NHG Clinical Practice Guidelines

M09 Acute Otitis Media (AOM)
M29 Feverish Illnes in Children
Table of contents

<table>
<thead>
<tr>
<th>Voorwoord</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preface</td>
<td>3</td>
</tr>
<tr>
<td>M09 NHG Clinical Practice Guideline Acute Otitis Media (AOM)</td>
<td>5</td>
</tr>
<tr>
<td>M29 NHG Clinical Practice Guideline Feverish illness in Children</td>
<td>25</td>
</tr>
</tbody>
</table>
Ruim 20 jaar geleden is de eerste standaard van het Nederlands Huisartsen Genootschap (NHG) uitgekomen. Daarmee is het richtlijnenproject van het NHG wereldwijd een van de langst lopende en meest succesvolle programma’s voor evidence based richtlijnenontwikkeling. In de loop van de jaren is de kwaliteit van de standaarden toegenomen. Belangrijke mijlpalen waren de keus voor een scheiding tussen aanbevelingen en onderbouwing met een notenapparaat begin jaren negentig en voor de toepassing van systematische literatuursearches op basis van uitgangsvragen rond de eeuwwisseling. Door de levensduur van het richtlijnenproject en de vlotte introductie van standaarden als onderwijsmateriaal in de (huis)artsenopleiding, is inmiddels een groot deel van de zittende huisartsenpopulatie in Nederland opgegroeid met de standaarden. De meest huisartsen in Nederland gebruiken de standaarden in de dagelijkse praktijk als leidraad. Over 10 jaar zal het aantal huisartsen in Nederland dat niet met de standaarden is opgeleid, op de vingers van een hand zijn te tellen.

Vanwege het grote belang van de NHG-Standaarden voor de huisartsen- en de kwaliteit daarvan heeft het NHG gemeend de starten met het vertalen van standaarden in het Engels. Daarmee komen de in Nederland geldende evidence based richtlijnen ter beschikking van doelgroepen buiten Nederland. Als pilot is begonnen met het vertalen van een tweetal standaarden:

M09 – Otitis Media Acuta en M29 – Kinderen met Koorts.

Afhankelijk van de ontvangst zal worden besloten uit het totale aanbod van circa 90 NHG-Standaarden meer standaarden te vertalen.

Voorwoord
About 20 years ago, the first clinical guideline of the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap, NHG) was published. This makes the NHG guidelines project one of the longest running and most successful programmes for the development of evidence-based guidelines in the world. Over the years the quality of the guidelines has improved. Important milestones were the decisions to distinguish between recommendations and support with footnotes in the early 1990s and to apply systematic literature searches on the basis of fundamental questions at the turn of the millennium. Given the long duration of the guidelines project and the rapid introduction of clinical guidelines as educational material in medical schools, a large proportion of the current general practitioner population in the Netherlands has grown up with these clinical guidelines. Most general practitioners in the Netherlands use the clinical guidelines in their daily practice as reference material. In 10 years’ time the number of general practitioners in the Netherlands who have not been trained with the clinical guidelines will have shrunk to almost none. Given the great importance of the NHG clinical guidelines for primary care medicine and its quality, the NHG intends to start translating them into English. This will make evidence-based guidelines applicable in the Netherlands available for target groups outside the Netherlands. As a pilot, the translation of two guidelines has been undertaken, namely: M09 Acute Otitis Media and M29 Feverish Illness in Children. Depending on their reception a decision will be made to translate more of the total of 90 NHG clinical guidelines.
Key messages

• In general the natural course of Acute otitis media (AOM) is mild and the condition has a favourable outcome. The intervention of GPs can be limited to providing information and prescription of pain relief.
• Antibiotic treatment is indicated in cases of severe or increasing illness or in the case of risk factors for complications.
• Consider antibiotic treatment in those children who show no improvement after three days.
• Consider antibiotic treatment in children with an episode of acute otitis media with otorrhoea at initial presentation and in children below the age of two with bilateral acute otitis media.

Introduction

The NHG Practice Guideline on Acute otitis media provides guidelines for the diagnosis and treatment of acute otitis media in children. Acute otitis media is understood to be an inflammation of the middle ear with a maximum duration of three weeks. Acute otitis media is generally associated with earache, symptoms of general illness, fever and sometimes purulent discharge (otorrhoea), and is characterised by a bulging tympanic membrane with change in colour (red or opaque). The characteristics of an acute infection distinguish acute otitis media from otitis media with effusion (OME); the latter condition is discussed in the NHG Practice Guideline OME.
Generally, acute otitis media is a condition that only causes symptoms for a few days and that rarely leads to complications. In most children only symptomatic treatment is required. The prescription of antibiotics is recommended for only few indications; in a number of other indications prescription can be considered. GPs are able to treat almost all cases of acute otitis media themselves. Referral to an ENT specialist is only indicated in the case of persistent symptoms despite adequate treatment.

**Background**

**Epidemiology**

AOM is a common condition: an estimated one-half to three-quarters of the general population experiences this condition at least once in their life, generally in early childhood. The incidence of AOM in GP surgeries is approximately 20 per 1,000 patients per year. More than half of these cases are diagnosed in children below the age of five. The incidence in this age group is approximately 175 per 1,000 patients per year. AOM becomes a rare condition after puberty. AOM can recur: 10 to 20% of all children experience at least three episodes of AOM in the first year of life. The probability of recurrent AOM is greater if the first episode of the condition occurs in the first year of life.

The condition generally has a favourable natural course: in more than 80% of children, the most severe symptoms resolve within two to three days. Children below the age of two with bilateral AOM have a greater chance of persistent pain and fever. Perforation of the eardrum occurs in approximately 4 to 8% of cases of AOM, causing discharge. Severe complications, including mastoiditis and meningitis, are very rare. Approximately 50% of children develop OME four to six weeks after an episode of AOM and approximately 25% still have this condition after three months.

Risk factors for complications are young age (below six months), anatomical ear, nose and throat abnormalities, such as those observed in Down's syndrome and cleft palate and a history of ear surgery or compromised immune system.

**Etiology**

Pneumococci are the most common pathogens causing AOM, causing the condition in 30 to 40% of cases. Haemophilus influenzae and Moraxella catarrhalis are also often cultured. Haemolytic streptococci are found in a very small percentage of patients only. No bacterial pathogen is found in approximately 40% of middle ear cultures. Episodes of AOM often follow upper respiratory tract infections. The viruses responsible for these infections can cause AOM themselves, and it is postulated that bacterial infections often develop following 'viral preparation' of the mucous membranes.
Diagnosis

Various signs and symptoms can be a reason to consider a diagnosis of acute otitis media. Earache and otorrhoea are the primary symptoms, but the GP should also consider this condition in infants and toddlers presenting with general symptoms, such as fever, irritability, night-time restlessness or gastrointestinal symptoms (abdominal pain, diarrhoea, vomiting, loss of appetite), even if there is no (indication for) earache or otorrhoea.

History

The GP should query the following:
- earache, otorrhoea, hearing impairment; unilateral or bilateral occurrence of these symptoms;
- general symptoms: fever, irritability, night-time restlessness, abdominal pain, vomiting, diarrhoea, refusal to eat or drink, drowsiness;
- symptoms of an upper respiratory tract infection (coughing, nasal discharge, sore throat);
- severity, duration and course of the symptoms;
- previous episodes of ear infection in the past twelve months;
- presence of grommets.

The GP checks whether there are any risk factors for complications: infants below the age of six months, anatomical ear, nose and throat abnormalities, such as those observed in Down's syndrome or cleft palate, a history of ear surgery or a compromised immune system.

Requests for care for ear symptoms often reach GPs by telephone. Although physical examination is required to confirm the diagnosis, a tentative diagnosis of AOM is often possible based on the patient history.

Certainty about the diagnosis - i.e. physical examination - is required if one or more of the following situations apply:
- severe or increasing illness;
- risk factors for complications;
- in all other cases in which the GP considers treatment with an antibacterial agent.

Telephone advice can be considered adequate in all other cases. The GP can then limit the intervention to a tentative diagnosis of AOM based on the patient history, provided that this occurs in concordance with the carers of the child.

Physical examination

The GP inspects both eardrums, comparing left and right; cotton buds, cerumen loops or a suction device to remove cerumen or debris are used if necessary. Irrigation is not recommended as this can be very painful during an
episode of AOM and because patients may have a hidden perforation of the eardrum. During otoscopy, the GP should observe:
− aspect of the eardrum: colour, vascular injection, opacity;
− position of the eardrum: normal, bulging or retracted;
− otorrhoea, perforation of the eardrum, presence of grommets.

The GP should be alert to symptoms indicating complicated disease, such as protrusion of the ear, tenderness in the mastoid area, neck stiffness or reduced consciousness in children appearing unwell or with risk factors for complications.

Additional examinations

No additional examinations are required to confirm AOM. [10]

Evaluation

The diagnosis of AOM is based on earache and/or general symptoms of illness, and one or more of the following signs and symptoms:
− a red, bulging or opaque eardrum;
− a clear difference in redness between the left and right eardrum;
− otorrhoea through a perforation of the eardrum or a grommet.

Vascular injection of both eardrums is a symptom that has little specificity for AOM as this can also occur during a common cold or can be caused by crying.

Management

Information

The GP explains the natural course and the - generally favourable - outcome of AOM. In more than 80% of cases in children aged two or more, the worst symptoms pass within two to three days and further follow-up is not required. The symptoms may last longer in younger children: half of the children below the age of two continue to experience symptoms of earache and/or crying for longer than eight days. [14] Generally speaking, antibacterial agents do not have a significant effect on the duration or severity of symptoms. However, they do work in the case of bilateral otitis media in children in this age group: the probability of being free of pain or fever within two days increases from approximately 50% to 75% in this age group. Sometimes, AOM causes the ear to discharge either through a perforation of the eardrum or through a grommet. This discharge generally clears up spontaneously within a week. However, if otorrhoea occurs soon after the onset of the middle ear infection, antibacterial agents can reduce the duration of pain and/or fever: in this instance, the probability increases from approximately 40% to 75%. Patients experiencing otorrhoea are recommended to avoid
swimming with their head underwater; this recommendation also applies to patients with a perforation without discharge, as irritation of the labyrinth can cause dizziness to occur. However, showering is allowed, as the probability of water entering the middle ear while showering is minimal.\[11\] It is not necessary to advise children with frequently recurring AOM to stop swimming altogether.\[11\]

Conductive hearing loss or hearing loss caused by fluid in the middle ear can occur during or several weeks after AOM. In most cases the hearing loss resolves by itself in the course of a few weeks to a few months.

The GP instructs the child’s carers to come for a follow-up appointment if the child’s condition deteriorates or if the child fails to improve.

If needed, the GP can support this information by providing the patient instruction letters about this condition (www.nhg.org, Patient information section).

Treatment

Symptomatic treatment

The GP starts symptomatic treatment in all cases. The treatment comprises adequate pain relief with paracetamol as the drug of choice. Orally, paracetamol is administered at a dosage of 10 mg/kg body weight four to six times daily. Suppositories are administered at a dosage of 20 mg/kg body weight two to three times daily (see table 1).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Paracetamol dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>oral dosage</td>
</tr>
<tr>
<td>children aged 3-12 months</td>
<td>2.5 ml syrup (24 mg/ml) 4-6 times daily</td>
</tr>
<tr>
<td>children aged 1-2 years</td>
<td>5 ml syrup (24 mg/ml) 4-6 times daily</td>
</tr>
<tr>
<td>children aged 2-4 years</td>
<td>6-7 ml syrup (24 mg/ml) or 1 tablet 120 mg 4-6 times daily</td>
</tr>
<tr>
<td>children aged 4-6 years</td>
<td>8 ml syrup (24 mg/ml) or 1.5 tablets 120 mg 4-6 times daily</td>
</tr>
<tr>
<td>children aged 6-9 years</td>
<td>10 ml syrup (24 mg/ml) or 0.5 tablet 500 mg 4-6 times daily</td>
</tr>
<tr>
<td>children aged 9-12 years</td>
<td>0.75 tablet (500 mg) 4-6 times daily</td>
</tr>
<tr>
<td>children aged &gt;12 years</td>
<td>1 tablet (500 mg) 4-6 times daily</td>
</tr>
</tbody>
</table>
The child’s parents or caregivers should be advised to administer the paracetamol at fixed times. Oral administration more rapidly leads to an analgesic effect (from approximately 30 minutes after administration; maximum plasma level 30 to 90 minutes after administration) than rectal administration does, but the effect resulting from rectal administration is sustained for longer. Rectal administration is often chosen in children for practical reasons (see the Dutch College Pharmacotherapeutic Guideline on Pain Relief).

