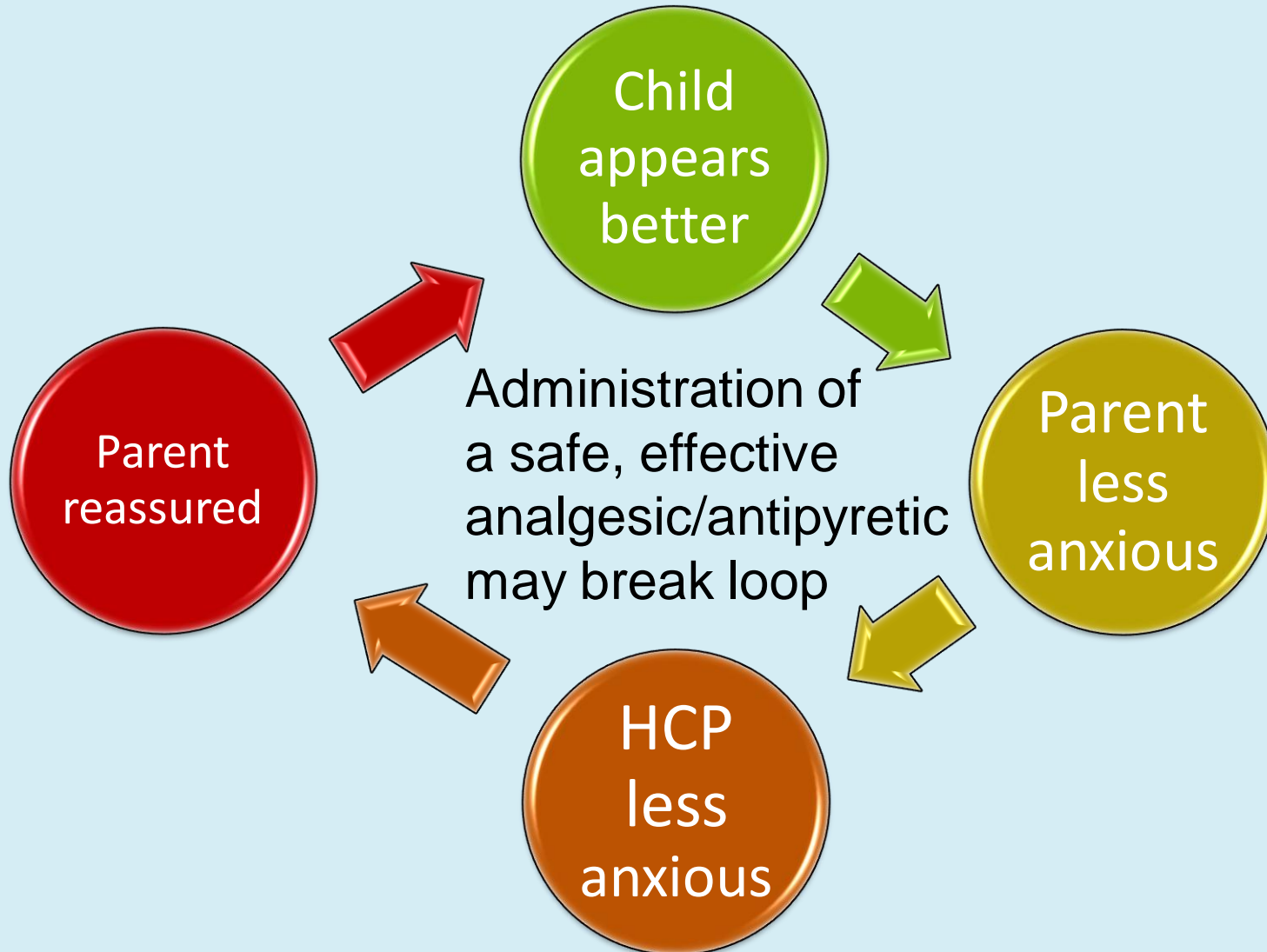
Fever phobia – breaking the loop

Clinch (2007) Child Adolesc Psychiatry Ment Health 1:7
Kai (1996) BMJ 313(7063):983-6