The effect of nose drops or sprays (xylometazoline or physiological saline solution) on resolving AOM has not been demonstrated. These can be prescribed if there are symptoms of a blocked nose. Topical treatment (e.g. lidocaine eardrops) is not recommended in the treatment of AOM, as it can hamper assessment of the eardrum later on. There are also insufficient data to support the effectiveness.

**Antibacterial treatment**

Antibacterial agents are not indicated in the majority of children with AOM. A wait-and-see approach is indicated in children who are not severely ill (aged over 6 months), in children with unilateral AOM and in children without otorrhoea. In contrast, antibacterial treatment is recommended:
- in severely ill children or when children become more seriously ill;
- in the case of risk factors for complications.

In addition, the GP, in consultation with the child’s parents or caregivers, considers starting treatment with oral antibacterial treatment if relief of fever and pain is important at an earlier stage:
- in children below the age of two years with bilateral AOM;
- in children with otorrhoea at initial presentation.

This also applies to children that have not shown clinical improvement within three days.

In all cases, amoxicillin is used as first-line treatment for a duration of one week at a daily dosage of 30 mg/kg body weight (see table 2). Azithromycin or cotrimoxazole is prescribed in children allergic to penicillin: azithromycin for a duration of three days at a daily dosage of 10 mg/kg body weight, and cotrimoxazole for a duration of five to seven days at a daily dosage of 36 mg/kg body weight (see table 2).

When an antibacterial agent is prescribed, the GP advises the child’s caregivers to come for a follow-up appointment if the symptoms have not improved within 48 hours of starting the medicine.

**Follow-up**

Follow-up in children with AOM is generally not necessary, except in the case of otorrhoea.

If a wait-and-see approach was initially taken for a case of otorrhoea, the GP prescribes oral antibiotics if the otorrhoea persists for more than one
<table>
<thead>
<tr>
<th>Table 2</th>
<th>Paediatric dosages of the recommended antibiotic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>age</strong></td>
<td><strong>weight</strong></td>
</tr>
<tr>
<td>0-1 years</td>
<td>&lt; 10 kg</td>
</tr>
<tr>
<td>1-2 years</td>
<td>10-12 kg</td>
</tr>
<tr>
<td>2-3 years</td>
<td>12-15 kg</td>
</tr>
<tr>
<td>3-5 years</td>
<td>15-20 kg</td>
</tr>
<tr>
<td>5-7 years</td>
<td>20-25 kg</td>
</tr>
<tr>
<td>7-9 years</td>
<td>25-31 kg</td>
</tr>
<tr>
<td>9-12 years</td>
<td>31-42 kg</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>100 mg/ml, 20 ml</td>
</tr>
<tr>
<td></td>
<td>25 mg/ml, 100 ml</td>
</tr>
<tr>
<td></td>
<td>50 mg/ml, 100 ml</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>40 mg/ml, 15 ml</td>
</tr>
<tr>
<td></td>
<td>40 mg/ml, 22.5 ml</td>
</tr>
<tr>
<td></td>
<td>40 mg/ml, 30 ml</td>
</tr>
<tr>
<td></td>
<td>250 mg tablet</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>48 mg/ml, 100 ml</td>
</tr>
<tr>
<td></td>
<td>480 mg tablet</td>
</tr>
</tbody>
</table>
week. When the otorrhoea has resolved - spontaneously or after the use of antibacterial agents - a follow-up visit is recommended after one month to assess whether the perforation of the eardrum has closed.

Consultation or referral

Refer any child with clinical signs and symptoms of mastoiditis or meningitis to an ENT specialist or a paediatrician respectively.

Consult an ENT specialist or refer the patient to this specialist in the following cases:

- failure to improve within 48 hours of starting antibacterial treatment;
- persistence of otorrhoea following a course of an antibacterial agent;
- persistent perforation of the eardrum one month after the onset of otorrhoea;
- children with frequently recurring AOM (three or more episodes per six months or four episodes per year).

Establishment

A working group started the revision of the NHG Standard on Acute otitis media in March 2005. The working group was composed of Dr R.A.M.J. Damoiseaux, Dr F.A.M. van Balen and W.A.M. Leenheer, all General Practitioners. In May 2006, the concept text was submitted for comments to a number of reviewers. The working group received comments from the following reviewers: Dr C.L.M. Appelman, Dr E.H. van de Lisdonk and Dr H. van Weert, all General Practitioners, Dr J.Q.P.J. Claessen and Dr A.G.M. Schilder on behalf of the Dutch Association of Otorhinolaryngology and Head & Neck Surgery, A.C. van Loenen, Hospital Pharmacist/Clinical Pharmacologist and Chief Editor of the Pharmacotherapeutic Compass, on behalf of the Health Care Insurance Board and M.J. Swart-Zuijderduijn, Pharmacist, on behalf of the Scientific Institute of Dutch Pharmacists. Mention of the reviewers’ names in this standard does not necessarily mean that the reviewers endorse all details of the standard.

The NHG Authorisation Committee commented on and authorised the standard in July 2006. Dr B.G.M. Kolnaar, General Practitioner and Scientific Staff Member of the Department of Standard Development and Science of the NHG, provided the working group and the editors of this standard with support and guidance.
Notes

Note 1 Acute otitis media in adults  As was the case with previous editions of this standard, insufficient usable research on acute otitis media in adults was found for this revision. Others encountered the same lack of data when generating a literature overview [Anonymous 2003]. Data collected from an international registration network of GP surgeries in 1986 showed that the symptoms and signs and the treatment administered in adults was essentially the same as that in children [Froom 1990, Culpepper 1993]. However, the working group is of the opinion that the lack of scientific data about the course, risk factors, diagnosis and treatment effects in adult cases of acute otitis media mean that the guidelines in children cannot be applied in adults per se.

Note 2 Diagnostic criteria  There is international agreement on the definition of acute otitis media [Gates 2002]. However, there is no agreement on the clinical criteria that should be met to make this diagnosis. An important difference between international guidelines is the criterion of ‘effusion in the middle ear’. Doctors in the United States especially take the view that the presence of fluid in the middle ear should be demonstrated in order to diagnose the condition with sufficient confidence. This is the case when patients present with otorrhoea (following tympanocentesis or otherwise), or decreased tympanic membrane mobility, preferably demonstrated by pneumatic otoscopy or - as a second choice - by tympanometry or acoustic reflectometry [Marcy 2001]. However, the latter examinations are hardly ever carried out in GP surgeries in the Netherlands or in other Western European countries. The criteria described in this standard are in line with the opinions of the Dutch Association of Otorhinolaryngology and Head & Neck Surgery and the procedures followed by GPs [Grote 1988]. According to the ICP-2, one of the following five criteria should be met: recent perforation of the eardrum with pus-like discharge, inflamed and bulging eardrum, one eardrum redder than the other, red eardrum with earache, blister formation on the eardrum [Gebel 2000].

Note 3 Data on the incidence of acute otitis media  Based on their overview of studies in first-line populations, Casselbrant and Mandel concluded that 19 to 62% of all children have at least one episode of acute otitis media before the second year of life, and that 50 to 84% have at least one episode before the fourth year of life. Most studies show the incidence to peak in the second half of the first year of life and the incidence to decrease afterwards [Casselbrant 2003].

The incidence rate of acute otitis media in GP surgeries is particularly high in the youngest children: the incidence in children decreases from 193 per 1,000 patients per year in children below the age of one and 139 in children aged one to four, to 52 in children aged five to nine and 14 in children aged ten to fourteen. The condition is far less prevalent in later life: from 7 per 1,000 patients per year in young adults to 2 in old age [Van der Linden 2004].
According to the literature overview mentioned above, 10 to 20% of all children have at least three episodes of acute otitis media in the first year of life [Casselbrant 2003]. An American cohort study showed that 39% of children aged seven had had at least six episodes of acute otitis media [Teele 1989]. Appelman found that 5.4% of all children in a Dutch first-line population of 684 children (from birth to age thirteen) in whom a GP had diagnosed acute otitis media were ‘otitis prone’, meaning to say that they had four or more episodes of acute otitis media in the subsequent year [Appelman 1992]. The probability of the condition recurring is greater if the first episode of acute otitis media occurred in the first year of life [Teele 1989, Kvaerner 1997].

It may be expected that the incidence of acute otitis media will decrease in the Netherlands after the introduction of pneumococcal vaccination in infants on 1 April 2006. However, the extent of the decrease in the long term cannot be predicted (also see note 23).

Note 4 The course of acute otitis media Adequate research of the early natural course of acute otitis media (including the first days) in an open population or in a GP practice was not found. The course in placebo groups in randomised intervention studies may provide some information. A meta-analysis of data from eleven placebo groups shows that the symptoms of 61% (95% CI 50-72%) of children subside within one day of the diagnosis, and that the symptoms of 80% (95% CI, 49-92%) of children subside within two to three days [Rosenfeld 2003]. Complete clinical recovery occurs after seven to fourteen days in 70% of children (95% CI, 49-92%); any residual otitis media with effusion has not been included in the analysis. The latter condition is still present after four to six weeks in approximately 50% of children and after three months in approximately 25% of children. Complications (mastoiditis, meningitis) are rare. These results are in line with those of other systematic overviews of intervention studies in which the course in the placebo groups was also summarised [Marcy, 2001, Glasziou 2003]. However, it should be noted that severely ill children are very poorly represented in intervention studies and therefore in these systematic overviews, so that these results cannot simply be reapplied to this group [Bain 2001]. Recovery after acute otitis media seems to take longer in very young children: Dutch research in children between the ages of six months and two years shows that half still have symptoms of earache or crying after eight days [Damoiseaux 2000b]. A meta-analysis of individual data of 824 children in the placebo groups of six randomised studies shows that children below the age of two with bilateral acute otitis media have double the risk of a longer disease course (pain and/or fever persisting beyond three days; absolute risk 55%) than children aged two or over with unilateral acute otitis media (absolute risk 25%) [Rovers, 2006]. With regards to the required clinical policy, the working group finds this sufficient reason to regard this age group as a separate category in addition to infants from birth to six months and children over the age of two.

Note 5 The incidence and course of otorrhoea In the course of one year, GPs diagnosed 2,254 cases of acute otitis media in a Finnish population of 14,200
children below the age of 16. Otorrhoea through a spontaneous perforation of the eardrum occurred in 4.6% of these cases [Pukander 1983].

A Dutch study in children below the age of two with acute otitis media (n=204) showed that 8% of patients developed a perforation of the eardrum with otorrhoea within ten days of the visit to the GP. The median duration of the otorrhoea was one day only. The median duration of the otorrhoea was four days in the 36 children that already had a perforation of the eardrum with otorrhoea caused by acute otitis media at initial presentation [Damoiseaux 2000b].

Note 6 The incidence of mastoiditis The incidence rate of mastoiditis has decreased drastically over the last decades due to both the use of antibiotics and the now milder clinical picture of the condition [Van Buchem 1989]. Based on the diagnoses in children below the age of 15 at the time of the discharge from hospital, Van Zuijlen et al assumed an incidence of mastoiditis of 3.8 per 100,000 patient years [Van Zuijlen 2001].

Note 7 Risk groups for complications It is assumed that children with acute otitis media that are either below the age of six months, have anatomical ear, nose and throat abnormalities, such as those observed in Down’s syndrome and cleft palate, or have a history of ear surgery or a compromised immune system have an increased risk of complications [Grote 1988]. However, adequate research into this has not been found.

Note 8 Etiology In all studies, the micro-organisms most frequently found in ear drainage cultures in cases of acute otitis media are pneumococci (30 to 40%). In addition, Haemophilus influenzae (20 to 30%) and Moraxella catarrhalis (10 to 20%) are often found. However, 40% of all middle ear cultures are found to be negative [Bluestone 2001]. All respiratory viruses can cause otitis media [Heikkinen 1999]. There are also indications that the immune response triggered by viruses enhances the sensitivity of the middle ear to bacterial invasion [Ruuskanen 1994]. A study in children below the age of 16 (n=2,254) with acute otitis media showed that 60% of patients had an upper respiratory tract infection in the two weeks before [Pukander 1983]. It is hypothesised that bacterial or viral infections cause abnormal Eustachian tube drainage or abnormal ciliary activity. At a young age, the Eustachian tube is shorter and wider and has a more horizontal course than in later life and it is therefore postulated that it provides bacteria with easier passage from the nasopharynx to the middle ear. Alongside adenoid hypertrophy, early age, male sex, winter season, the use of dummies and childcare attendance are risk factors for the development of acute otitis media. Passive smoking is a risk factor for the development of upper respiratory tract infections in general and therefore also for the occurrence of acute otitis media [Casselbrant 2003, Uhari 1996].

Note 9 The diagnostic value of the history and physical examination There is insufficient data available about the diagnostic value of the history and physical examination for acute otitis media. Research into this is hampered by the
lack of a valid and usable gold standard. Pus drainage following tympanocentesis is considered as such, but tympanocentesis in patients in whom there is insufficient certainty about the presence of acute otitis media - necessary for valid diagnostic research - is not ethically acceptable. In their systematic overview, Rothman et al found only five studies usable to some extent (four about historical findings, one about otoscopic findings) [Rothman 2003]. They drew the following conclusions: from the historical findings researched (earache, children pulling or rubbing the ear, fever, coughing, nasal discharge, excessive crying, loss of appetite, vomiting, throat ache, headache, disturbed sleep and carers’ suspicion of acute otitis media), earache seemed to have the highest diagnostic value (positive LR 3.0 to 7.3; however, negative LR only 0.6 to 4.0). In addition, children pulling the ear and the carers’ suspicion of acute otitis media also seemed to have some value (positive LR 3.3 and 3.4 respectively; however, negative LR 0.7 and 0.4 respectively). From the otoscopic findings, a bulging or opaque eardrum make acute otitis media very likely (positive LR 51 and 34 respectively), but clear redness also contributes somewhat to the diagnosis (positive LR 8.4).

Otoscopy only has a diagnostic value if the findings from this examination are sufficiently reliable. Appelman et al performed research into this by comparing the otoscopic findings of the eardrums of children with (a clinical suspicion of) acute otitis media made by GPs with those made by ENT specialists. The findings were similar in children aged two and over, but moderate in younger children [Appelman 1993].

Note 10 Additional examinations Pneumatic otoscopy and tympanometry aim to demonstrate middle ear effusion. Fluid is also present in the middle ear in most cases of acute otitis media. Both examinations are valuable if it is important to demonstrate the presence of fluid. For more details, please refer to the NHG Standard on Otitis Media with Effusion.

Palmu et al conducted a study in a cohort of 329 children to determine the value of tympanometry to predict the course of acute otitis media [Palmu 2002]. It was not possible to use the tympanogram curves to predict the course.

The working group therefore does not consider it necessary to perform additional examinations to diagnose acute otitis media.

Note 11 Swimming Swimming with the head underwater can lead to irritation of the labyrinth in patients with a perforation of the eardrum. Water is thought to enter the middle ear through the perforation. The recommendation in children with a perforation of the eardrum is different to the recommendation in children with grommets, as the probability of water passing through the narrow lumen of the grommet into the middle ear is only small. Please refer to the NHG Standard on Otitis Media with Effusion for recommendations concerning grommets.

Usable research about the once postulated relationship between regular swimming and recurrent acute otitis media was not found. Based on consen-
sus, the working group therefore recommends GPs not to advise children with recurrent otitis media to stop swimming altogether.

**Note 12 Decongestants** The postulated mechanism of decongestant nose drops is a reduction of the swelling of the nasopharyngeal mucous membrane, causing improved drainage of the middle ear. A Cochrane review about this topic showed hardly any effect of decongestants (nor of antihistamines) [Flynn 2004]. However, most of the included studies used oral medication, in contrast to the nose drops commonly used in the Netherlands. Some patients positively appreciate the improved (temporary or otherwise) nasal patency. As temporary use is not found to lead to disadvantages, the use of decongestants is included in the standard as optional.

**Note 13 Antibiotic agents in the treatment of severe illness** Severely ill children are often excluded from studies into the effect of antibiotics on acute otitis media [Bain 2001, Damoiseaux 2000a, Le Saux 2005]. As a result, there is neither proof that these medicines have an effect in this group of children, nor proof that they do not.

Based on consensus, the working group recommends that GPs prescribe antibiotics to children who are severely ill when they visit the GP or who become more ill during the course, despite the fact that there is neither proof that these medicines have an effect, nor proof that they do not.

**Note 14 Antibiotic agents in risk groups for complications** The working group subscribes to the recommendations from the Dutch Association of Otorhinolaryngology and Head & Neck Surgery to prescribe antibiotic agents in cases of acute otitis media in patients in the risk groups for complications (see note 7) [Grote 1988]. However, adequate research into the effect of these medicines in these patients has not been found.

**Note 15 Antibiotic agents (general)** A Cochrane review of the effectiveness of antibiotic treatment of acute otitis media in children (ten studies; 2,287 children) investigated the following outcome measures: pain after 24 hours, pain on the second to the seventh day, perforation, vomiting, diarrhoea, rash, deafness and recurrent acute otitis media [Glasziou 2003]. It was found that there was no effect on the pain in the first 24 hours, a moderate reduction of pain on the second to the seventh day, no effect on recurrent acute otitis media and no effect on deafness. Vomiting, diarrhoea and rash were clearly more common after the use of antibiotics. In summary, this review suggests that an early start of these medicines in cases of acute otitis media has a limited effect; it takes 15 children to be treated with these medicines to prevent one child from still having some earache after two to seven days.

A meta-analysis based on individual patient data of 1,643 children showed that antibiotic agents have very different effects on pain reduction and/or disappearance of fever in the treatment of acute otitis media in certain subgroups [Rovers, 2006]. The effect (on pain or fever after two to seven days) in the entire group was an absolute risk reduction of 13% (95% CI 9-17%).
which corresponds to an NNT of 8. This effect, and smaller effects still, are seen in children aged over two (NNT 10), in children with unilateral acute otitis media (NNT 17) and in children without aural discharge (NNT 8). The effects are so small that a wait-and-see approach in these groups is most certainly justified. However, the effect on pain or fever after two to seven days was considerably greater in children below the age of two with bilateral acute otitis media and in children with aural discharge at initial presentation (NNT 4 and 3 respectively), although the effect of the antibiotic agent was no longer significant in either group after seven to ten days.

**Conclusion** It has been demonstrated that antibiotic agents do not have a relevant effect on acute otitis media, at least in children who are not severely ill and who are not part of a risk group. However, such medicines increase the probability that children below the age of two with bilateral acute otitis media and children with aural discharge at initial presentation are free of fever and pain after two days. This is the reason why GPs should consider (in consultation with the child’s carers) prescribing antibiotics in these children, at least if this effect is considered important in the individual case.

**Note 16** Antibiotic agents when patients fail to improve Only one study was found into the effect of antibiotic agents in children with acute otitis media who fail to improve sufficiently after three to four days of symptomatic treatment (Van Buchem 1985). In this study, GPs initially gave all 4,900 children aged between 2 and 12 years symptomatic treatment. In children who still had fever and/or pain after three to four days (3% of the total group), antibiotic agents proved to be more effective than myringotomy.

It is not clear whether this finding also holds for younger children. As remarked before (see note 4), children below the age of 2 often take longer to recover (50% still have symptoms of crying or earache after eight days) and antibiotic agents have only been shown to have a relevant effect in subgroups and only if the medicine was administered from the beginning of the episode (see note 15).

While there is insufficient evidence to substantiate this, the working group recommends that treatment with antibiotics is still started when children fail to improve after three to four days of symptomatic treatment (in consultation with the parents).

**Note 17** Recommended antibiotics Hardly any comparative research has been conducted on different antibiotic medicines for the indications formulated in the standard. Differences in effectiveness between narrow-spectrum penicillin and amoxicillin or amoxicillin-clavulanic acid in the treatment of acute otitis media could not be demonstrated in a meta-analysis [Rosenfeld 1994]. Most Western countries also prefer broad-spectrum antibiotics (amoxicillin or amoxicillin-clavulanic acid with possibly cotrimoxazole as an alternative) on the basis of pathophysiological considerations (better penetration into the middle ear) [From 1997]. There have been good experiences with amoxicillin in the Netherlands for some time now.
Azithromycin and cotrimoxazole can be prescribed if there is a contraindication for amoxicillin [Pharmaceutic Aid Committee 2006]. Azithromycin can be administered less frequently and has a similar effect [Ioannidis 2001].

**Note 18 Eardrops**  In practice, antibiotic eardrops are frequently prescribed (especially by ENT specialists) in case of persistent aural discharge through a grommet or through a perforation of the eardrum caused by acute otitis media. Please refer to the NHG Standard on Otitis Media with Effusion for the guidelines on the treatment of aural discharge through a grommet.

The authors of a systematic overview of studies into the effect of local antibiotics (drops) compared with systemic antibiotics in the treatment of chronic otorrhoea (persisting for more than two weeks) found only few usable studies [Madfadyen 2006]. Two studies showed that quinolone drops were more effective than systemically administered antibiotics. However, most of the patients included in these studies were adults. Whether these results are also relevant in children and for eardrops containing other antibiotics is not known.

Based on the above, the working group is of the opinion that eardrops for persistent aural discharge through a perforation of the eardrum caused by acute otitis media have no place in the GP surgery.

**Note 19 Acute mastoiditis**  The clinical picture of an acute mastoiditis comprises one or more of the following symptoms: general symptoms of illness, protrusion of the ear, prolapse of the posterior superior wall of the ear canal, increasing temperature and pain (spontaneous and during palpation of the mastoid area). CT scans confirm the diagnosis. The treatment consists of tympanocentesis, antibiotics (intravenous) and possibly mastoidectomy [Huizing 2003].

**Note 20 Tympanocentesis**  Tympanocentesis is now only rarely carried out in patients with otitis media, as current views suggest that there is hardly any indication for this. There are views that tympanocentesis can still be beneficial to relieve severe pain caused by a bulging eardrum (only effective in the early phase). Tympanocentesis is otherwise conducted to confirm the diagnosis of acute otitis media in infants and to collect material for culturing. However, these indications are part of specialist medical care.

**Note 21 Persistent otorrhoea**  Prolonged otorrhoea can indicate mastoid involvement or a chronic inflammation of the middle ear with or without cholesteatoma formation [Huizing 2003].