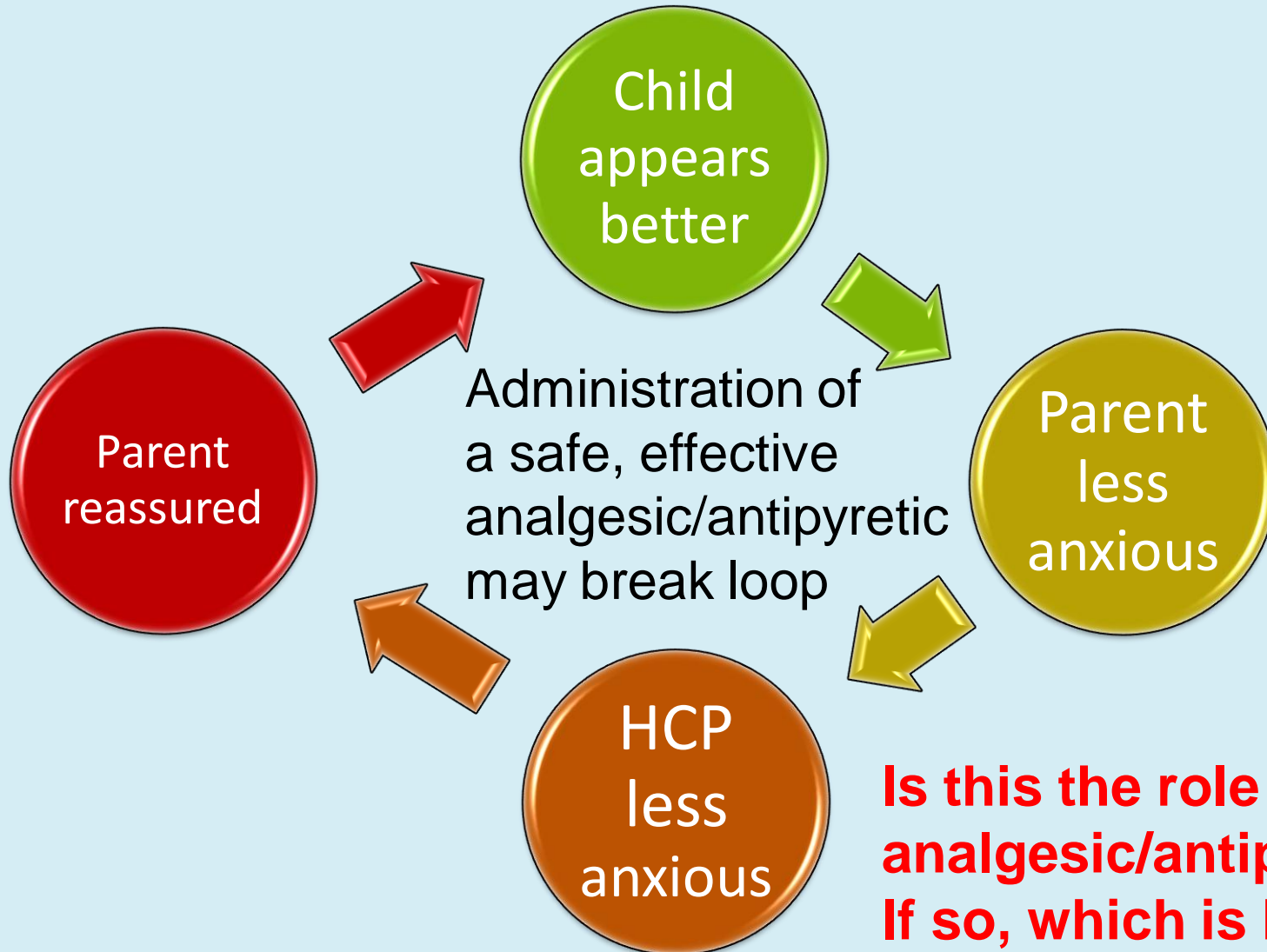
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Fever phobia – breaking the loop

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**Is this the role of the analgesic/antipyretic?
If so, which is best?**

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