**Note 22 Persistent perforation of the eardrum**  Perforations of the eardrum exceeding 25% of the area of the eardrum lead to a clear loss of hearing, though generally less than 35 dB. Perforations of the eardrum sometimes rapidly cause the ear to discharge after exposure to water. If perforations are persistent, then myringoplasty is indicated for disturbing loss of hearing or if the patient wants to swim [Huizing 2003].
**Note 23 Recurrent acute otitis media** In studies and international guidelines, recurrent acute otitis media is often defined as having three or more episodes per six months or four episodes per year [Dowell 1998]. Patients with frequent acute otitis media are tested for infectious foci (adenoid and nasal sinuses) that can be cleaned or removed (e.g. by adenotonsillectomy). An American study showed that adenotonsillectomy (optionally combined with tonsillectomy) only had a limited, short-term effect [Paradise 1999]. A Finnish study showed no effect of adenotonsillectomy on recurrent acute otitis media [Koivunen 2004]. Grommets and a maintenance treatment with antibiotic medicines are also therapeutic options for the prevention of frequent episodes of acute otitis media. Williams et al conducted a meta-analysis of the effectiveness of a maintenance treatment with antibiotic medicines for frequent episodes of acute otitis media (at least three episodes in the previous twelve months) [Williams 1993]. The outcome measure was the number of episodes of acute otitis media per patient month. Pooling showed that there was approximately one fewer episode of acute otitis media per patient per year in the group treated with antibiotics (n=490) than in the placebo group (n=468) (antibiotic group versus placebo group 0.08 and 0.19 episodes of acute otitis media respectively per patient month, difference of 0.11; 95% CI 0.03-0.19). Casselbrant et al conducted a randomised placebo-controlled study in children aged between seven and thirty-five months (n=264), in which the value of prophylactic maintenance treatment with amoxicillin, the placement of grommets and a placebo treatment for the prevention of recurrent episodes of acute otitis media were compared successively for a period of two years [Casselbrant 1992]. Recurrent acute otitis media was defined as three episodes in six months or four or more episodes in twelve months. The average number of recurrent episodes in one year was 0.6 in the group treated with amoxicillin (significant difference versus placebo), 1.02 in the group in which grommets were placed (not significant versus placebo) and 1.08 in the placebo group. The authors concluded that prophylactic antibiotic treatment led to fewer recurrent episodes, while grommets did not have this effect. In contrast, the placement of grommets did lead to episodes of acute otitis media with fewer symptoms (less pain).

Vaccination against pneumococci is also mentioned as a preventative measure against frequent acute otitis media. However, a Dutch study and a systematic literature overview showed that this vaccination does not have an effect in children that already have recurrent otitis [Veenhoven 2003, Stratemans 2004]. Vaccination with a conjugated pneumococcal vaccine in all children from birth resulted in the number of episodes of acute otitis media to decrease by 6% (randomised controlled research; n=1,662) [Eskola 2001]. The number of children with frequent acute otitis media also reduced as a result [Black 2000]. However, the negative effects of such an approach are as yet unclear. The long-term consequences of the serotype replacement observed in various studies are as yet unknown [Veenhoven 2003, Damoiseaux 2002].

In conclusion, the placement of grommets, optionally combined with adenotonsillectomy, is an alternative for the prevention of recurrent episodes of acute otitis media when prophylactic treatment with antibiotic agents delivers...
insufficient effect or when carers reject these medicines. However, both have a limited effect.

As recommended by the Health Council of the Netherlands, the vaccination against pneumococci in all children from birth was introduced nationwide from 1 April 2006. With this vaccination, the Health Council aims to reduce the number of cases of severe invasive conditions caused by pneumococci (meningitis, sepsis, pneumonia) [Health Council of the Netherlands 2005].

**Literature**

1. In case of references to NHG products: see www.nhg.org
47. Williams RL, Chalmers TC, Stange KC, Chalmers FT, Bowlin SJ. Use of antibiotics in preventing recurrent acute otitis media and in treating otitis media with effusion: A meta-analytic attempt to resolve the brouhaha. JAMA 1993;270:1344-51.
Key messages

• Fever is usually caused by a viral infection. Recognising children with a serious underlying disease in time is important.
• Warning symptoms are more important than the height of the fever.
• Children under the age of 3 months are at higher risk of a serious underlying disease.
• Temperature measurements in children under the age of 3 months must be verified rectally.
• A distinction is made between observations by parents and assessment by the GP. The parents/caregivers need to watch out for alarm symptoms; the GP assesses whether there are warning symptoms that can be objectified.
• Information about the child’s past medical history is requested during telephone triage.
• In children under the age of 2 with fever without apparent source, after history-taking and physical examination, urine testing should now be performed on the same day.
• In cases of fever without apparent source, reappraisal is recommended within 24 to 48 hours.
• A typical febrile convulsion is a benign condition.
Introduction

The NHG Clinical Practice Guideline on Feverish illness in Children provides guidelines for the diagnosis and treatment of children with fever of brief duration (1 week at most). What to do in the event of a febrile convulsion is covered in a separate paragraph. Fever is an elevation of body temperature above 38.0 °C\textsuperscript{[1]}. Body temperature is preferentially determined via a rectal reading. Other forms of temperature measurement, such as infra-red tympanic thermometers, are less reliable\textsuperscript{[2]}. Fever is almost always caused by infectious diseases. The vast majority of infections is caused by viruses. The clinical guideline provides recommendations for recognising children at high risk of serious illness and for advice and instruction of parents/carers of children with feverish illness. The clinical guideline indicates under which conditions additional examinations are warranted to identify infectious diseases, and which conditions require specific treatment, such as meningitis. This clinical guideline does not contain specific information on what additional testing is required and which treatment for specific infectious diseases is indicated. For more information, please refer to the relevant clinical guideline.

Background

Epidemiology

Fever is one of the most common disease symptoms. Given the variety of different definitions of fever and the different methods used to determine its height, it is difficult to obtain incidence data. Fever is most common in the age group of 0 to 4 years\textsuperscript{[3]}.

Pathophysiology

Fever usually occurs in response to the intrusion of micro-organisms into the body. It is a normal physiological response, in which the release of cytokines initiates a cascade of reactions. The thermoregulatory mechanism in the hypothalamus responds by essentially turning up the body-thermostat\textsuperscript{[4]}. Body temperature can only rise to above 42 °C in cases of intracerebral infection (rare) or in cases of hyperthermia.

Hyperthermia in children may occur if body heat cannot be released sufficiently\textsuperscript{[5]}. 
Diagnostic guidelines

Remote assessment by telephone

The GP, practice secretary or practice nurse actively asks about the following characteristics and alarm symptoms to determine if and when the child needs to be assessed.

The child with fever must be seen on a very short notice if one or more of the alarm symptoms listed in the box below are present.

### Alarm symptoms

Serious illness, quickly worsening condition, fluid intake less than half of normal, drowsiness, inconsolable crying, rash appearing during fever, a change in skin colour, changed breathing, moaning, apnoea; children younger than 1 month.

The recommendation is that children with feverish illness should be seen the same day in case of:

- Age between 1 and 3 months;
- Compromised immune status or relevant comorbidity, for example children with congenital heart and lung conditions;
- Fever for more than three days[^6] or fever recurring after a number of fever-free days.

If the above characteristics or alarm symptoms are absent, the recommendation is to assess the child with fever the same day if:

- The severity of the child’s condition cannot be ascertained sufficiently over the phone;
- The telephone conversation is complicated by irritation or even aggression, difficult communication or a difference of opinion with the parents/caregivers;
- Persistent parent worry.[^7]

In all other cases, a longer term appointment or self-care advice will suffice. A home visit to a child with feverish illness is generally not indicated.

History

The GP asks about general signs and symptoms

- Duration of the fever[^6,8]
- An impression of the child’s condition;[^9] in the very young, parents/carers can be asked about symptoms of drowsiness (is the child walking around, does the child make eye contact) and crying (more than normal, can the child be consoled);
Ask about urine production and fluid intake. In infants, less than half of normal (daily) intake is a alarm symptom.

The GP then checks for the presence of signs and symptoms that are associated with specific diseases:
- Skin: skin lesions/rash;
- Central nervous system: decreased level of consciousness (less to no contact with the child), vomiting and/or headache;
- Ear-nose-throat: throat ache, earache or rhinitis
- Respiratory tract: breathing difficulties, coughing or shortness of breath and (in nursing infants) poor feeding;
- Digestive tract: vomiting and/or diarrhoea, possible relation to food intake;
- Urogenital tract: stomach complaints, painful or burning sensation while urinating, increased frequency of urination;
- Hydration: urine production (in young children: enough wet diapers, at least 4 per 24 hours). Drooling and ample tear production make dehydration unlikely.

The GP also asks about or checks the patient file for the following:
- Relevant comorbidity, such as children with congenital heart, lung or urinary tract conditions, or immunocompromised children;
- Vaccination status and most recent vaccination;
- Medication use (including immunosuppressants);
- Illness in the child’s environment, for example cold sores;
- Recent stay in a foreign country.

Physical examination

The objective of physical examination is to determine the severity of the illness and find a potential source for the fever. The GP calmly approaches the child, preferably at his or her own level. Children do find examination of the ear, nose and throat most unpleasant. It is therefore recommended that this part of the examination is reserved for the end. Every child is examined fully, unless there is an obvious source for the fever. Good observation is a key part of the physical examination. Areas for attention during the examination are:
- Temperature (always check rectally in children under the age of 3 months);
- Is the child in a poor condition: irritability, decreased level of consciousness (less to no contact), response to parents, crying and consolability;
- Skin: colour – pale, cyanotic, patchy or grey; pale extremities; (maculopapular) exanthema or purpura (spots that cannot be pressed away); capillary refill (increased > 1.5 to 2 seconds) should be determined on the sternum;
- Signs and symptoms of meningitis: bulging fontanel, Brudzinski’s sign, Kernig’s sign or Vincent’s sign;
- Inspection of the thorax to assess respiratory rate; count for one minute (tachypnoea is defined as a rate of > 60/min in children younger than 2 months, > 50/minute in children between 2 months and 1 year and > 40 in children over the age 1. In individuals over the age of 18, tachypnoea is
defined as a respiratory rate of > 25/minute). Note chest in-drawings and nasal flaring. Listen for crackles in the chest and look for abnormalities during auscultation and percussion.\[^{[11]}\]

- Inspection, auscultation, percussion and palpitation of the abdomen;
- Kidney pain in the flanks;
- ENT: inspection of ears, nose, throat and mouth, palpation of regional lymph nodes and assessment of mucous membrane hydration.

**Additional examinations**

Additional blood testing is of no added value.\[^{[14]}\]

Urine testing for urinary tract infection (UTI) is indicated on the same day in:
- Children under the age of 2: if history or physical examination do not reveal an source for the fever;\[^{[15]}\]
- Children over the age of 2: if there are signs of a UTI, or in the event of fever lasting more than 3 days without a clear source.

In the event of abnormal urine test findings, always perform a urine culture (for criteria, see the NHG Clinical Practice Guideline UTI).

If there is any doubt about the presence of pneumonia, consider a chest x-ray. The diagnosis pneumonia is most likely in the event of fever combined with coughing, tachypnoea, chest in-drawing or abnormalities on auscultation.\[^{[11]}\] (see also the NHG Clinical Practice Guideline Acute Coughing).

A chest x-ray has no added value for children with fever without a source after completion of the physical examination and history-taking.

**Assessment**

The GP determines whether there are any warning symptoms present (see box).

---

**Warning symptoms**

The child seems seriously ill upon physical examination, with a decreased level of consciousness, persisting vomiting, purpura, signs of severe tachypnoea and/or dyspnoea, decreased peripheral circulation, pale, mottled, and/or ashen countenance, meningeal signs.

If one or more warning symptoms are present, the child should be referred to a paediatric specialist.

After history-taking and physical examination, the following diagnoses may be considered.
- Upper respiratory tract infection: throat ache, ear-ache, swallowing complaints or rhinitis, or abnormalities upon examination of the ENT area (see
NHG Clinical Practice Guideline Sore throat, NHG Clinical Practice Guideline OMA and NHG Clinical Practice Guideline Rhinosinusitis);

- Lower respiratory tract infection: coughing, tachypnoea, dyspnoea and/or abnormalities upon auscultation (see also NHG Clinical Practice Guideline Acute Coughing);

- Gastro-enteritis: vomiting and/or diarrhoea. In the event of persisting abdominal pain, the possibility of appendicitis, UTI or pneumonia should be considered (see NHG Clinical Practice Guideline Acute Diarrhoea);

- Urinary tract infection: suspected in case of abnormal urine testing (for criteria, see NHG Clinical Practice Guideline UTI);[16]

- Vaccinations: fever is a possible side-effect following recent inoculation;[12]

- Fever without a source: if physical examination does not yield any indications for a specific diagnosis, this is called fever without a source;[17]

- Sepsis: a septic child generally appears seriously ill; clinical signs consistent with sepsis include a prolonged capillary refill (pale, cyanotic or ashen skin colour), decreased level of consciousness (less contact), inconsolable crying and/or moaning;[18]

- Meningitis: clinical signs that may indicate this condition include (persistent) vomiting, meningeal signs, decreased level of consciousness (less contact), purpura, pale, cyanotic, ashen or mottled skin colour, inconsolable crying and/or moaning.[10]

Guidelines on management and treatment

Information and advice

Clear explanation of fever makes it easier for parents or caregivers to deal with children with fever. The following is important:

- Fever is a body temperature over 38.0 °C.[1] Usually fever is a sign of infection. Fever causes dehydration and children with a feverish illness should therefore be given extra fluids.[19] Most children lose their appetite when they are feverish, and they should not be forced to eat.

- Fever generally does not require specific treatment. It is not necessary to actively reduce the body temperature. Antipyretics do not help to speed up recovery, although the fever-reducing and analgesic properties can help children to feel better.[20] It is not necessary for a child with a feverish illness to stay indoors or in bed. Dress the child in light clothing and ensure that the environment is not too warm, as body heat is released via the skin. Applying cold compresses or sponging is not recommended.[21]

- The most important reason for measuring the body temperature is to determine whether or not a child has a fever. One measurement per day will suffice. The temperature should be taken rectally as other ways of measuring are less accurate.[28] Observing the child and noting any changes in behaviour are more important than continually taking the child’s temperature. Generally speaking, the higher the temperature, the more
worried the parents are, but in reality the extent to which the child seems unwell is more important than the temperature itself. Pay much personal attention to the child; this also provides a good opportunity to observe the child.

− Should any alarm symptoms appear (see also remote assessment by telephone), a follow-up contact is mandatory.

To support verbal information, the following NHG patient information letters: Aandachtspunten bij het zieke kind [What to watch out for in unwell children], Kinderen met koorts algemeen [Children with feverish illness, general information] and Koortsstuip [Febrile convulsions] can be given. These letters are based on the NHG Clinical Practice Guideline and contain information about fever in children and the treatment required. (See http://www.nhg.org, patient information section for an overview of all NHG patient information letters.)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Recommended dosage for paracetamol (based on weight and short-term use; less than 3 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>weight and age</td>
<td>oral, maximum dose 90/mg/kg/day (syrup 24 mg/ml)</td>
</tr>
<tr>
<td>3 kg (birth)</td>
<td>2 ml four times daily</td>
</tr>
<tr>
<td>6 kg (3 months)</td>
<td>4 ml four times daily</td>
</tr>
<tr>
<td>10 kg (12 months)</td>
<td>6 ml four times daily</td>
</tr>
<tr>
<td>15 kg (3 years)</td>
<td>9 ml four times daily or 240 mg tablet four times daily</td>
</tr>
<tr>
<td>20 kg (5 years)</td>
<td>1 tablet (240 mg) four times daily</td>
</tr>
<tr>
<td>25 kg (7 years)</td>
<td>1 tablet (500 mg) four times daily</td>
</tr>
<tr>
<td>30 kg (9 years)</td>
<td>1 tablet (500 mg) five times daily</td>
</tr>
<tr>
<td>42.5 kg (12 years)</td>
<td>1 tablet (500 mg) six times daily</td>
</tr>
</tbody>
</table>

Source: Pharmacotherapy Guideline on Pain Relief (http://www.nhg.org)

Medical therapy

Reducing fever is not an end in itself. In case of pain or discomfort, paracetamol may be given in concordance with the parents (see table 1).\(^{22,23,24}\)
Response to paracetamol has no relation to the severity of the underlying condition.\(^{[68]}\)

How to handle fever without a source

If history and physical examination do not reveal an obvious cause for the fever, this is called ‘fever without a source’. In most cases, the infection is harmless, however in exceptional cases a serious condition may develop.\(^{[27]}\) It is important to carefully instruct parents/carers and discuss when to contact their GP practice (see follow-up). In children younger than 3 months, signs and symptoms indicating serious infection may be lacking or non-specific. Because vaccinations in children younger than 3 months do not provide sufficient protection, the chances of infection by bacterial pathogens such as Haemophilus influenzae and pneumococci are increased. All children younger than 3 months with feverish illness without a source are referred to a paediatrician. Children older than 3 months suffering from feverish illness without a source without warning symptoms should be reassessed (by telephone or in person) after 24 to 48 hours.

Follow-up

Parents are instructed to contact the GP practice (again) for follow-up in the following cases:
- Alarm symptoms ( Seriously ill, quickly worsening condition, poor fluid intake (less than half of normal), drowsiness, inconsolable crying, rash appearing during fever, a change in skin colour, changed breathing, moaning, apnoea);
- If they feel a need for reassessment;
- After 24 to 48 hours for children older than 3 months and fever without a source.

Referral

A child with feverish illness only rarely needs to be referred. Indications for referral are:
- All children younger than 1 month;\(^{[68]}\)
- All children between the ages of 1 and 3 months, unless there is a clear source for the fever;
- Presence of warning symptoms (see assessment and follow-up)
- Suspected meningitis or sepsis;\(^{[10,18]}\)
- Signs of dehydration, particularly in children under the age of 1 year;
- A need for diagnostic certainty.
Febrile convulsions

Two to five percent of all children suffer at least one febrile convulsion during childhood.\textsuperscript{[26]} In a GP practice with a list of 2350 patients, a GP will see less than one febrile convulsion each year. Most febrile convulsions occur between the ages of 16 and 18 months. Most fits occur in children without any neurological past medical history, in the age group of 6 months to 5 years, during a period of fever.\textsuperscript{[27]} Typical febrile convulsions do not lead to brain damage. Many parents are afraid that their child will have a febrile fit during high fever, but the vast majority of febrile convulsions occur at the beginning of a febrile period. In about half of all cases, the febrile convulsion is the first sign of feverish illness. About one third of children with febrile convulsions have another fit in the next febrile period. Most recurrences occur within six months. The risk of recurrence is higher in cases of non-typical febrile convulsion. There seems to be a genetic predisposition for febrile convulsions. The probability of suffering from a febrile convulsion is higher if one or more first-degree relatives did suffer from a febrile convulsion in the past.\textsuperscript{[28]}

Diagnosis of febrile convulsions

A typical febrile convulsion begins with a tonic-clonic seizure with a decreased level of consciousness. The seizure does not last longer than 15 minutes, and is followed by a post-ictal phase that can last up to one hour. During this post-ictal phase, a source for the feverish illness should be sought, particularly signs of meningitis.\textsuperscript{[29]} These symptoms are difficult to identify in the post-ictal phase, and are often lacking in children under the age of 1 year. The child also cannot be assessed properly if diazepam is given. In these cases, reassess the child again later the same day. No additional examinations are required in case of a typical febrile convulsion.

Management of febrile convulsions

While the parents or carers are on the telephone, instruct how the airway can be kept free. Have the child placed on his front or side, with the head down. An immediate home visit is indicated. If the child is still convulsing upon arrival, diazepam is administered rectally.\textsuperscript{[30]} The dosage is age-dependent: under the age of 1 year 0.5 mg/kg of body weight, 1-3 years 5 mg, older than 3 years 10 mg of diazepam rectally. If the convulsion persists, the same dose should be repeated after ten minutes. If the child still displays seizures after fifteen minutes, an emergency admission is indicated. If the child is already in the post-ictal phase when first assessed by the GP, or has responded well to the treatment, a structured follow-up (by telephone or otherwise) must be ensured. If there is any doubt, the child should be reassessed again after a few hours.

In a typical febrile convulsion, consciousness is restored within 60 minutes, unless diazepam has been administered. For reassurance, a rectiole with the correct dose of diazepam (or a prescription for a rectiole) may be left with the
parents or caregivers, together with clear instructions on what to do in the event of another convulsion. Antipyretic treatment is not helpful in preventing recurrence. Prescription of anti-convulsive medication to prevent recurrence of febrile convulsions is contra-indicated.\[31\]

Sharing information with the parents/carers is very important in handling febrile convulsions, with an emphasis on the benign nature of a febrile convulsion, the chances of recurrence and what to do in such an event.\[32,33\]

Consultation and referral in case of febrile convulsions

In the following cases, serious illness is suspected and referral to a paediatric specialist is indicated:

- A febrile convulsion in a child with feverish illness younger than 6 months;
- A recurrent febrile convulsion during the same febrile episode;
- A febrile convulsion lasting longer than fifteen minutes;
- A febrile convulsion with focal signs: meningeal signs, signs of meningitis, purpura and/or a decreased level of consciousness.

**Establishment**

In September 2006, a working group of six General Practitioners started writing the NHG Clinical Practice Guideline Children with Feverish Illness. The working group consisted of M.Y. Berger, L.J. Boomsma, F.W. Albeda, R.H. Dijkstra, T.A. Graafmans, J.R. van der Laan and W.H. Lemmen, all MDs and General Practitioners. No conflicts of interest were reported.

Comments were also received from a number of referees, namely: J.M.E. Quak, paediatric nephrologist and Prof H.A. Moll, paediatrician, both on behalf of the NVK; Dr M.A.H. Fleuren on behalf of TNO Quality of Life; Dr M. van Stuijvenberg, paediatrician; P.J.M. Uitewaal, GP; A. Brand and C.A. de Kock, GPs, on behalf of the NHG Standards Advisory Council; Dr H. van Weert, editor-in-chief of Huisarts & Wetenschap; A.C. van Loenen, hospital pharmacist, clinical pharmacologist and editor in chief of the pharmacotherapeutic formulary Farmaceutisch Kompas, on behalf of the Health Care Insurance Board. Referees do not necessarily all support every detail.

In March 2008, the standard was authorised by the NHG Authorisation Committee.

N. Oteman, GP in Schoonhoven and scientific employee in the Guideline Development and Science department of the NHG, provided the working group and the editors of this standard with support and guidance.
Notes

Note 1 Fever Practically all of the literature refers to fever as a body temperature $\geq 38.0 \, ^\circ C$ [Bonadio 1994, Baraff 1993]. This limit was also used in this set of guidelines.

Note 2 Temperature measurement Palpation: Parents often diagnose fever by feeling the forehead. A study in Zambia showed that in 94% of children (aged 1 month to 16 years), parents were able to recognise fever with a positive predictive value of 39%. If parents thought they did not feel fever, this proved accurate in 95% of children. If parents indicate their child has a fever during triage because of palpation, they are correct a good half of the time. Therefore, a temperature increase must always be verified using a rectal measurement [Whybrew, 1998].

Axilla: The conclusion of a meta-analysis of 20 articles (n=3,201 children ages 0 to 18) showed that axillary temperature measurements often differ from rectal temperature. In general, axillary temperature was lower, but the difference varied from 0.17 °C in infants (95% CI $-0.15$ to 0.5) to 0.93 °C ($-0.15$ to 1.98) in older children. In infants, axillary temperature correlated better with rectal measurements, but this was only a small group. The general conclusion is that axillary temperature measurement is insufficiently reliable compared with rectal temperature measurement. No data is available on sensitivity and specificity of axillary measured temperature compared with rectally measured temperature. [Craig 2000].

Ear thermometer: In a meta-analysis of 44 studies (n=4,441 children aged 0 to 16 years), large differences were found between the rectal thermometer and the ear thermometer. The differences were not correlated with temperature or child age. It cannot be ruled out that the presence of acute otitis media influenced the correlation, as the involved studies did not supply sufficient data on this subject. Measured temperatures deviated in both directions. The average difference between rectal and ear measurements was 0.29 °C [Craig 2002]. The pooled estimate for ear thermometer sensitivity was 63.7% (95% CI 55.6 to 71.8) and specificity was 95.2% (93.5 to 96.9) compared to a rectally measured temperature of $> 38 \, ^\circ C$. There were few false-positives. This means that if an ear thermometer registers fever, the likelihood of fever is high.

Conclusion: During telephone triage, all reports of fever – regardless of how it is measured – must be taken seriously, as all measurement methods are reasonably good at predicting the presence of fever. The ear thermometer is the most practical, but is less reliable than rectal measurement. In children under the age of 3 months, it is important to be certain of whether they are febrile. It is recommended that rectal temperature always be taken in this group.

Note 3 Epidemiology The Second Dutch National Study of general practice returned an incidence for the diagnosis of fever of 6.7 per 1,000 patients per year for all age groups pooled, with an incidence of 122 during the first year of life and of 41.5 in the age group 1 to 5 years. In the age group 5 to 14 years,
the incidence is 7.2 per 1,000 patients per year. There is no difference between Dutch and immigrant children [Van der Linden 2004]. According to the Transition Project, incidence of a consultation for fever in general practice is about 430 per 1,000 children per year in the age group 0 to 4 years. In about 23% of cases where fever is the reason for consultation, the diagnosis is a viral infection. This is followed by upper respiratory tract infections (16%) and acute otitis media (14%) [Lamberts 1994, Van der Linden 2004]. For the period 2001 to 2004, there were 20 hospital admissions per 100 0-year-olds with the discharge diagnosis perinatal conditions in the Netherlands [Roedig 2007].

**Note 4 Pathophysiology** Under the influence of exogenous pyrogens such as viruses, bacteria and toxins, but also due to immune complement reactions, macrophages and endothelial cells are triggered to produce ‘endogenous pyrogens’, mostly interleukin-1, interleukin-6 and TNF-alpha. Interleukin-1 acts upon the endothelial cells in the anterior hypothalamus (and does not pass the blood-brain barrier), releasing prostaglandins, mostly of the PGE2 type, which act on the thermostat in the anterior hypothalamus via cyclic AMP, leading to an increase in the set point. The thermoregulatory centre in the anterior hypothalamus receives information from skin and muscles via afferent neurons, and also contains cells that measure temperature changes in the blood. These cells respond to temperature changes of 0.02 °C. Cells with a thermostat function are located adjacent to them. These cells regulate the temperature set point. In case of fever, the set point is set to a higher value. Interneurons transmit the information from the anterior hypothalamus to the posterior hypothalamus, which regulates the production and release of heat via the autonomous nervous system (sympathetic and parasympathetic nervous activity, respectively). At the start of a febrile period, the set point is set to a higher value and heat is retained through vasoconstriction in the skin and increased muscle activity (sympathetic activity). The patient experiences cold. At the end of a febrile period, the skin starts radiating heat due to vasodilation, after which the patient starts sweating and feels clammy due to evaporation (cold and wet; parasympathetic activity). This is a negative feedback mechanism. Multiple inhibiting factors have been identified in the hypothalamus-pituitary axis that limit body temperature to a maximum of 42 °C, and rarely allows body temperature to rise above 41 °C [Roberts 1979, Bernheim 1979, Dinarello 1984, Dinarello 1988, Endres 1987, Robbins 1999].

**Note 5 Hyperthermia** Young children exposed to high temperatures, for example because they are placed too close to a heat source, or left in a car in hot weather, may suffer hyperthermia. The body temperature can rise to 44 °C. The young infant’s lower capacity for perspiration contributes to hyperthermia. The skin often becomes warm and dry; the child is apathetic and has red cheeks. Tachypnoea may occur, followed by stupor, coma and convulsions. Mortality and morbidity (brain damage) of hyperthermia are high. When lowering temperature, attention must be given to potential fluid and
electrolyte imbalance [Behrman 2004]. Unlike during infections, the body temperature regulation mechanisms function normally in hyperthermia.

**Note 6 Duration and course of fever** Some studies have found a weak association between the duration of fever and its course. The longer the fever lasts, the higher the risk of a severe course [Berger 1996, Hsiao 2007, Richardson 2007, Trautner 2006, Bleeker 2007]. Another study found that fever lasting longer than 3 days was associated with a significantly greater probability of severe infection [Goh 2006]. Two other studies however found that the probability of severe infection increased as the febrile period decreased [Teach 1997, Haddon 1999].

**Conclusion:** There is insufficient evidence to support a relationship between the duration of fever and the severity of the condition. In case of persistent fever, a secondary bacterial infection with a potentially more severe course must be considered.

**Note 7 Worried parents** General practitioners who had actually come in contact with a child with sepsis or meningitis and who indicated they could provide ‘learning moments’ in addition to the listed warning symptoms, almost unanimously mentioned ‘uneasy parents’. These are general practitioners who, in hindsight, felt they could have referred sooner. Almost all of these general practitioners noted the parents were capable of verbalising their unease if asked about it specifically [Fleuren 2002].

**Note 8 Height of the fever** The question of whether the height of the fever can help differentiate between a severe and a mild infection is difficult to answer. There seems to be an association between the height of the temperature and the presence of a urinary tract infection [Zorc 2005, Gorelick 2000]. The association between a severe infection and the height of the temperature is the strongest in young children [Pantell 2004]. There also seems to be an association between the pathogen and the height of the temperature for pneumococcal bacteraemia [Kupperman 1998]. Others did not find any relationship between the height of the fever and the probability of severe infection [Nademi 2001, Hsiao 2006]. Research into this association has only been performed in hospital settings. The low incidence of bacteraemia in primary care limits the value of this clinical data [Lee 1998, Pantell 2004].

**Conclusion:** There is insufficient evidence to support the assertion that the height of the temperature is an independent predictor of a severe course of the infectious disease. The added diagnostic value is therefore minimal.

**Note 9 Evaluation of severity of illness** Over the years, various observational scales have been developed to differentiate children at high risk of bacterial infection from children with a viral or other infection and a benign course. McCarthy was one of the first to attempt this [McCarthy 1980]. This observational scale proved of no added value compared to ‘traditional’ history-taking and physical examination [McCarthy 1987]. In addition to the McCarthy scale, the Yale Observation Scale (YOS) and the Young Infant Observation
Scale (YIOS) were developed for children with fever without a focus. The goal was twofold; first, to identify children with the highest risk of bacterial infection in order to allow selective antibiotic therapy, and second, to prevent unnecessary hospital admissions for children with non-severe infections. Because YOS and YIOS missed too many children with severe infections, the Philadelphia and Rochester protocols were drafted, which included additional tests (e.g. blood tests) and a chest x-ray [Baker 1993, Baker 1999, Anbar 1986, Dagan 1985]. Validation of these protocols showed high sensitivity – around 98% - and relatively low specificity, varying between 23.2 and 39.4% [Garra 2005]. Both protocols can therefore only be used to rule out a severe bacterial infection. Due to the low prevalence of severe bacterial infections in children with fever in general practice, a test with a high specificity would be very useful. No data is available on the usefulness of both YOS and YIOS in Dutch general practice.

Conclusion: The use of above-mentioned observational scales and protocols is advised against. A few items from history included in the YOS/YIOS are copied in this guideline.

Note 10 Bacterial meningitis  Background: Bacterial meningitis occurs 700 to 800 times per year in children in the Netherlands. The highest meningitis incidence is found in the second half of the first year of life, around the age of 7 months. The most common cause of bacterial meningitis is still the pneumococcus, which will likely change due to the introduction of the pneumococcal vaccine in 2006 [Netherlands Meningitis Foundation 2008, Fleuren 2002, Fleuren 2004].

Clinical features: classic symptoms – headache, neck stiffness and skin rash – occur in 33%, 39% and 66% of cases, respectively. The combination of all three symptoms only occurs in 13% of cases [Granier 1998].

Meningeal irritation: Meningeal irritation may be determined using Brudzinski’s sign (reflexive bending of legs upon flexion of the head), Kernig’s sign (severe pain upon extending the bent knee) and Vincent’s sign (keeping the back straight when sitting with extended knees) or diaper pain (crying when raising the buttocks when the child is supine). In only one-third of cases of meningeal irritation a bacterial meningitis is present. Nevertheless, lumbar puncture is indicated for all children with meningeal irritation [Van Eeuwijk 2003].

Skin rash: maculopapular exanthema that is not yet haemorrhagic may occur at the beginning of a meningococcal sepsis. Meningococcal sepsis may also manifest with urticaria [Winterberg 1996]. The majority (82-97%) of children aged 1 to 4 with meningococcal sepsis does have a haemorrhagic rash, however. In the age group 4 to 15 years, this is true for 69-75%.

Age: In young children, symptoms are often non-specific. They may exhibit elevated or decreased body temperature, changes in consciousness, irritability, hypotonia and eating disorders. In one third of cases, a bulging fontanel is present [Roord 2001, Granier 1998]. Children aged 5 to 6 years often present with headache. Fever is almost always present upon hospital admission, but is less common in infants younger than 5 months [Roord 2001].
**Course:** A retrospective study among general practitioners and parents of 448 children with a meningococcal sepsis or meningitis attempted to chart the disease course. This revealed that classic symptoms such as haemorrhagic rash, decreased consciousness and meningeal irritation often occurred late, on average only after 13 to 22 hours. In 72% of children, there were early symptoms of sepsis. The most common symptoms – muscle aches in the legs, cold extremities and abnormal skin colour – occurred between four and six hours after the beginning of the disease [Thompson 2006]. Two types of disease course may be identified. In the first, the child is ill for one to a few days, with fever and signs of an upper respiratory tract infection (caused by Staphylococcus pneumoniae and Haemophilus influenzae). In the other, less common form, the course is acute and fulminant, and sometimes fatal. In this case, signs of sepsis and meningitis (primary cause *Neisseria meningitidis*) appear within a few hours [Roord 2001, Granier 1998]. In the case of Meningitis, the greatest morbidity and mortality is caused by the pneumococcus [Roord 2001].

**Conclusion:** Children with fever must undergo extensive physical examination, among other things to detect meningitis. The absence of classic symptoms, particularly in infants, does not entirely rule out meningitis. In these cases, watch for general alarm symptoms and symptoms, and ensure good follow-up or refer to a paediatrician if meningitis is suspected.

**Note 11 Pneumonia** A systematic literature review shows there is no gold standard for differentiating between a viral and bacterial pneumonia. The meta-analysis ultimately included five studies that attempted to compare chest x-rays to a reference test. No studies used bronchoalveolar lavage or pulmonary aspiration as a reference test to determine whether the patient had a bacterial pneumonia. Performing a chest x-ray does not seem useful in order to differentiate between a viral and a bacterial pneumonia [Swingler 2000].

Little research has been conducted examining the relationship between clinical symptoms and the presence of pneumonia in primary care. Data is however available from hospital studies.

Palafox et al examined whether tachypnoea (using the WHO definition) is a sufficiently valid characteristic to diagnose pneumonia in children with a respiratory infection. A total of 110 children, aged 3 months to 5 years with an acute respiratory infection, 51 of whom with *tachypnoea*, were included. The clinical diagnosis of pneumonia was made in 35 children (32%), confirmed via chest x-ray, the gold standard for diagnosing pneumonia. The sensitivity of tachypnoea as a sole clinical sign was 74%, specificity was 67%. In children with less than three days of fever, sensitivity and specificity were both lower. Age and undernourishment had no effect. The presence of *retractions* was also a discriminating factor, with a sensitivity of 71% and a specificity of 59%. *Abnormal auscultation* was far less reliable, with a sensitivity of 46% and a specificity of 79%. The absence of audible abnormalities does not rule out pneumonia. The diagnosis was made most reliably in children under the age of 6 months with tachypnoea [Palafox 2000].
Another hospital study was a prospective trial in 147 children suspected of pneumonia. The clinical signs that best predicted pneumonia were determined retrospectively (with a chest x-ray as a golden standard). The most sensitive parameters were: 

- **tachypnoea** (sensitivity 99%, specificity 88%)
- **coughing** (sensitivity 98%, specificity 70%)
- **retractions** (sensitivity 88%, specificity 77%)
- **fever** (sensitivity 78%, specificity 42%).

The most relevant finding was tachypnoea; its absence almost entirely ruled out pneumonia [Shamo’on 2004].

A third prospective study also found an association between tachypnoea and pneumonia. The prevalence of pneumonia in this study was 7%. Per degree of temperature increase, respirator rate increased by 2.5 per minute. This study showed tachypnoea had a sensitivity of 73.8% and a specificity of 76.8%. The positive predictive value of tachypnoea is only 20%, while the negative predictive value and the lack of tachypnoea is 97.4% [Taylor 1995].

**Conclusion:** Pneumonia is likely in the event of fever combined with coughing, tachypnoea, retractions or abnormalities upon auscultation. Tachypnoea is the most sensitive symptom. The absence of these symptoms makes the probability of pneumonia very low. The working group therefore recommends against routine chest x-rays for children with fever without pulmonary complaints.

**Note 12 Vaccinations** Most vaccines can cause a fever within 24 to 48 hours of administration. Clinical studies indicate that the number of fever reactions is higher when the pneumococcal vaccine and hexavalent (Dtal/Hib/Hepatitis B) vaccine are given together than if a hexavalent vaccine is given alone. Fever is frequently (> 10%) reported in association with the meningococcus C vaccine. For the BMR vaccine, fever only occurs five to twelve days after vaccination [Pharmaceutical Aids Committee 2007].

**Note 13 Immunocompromised patients** A patient may be immunocompromised due to any number of conditions and treatments. Conditions that affect the immune system include HIV infection, Down’s syndrome, combined immunodeficiency syndrome, hypogammaglobulinemia, agammaglobulinemia, leukaemia, lymphomas and generalised malignancies. Immunosuppressive therapies are treatments with corticosteroids, cytostatic agents, radiotherapy, status post splenectomy or bone marrow transplantation.

**Note 14 Additional blood tests** Little to no primary care research has been done examining the added value of blood testing in children with a fever. Most children with fever have a viral infection with a benign course. A small proportion of them will develop a bacterial infection with a serious course, such as meningitis or sepsis. The question is whether blood testing in a primary care setting can identify those children with the highest risk of a severe disease course. Severely ill children will be referred to a hospital, and the question is whether blood testing in children with a good clinical condition has any consequences.
Initially, blood testing was primarily focused on the number of white blood cells. Various studies among children with fever in hospital care showed that a high white blood cell count had a sensitivity of 69-80% and a specificity of 58-80% for predicting severe bacterial infection. These values are based on a cut-off value of $15-18 \times 10^9/l$ [Isaacman 2000, Isaacman 2002, Pulliam 2001].

Two studies looked at the value of the neutrophil count, with a cut-off value of $10.2$ and $10.6 \times 10^9/l$. The sensitivity for bacterial infection was 69-71%, and the specificity was 76-79% [Pulliam 2001, Isaacman 2002].

More studies have been conducted assessing CRP, particularly in children younger than 36 months. Table 2 provides an overview of various cut-off values and sensitivity and specificity for predicting bacterial infection with a potentially severe course. All studies were performed in a hospital setting.

A systematic review of 46 articles assessed the role of procalcitonin (PCT) as an early marker of severe infection in children. PCT has a sensitivity varying from 83-100% and a specificity of 70-100% for diagnosing sepsis and meningitis. The cut-off value varies in the studies, but in general, 2 ng/ml is used to differentiate between viral and bacterial infections. The role of PCT in diagnosing a bacterial pneumonia remains unclear. This is largely because a bacterial pneumonia is often diagnosed using a chest x-ray, which cannot be considered a gold standard. The specificity of PCT for diagnosing pyelonephritis is 82-86%, and the sensitivity is 70-73% when compared to renal scintigraphy (DMSA scan) as the gold standard. In a hospital population of children with fever without a focus, a sensitivity of 93% and a specificity of 74% have been found for tracing a severe bacterial infection. Unfortunately, this study also made the diagnosis of bacterial pneumonia based on a chest x-ray [Van Rossum 2004].

**Conclusion:** There is no single laboratory test that is sufficiently specific to identify the early stages of an infection with a potentially serious course in children. PCT seems to be the most promising marker for the future. However, there is insufficient evidence available from primary care research to assess the value of PCT in general practice. Given the low a priori probability of severe infection in primary care (which will probably be lowered even further thanks to the introduction of the Hib and pneumococcal vaccines), markers would have to become even more specific [Black 2004, Lee 1998, Kourtis 2004]. Additional blood testing in general practice is therefore not recommended.

<table>
<thead>
<tr>
<th>study</th>
<th>cut-off value (mg/l)</th>
<th>sensitivity (%)</th>
<th>specificity (%)</th>
<th>relative risk in the event of a positive result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galetto-Lacour 2003</td>
<td>40</td>
<td>79</td>
<td>79</td>
<td>6.1</td>
</tr>
<tr>
<td>Carol 2002</td>
<td>30</td>
<td>81</td>
<td>89</td>
<td>3.79</td>
</tr>
</tbody>
</table>
Note 15 Risk factors for developing a urinary tract infection (UTI)  A study among children with fever in a hospital setting showed that 3-10% of children younger than 3 months had a urinary tract infection [Newman 2002]. It is estimated that 5% of all children with fever without a focus suffer from a urinary tract infection [Hoberman 1993]. In newborns and infants, the classic symptoms of a urinary tract infection are often lacking [Van Wijk 1998]. Additional urine testing is therefore recommended in high-risk groups. Three different studies identified comparable risk factors, and none were performed in a primary care setting. In a cross-sectional study in the emergency department among girls younger than 2 years and boys younger than 1 year with a temperature of over 38.5 °C, young age (< 12 months old), uncircumcised males, fever without a focus, supra-pubic discomfort during medical examination and fever higher than 39 °C were found to be independent risk factors [Shaw 1998]. In a prospective tertiary care study among 1,469 girls with fever without a focus (> 38.3 °C), the following risk factors were identified: age less than 12 months, Caucasian race, temperature higher than 39 °C, more than two days of fever and the absence of an origin for the fever [Gorelick 2000]. A prospective study among paediatricians working outside the hospital showed that the duration of fever, high temperatures, young age and not being circumcised could be identified as risk factors.

Conclusion: Young age, uncircumcised males and high fever are associated with the occurrence of a urinary tract infection. In children under the age of 2 years, symptoms consistent with a urinary tract infection may be difficult to identify. The working group chose to perform urine tests on the same day on children under the age of 2 with fever without a focus. The reason is that children under the age of 2 are at greater risk of developing kidney damage after a urinary tract infection (see note 16).

Note 16 Treatment of urinary tract infections  Urinary tract infections in young children can quickly lead to renal damage, and always require immediate antibiotic treatment [Hansson 1997, Pylkkänen 1981]. Retrospective British research found kidney damage in 5% of all children referred with a urinary tract infection [Coulthard 1997, Pylkkänen 1981]. Another British study in children with a history of urinary tract infection showed that the probability of developing new renal damage decreases in children past the age of three

<table>
<thead>
<tr>
<th>study</th>
<th>cut-off value (mg/l)</th>
<th>sensitivity (%)</th>
<th>specificity (%)</th>
<th>relative risk in the event of a positive result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulliam 2001</td>
<td>70</td>
<td>79</td>
<td>91</td>
<td>13</td>
</tr>
<tr>
<td>Isaacman 2002</td>
<td>44</td>
<td>63</td>
<td>79</td>
<td>3.3</td>
</tr>
<tr>
<td>Gendrel 1999</td>
<td>20</td>
<td>73</td>
<td>88</td>
<td>5.43</td>
</tr>
<tr>
<td>Thayil 2005</td>
<td>50</td>
<td>75</td>
<td>68.7</td>
<td>5.23</td>
</tr>
</tbody>
</table>
It is assumed that pyelonephritis may eventually lead to hypertension and renal insufficiency [Jacobson 1989].

**Note 17** Fever without a focus  By far the most research into children with fever without a focus is conducted in a hospital setting, mostly in the emergency and paediatric departments. This means data is not easily translated to primary care. In children younger than 3 months, clinical presentation is often atypical, making the presence of bacterial infection difficult to predict [Ishimine 2006, Baker 1999, Klassen 1992, Bleeker 2002]. Children over the age of 3 months have a lower risk of bacterial infection than young infants, as good protection is only achieved after three vaccinations [Oostenbrink 1999]. Furthermore, only a small percentage of bacterial infections in this age group is caused by the pneumococcus [Baker 1993]. The introduction of the Hib vaccine has significantly decreased the number of *Haemophilus influenzae* infections [Lee 1998, Sur 2007, Bleeker 2002]. The pneumococcal vaccine was also introduced in the Netherlands in 2006. It is expected this will further reduce the number of bacterial infections caused by the pneumococcus [Black 2004]. A small percentage – an estimated 0.02% - of children has a meningococcal infection [Lee 1998]. Ninety percent of children over the age of 3 months with a meningococcal infection have a clinical picture consistent with meningitis or meningococcal sepsis, and 10% have an unexpected meningococcal bacteraemia. A retrospective study showed that additional blood testing did not affect treatment policy in children who later proved to have positive blood cultures with meningococci [Kuppermann 1999]. Observational scales such as the YOS also proved not to be useful for identifying occult bacteraemia in a clinical setting [Teach 1995]. About 5% of children with fever without a focus are found to have a urinary tract infection [Hoberman 1993].

**Conclusion:** In children younger than 3 months with fever without a clear focus, the clinical presentation of severe disease is often atypical. It is important to consider bacterial infections in this group in particular. The working group therefore recommends that all children under the age of 3 months without a clear focus for the fever be referred to a paediatrician. Early urine testing is advised for children younger than 2 years without a clear focus for the fever.

**Note 18** Children younger than 1 month  The probability of a severe course of an infectious disease is greater in newborns. Infants younger than 1 month do not have a fully mature immune system and are unprotected by vaccines. Additionally, presentation may be very non-specific [Bleeker 2002]. Infections occurring during or shortly after birth are often caused by long-term ruptured membranes (> 24H) or are acquired during passage through the birth canal. An infection occurring within the first 28 days after birth is a perinatal infection [Merkus 2008]. Common pathogens are the Group-B Streptococcus (GBS), *Listeria monocytogenes*, the herpes simplex virus, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Klebsiella spp*, *Haemophilus influenzae*, the hepatitis B virus and *Chlamydia spp*. In premature infants, necrotising
enterocolitis (NEC) must also be considered as a differential diagnosis in the first month.

The course of infections in newborns depends on the virus or bacteria causing it. Contamination can lead to sepsis. A viral or bacterial infection in a newborn can quickly worsen, and lead to death within a few hours. The prognosis of an infected newborn is heavily dependent on the timing of the diagnosis and start of treatment. Mortality among newborns with sepsis lies around 20-50%. Sepsis caused by a Group-B Streptococcus has a mortality – even under optimal treatment – of 40%. Mortality for a generalised herpes infection is 70%. Surviving children run the risk of brain damage following certain infections. This is particularly common after meningitis, with the herpes simplex virus an *E. coli* being two notorious pathogens (see also http://www.rivm.nl/vtv/object_class/kom_problgeboren.html) [Van den Brande 1998]. Based on this information, the working group decided to refer all children under the age of 1 month with fever to the paediatrician.

**Note 19 Fluid balance** Children under the age of 2 years are most sensitive to dehydration. Infants are more likely to suffer dehydration than older children and adults, as increased fluid loss in infants leads to swift changes to extracellular volume [Kist-Van Holthe 1999]. Infants also lose a relatively larger amount of fluid via the skin than an adult due to their large surface area to volume ratio. Finally, the infant’s renal concentration ability in the event of hypovolaemia is limited, contributing further to dehydration. Sufficient fluid intake is required to compensate for the fluid loss caused by fever. Based on the literature, no recommendations can be made regarding whether hot, cold or lukewarm fluids should be administered.

**Note 20 Some ideas people have about fevers** Parents are often needlessly afraid of complications caused by fever [Crocetti 2001]. Fever need only be treated when the child is experiencing discomfort [Taylor 2006]. Evidence shows that parents are mostly frightened of the harmful effects of fever, such as convulsions (40% of parents), brain damage (12%), death (2%) and coma (1%). Many parents also believe that a fever will continue to increase if left untreated [Stephenson 1988]. Research among a representative sample of the Norwegian population shows that a third of people think that a body temperature over 40.5 °C is life-threatening [Eskerud 1991].

Fever in children is a symptom for which help is often sought outside office hours. Fear of the consequences of fever and earlier experiences of medical intervention play a significant role in this [Kai 1996]. Parents often experience inconsistencies in the approach of care providers and they are not sensitive to reassurance (for example: ‘It’s only a virus’) [Blumenthal 1998]. No literature could be found about beliefs ethnic minority parents may hold concerning fever in children.

**Conclusion.** There are many misconceptions about fever. It is therefore important to provide parents and carers with a comprehensive explanation.
**Note 21** *Non-medical lowering of temperature*  A Cochrane review showed that sponge-bathing has some effect on body temperature. The seven included (quasi) randomised trials were heterogeneous and all had methodological limitations. The authors of the review concluded that the physical methods alone are not useful in lowering temperature, but that combination with an antipyretic may lead to swifter temperature drops [Meremikwu 2002]. Sponge-bathing can be unpleasant for the child. As temperature decrease is not an end in itself, sponge-bathing is not recommended.

**Note 22** *Choice of antipyretic*  Various studies have compared the efficacy of paracetamol and ibuprofen (see *table 3*).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Effects of paracetamol versus ibuprofen on temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>author and year</strong></td>
<td>type of study</td>
</tr>
<tr>
<td>Goldman 2004</td>
<td>Systematic review (14 trials, 11 RCTs)</td>
</tr>
<tr>
<td>Perrot 2004</td>
<td>Meta-analysis (17 studies)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlewyn-Lajeunesse 2006</td>
<td>RCT</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Studies have also been done examining the effect and height of the dosage. An RCT with 121 children showed that paracetamol administered with a rectal loading dose of 30 mg/kg was more effective and faster when it came to lowering temperature than a dose of 15 mg/kg [Treluyer 2001]. For ibuprofen, a dose of 10 mg/kg proved more effective than 5 mg/kg [Goldman 2004].

**Conclusion:** Paracetamol and ibuprofen are comparable in terms of effectiveness for lowering body temperature. Ibuprofen may initially work slightly
faster and more powerfully, but the effect is comparable to paracetamol after a few hours. The combination of both medicines may be more effective for lowering body departure, but, given the high risk of dosage errors, monotherapy with paracetamol is the recommended treatment for lowering temperature. This standard recommends only combating fever in the event of pain or discomfort. Combating fever is not an end in itself.

**Note 23 Side-effects of paracetamol and ibuprofen** In terms of side-effects, a paracetamol overdose may cause acute liver damage. A review article shows that this very rarely occurs in children. It is nonetheless important to realise that glutathione is important for paracetamol detoxification. Malnutrition and interactions with other medication and alcohol can reduce this detoxifying effect, leading to an increased risk of toxic effects. In children younger than 7 years, even a dose of 200 mg/kg did not lead to severe problems [Bromer 2003]. Other authors set the cut-off for overdose lower (140 mg/kg) [Lall 1998]. While paracetamol is safe to use, parents often dose it incorrectly due to incorrect weight estimation, calculation errors and the like. Studies conducted among 100 parents showed that 30% dosed correctly, 13% dosed correctly despite incorrect calculations, 48% under-dosed and 9% overdosed [Simon 1997].

Short-term use of ibuprofen in an RCT with 27,065 children showed the risk of gastrointestinal bleeding was 7.2 (95% CI 2 to 18) per 100,000 children. This was not significantly different from the risk for paracetamol. The number of cases of renal insufficiency (5.4 per 100,000 children) was not significantly different compared with paracetamol use. The limitation of this study is that not all children were screened as standard; renal failure or gastrointestinal bleeding was determined based on complaints [Lesko 1995, Lesko 1997].

Ibuprofen may cause kidney damage in children with decreased kidney function or signs of dehydration [Moghal 1998].

**Conclusion:** Severe side effects rarely occur with paracetamol. Use of ibuprofen does not seem to cause a significant increase in side-effects. However, as additional tests were only performed in the event of complaints in the large groups studied, no definitive statements can be made.

**Note 24 Ibuprofen dosage** Because ibuprofen is available over the counter, ibuprofen dosage is included in this note for the sake of completeness (see table 4). Paracetamol remains the recommended treatment in cases of pain or discomfort.

**Note 25 Response to antipyretics and course** A literature search only revealed five prospective cohort studies examining the predictive value of lowered body temperature following paracetamol administration for disease course. In these five studies, temperature was measured in a variety of ways, and differing doses of paracetamol were given. However, all studies came to the same conclusion: lowering of body temperature after paracetamol administration was not a predictor for disease course [Weisse 1987, Torrey 1985, Yamamoto 1987, Baker 1987, Richardson 1999].
Note 26 Incidence of febrile convulsions A large retrospective study in Rotterdam (3,570 children) found that 3.9% of the children have had at least one febrile convulsion [Vink 1990]. A stratified sample among 103 general practices in the Netherlands showed the incidence of febrile convulsions to be 4.8 per 1,000 patient years. The probability of febrile convulsion between the ages of 3 months and 6 years was estimated at 2.7% [Speelman-Verburgh 1996].

Note 27 Typical and atypical febrile convulsions A typical febrile convulsion consists of a persistent extension cramp (tonic) followed by a series of generalised seizures (clonic), followed by a post-ictal phase of lowered consciousness with complete recovery within 60 minutes. A febrile convulsion is the occurrence of the above event in children between the ages of 6 months and 5 years with fever (38 °C), without signs of intracranial pathology. An atypical fever convulsion entails a duration of longer than 15 minutes and focal aspects or recurrence within the same febrile period, particularly within 24 hours. This may indicate a higher risk of severe pathology, including meningitis. A typical febrile convulsion is not associated with an increased risk of epilepsy [Sadleir 2007].

Note 28 Risk factors for febrile convulsion Predisposition to febrile convulsions is largely determined by a positive family history of convulsions [Verity 1985]. A large-scale study in Rotterdam showed that children with a positive family
history had a 4.5 times higher risk of febrile convulsions [Offringa 1991]. Children with long admissions to neonatology units, frequent stays in day care centres or slowed development were more likely to suffer febrile convulsions [Brouwer 1996].

**Note 29 Additional examinations in the event of a febrile convulsion** A review estimated the probability of meningitis in the event of a febrile convulsion to be 0-4%. It is worth noting that bacterial meningitis is very unlikely if no warning symptoms are found during physical examination, specifically petechial bleeding, neck stiffness or lowered consciousness [Offringa 2001]. A second review put the probability at 0.23% [Sadleir 2007].

**Note 30 Medication for terminating febrile convulsions** A prospective randomised trial in secondary care compared intranasal midazolam (0.2 mg/kg) to intravenous diazepam (0.3 mg/kg). A total of 47 children, aged 6 months to 5 years, were included. No significant side-effects were reported in either group, and both medications were effective in terminating the seizure [Lahat 2000]. A second RCT performed in the emergency department compared buccal midazolam to rectal diazepam. Dosage was age-related, varying from 2.5 to 10 mg. A total of 177 patients from the age of 6 months were included, however children with a diagnosis of epilepsy were not excluded. The population was therefore heterogeneous, with convulsions caused both by fever and epilepsy. Only 56 children had a febrile convulsion. The conclusion in this heterogeneous group was that buccal midazolam was more effective than rectal diazepam in combating the convulsion and preventing recurrence [McIntyre 2005]. A third prospective study conducted in secondary care included a total of 43 children aged 2 to 12 months, and compared buccal midazolam with rectal diazepam. In this study, only 12 children were found to have a febrile convulsion. Buccal midazolam proved just as effective as rectal diazepam [Baysun 2005].

**Conclusion:** Rectal diazepam remains the medication of choice for febrile convulsion. Advantages of midazolam have not been demonstrated convincingly. A prospective trial conducted in a primary care setting with large groups of patients could clarify the value of midazolam for this indication.

**Note 31 Prophylaxis for febrile convulsions** A meta-analysis of nine RCTs examined the question of whether prophylaxis can be given to prevent recurrent febrile convulsions. The risk of recurrent convulsions was significantly lower under continuous administration of phenobarbital or valproate compared with placebo. Administration of pyroxidine or phenytoin compared with placebo did not show a significant difference. Intermittent administration of diazepam also did not show any significant difference compared to placebo. The number needed to treat (NNT) to prevent a convulsion was four for valproate and eight for phenobarbital [Rantala 1997]. There is no evidence that anti-convulsive medication decreases the risk of developing epilepsy. However, it is known that anti-convulsive medication has significant side-effects, such as irritability, lethargy and ataxia [Sadleir 2007]. There is insufficient
evidence to support the assertion that paracetamol or ibuprofen use may prevent a convulsion [Van Stuijvenberg 1998b, Baumann 2000].

**Conclusion:** Only valproic acid and phenobarbital are effective in preventing recurrent febrile convulsions. As febrile convulsions are a benign condition, and these medications have significant side-effects, prophylaxis is recommended against.

**Note 32 Prognosis** Children with epilepsy have been found to have a higher prevalence of past febrile convulsions [Baumann 2000]. If risk factors are present, such as an atypical febrile convulsion, problems in the child’s past medical history (developmental disorders or motor disorders) and convulsions without fever in first-degree family members, the risk of developing epilepsy is significantly higher [Brouwer 1996]. There is no evidence that children function less well cognitively following a febrile convulsion [Sadleir 2007, Verity 1998, Brouwer 1996].

**Note 33 Educating parents** A retrospective questionnaire study among parents with children who had suffered a febrile conversion showed high anxiety levels among parents. Forty-seven percent of parents were afraid that their child would die during the convulsion. Twenty-one percent indicated they were no longer worried about the outcome thanks to good information provision. The study showed that non-Western parents were more fearful. It is worth noting that this study took place in secondary care [Van Stuijvenberg 1998a].

**Literature**

1 In case of references to NHG products: see www.nhg.org


31 Fleuren MAH, Paulussen TGWM. Vroegsignalering van meningitis en sepsis door huisartsen. TSG 2004;82:97-103.


100 Trautner BW, Caviness AC, Gerlacher GR, Demmler G, Macias CG. Prospective evaluation of the risk of serious bacterial infection in children who present to the emergency department with hyperpyrexia (temperature of 106 degrees F or higher). Pediatrics 2006;118:34-40.