PRACTICE

UNCERTAINTIES

Is combining or alternating antipyretic therapy more beneficial than monotherapy for febrile children?

Mona Nabulsi

Although fever is a beneficial host response, it is an important cause of anxiety for parents and doctors. The quest for effective treatment has led to new combination regimens of antipyretic drugs for febrile children. These are popular among caregivers and healthcare providers, but they have been tested in clinical trials only recently. The new regimens consist of combinations of ibuprofen and paracetamol (acetaminophen) given at variable time schedules. The main concern about these treatments is safety, because they may increase the risk of renal toxicity, as a result of reduced glutathione in the kidney and tubular necrosis, or the risk of infection with invasive group A streptococci. Therefore we need to know whether these combinations are more effective than, and as safe as, monotherapy in children with fever.

What is the evidence of the uncertainty?

A systematic search of PubMed, Medline, CINAHL, Cochrane, and Embase databases for systematic reviews and randomised clinical trials, published in any language, using the MeSH terms or keywords “fever” and “ibuprofen” and “acetaminophen or paracetamol” retrieved five randomised controlled trials that compared antipyretic combinations with monotherapy (table). No systematic reviews were found on this subject. The Jadad scale was used to assess the quality of the retrieved studies.

In two studies, administration of combined ibuprofen and paracetamol at the same time was compared with ibuprofen monotherapy and found to be as effective as ibuprofen and marginally better than paracetamol. Both studies, however, had problems with validity, such as lack of blinding or information on reasons for withdrawal; no temperature recordings beyond two hours, which compromised detection of further drug effects; and inability to recruit the calculated sample size (table).

In the other three studies, ibuprofen and paracetamol were alternated every three or four hours. Alternating therapy was superior to ibuprofen or paracetamol monotherapy in two studies and marginally superior to paracetamol in one. The studies, however, were of moderate quality and used variable drug doses and regimens (table). Important problems with validity were small sample sizes, lack of placebo control or adequate double blinding, and the use of small antipyretic doses that may have biased the results in favour of the alternating regimen. In addition, the mean difference in temperature between the alternating and monotherapy groups was clinically insignificant (≤1°C) in two studies. No significant adverse events were reported. However, objective laboratory screening for liver and renal toxicities was performed in one study only, and the other investigators monitored toxicity clinically. Because classic laboratory testing with urine analysis or blood urea nitrogen and creatinine may fail to detect early renal toxicity, the safety of antipyretic combinations remains uncertain.

Is ongoing research likely to provide relevant evidence?

A search of National Institutes for Health, World Health Organization, and Australian New Zealand clinical trials registries for ongoing studies in febrile children identified one open label three arm trial (NCT00267293), which aims to compare ibuprofen monotherapy with combined ibuprofen-paracetamol or with alternating ibuprofen-paracetamol. In addition, guidelines on feverish illness in children from the National Institute for Health and Clinical Excellence (NICE) mention an ongoing Health Technology Assessment study of combined paracetamol-ibuprofen treatments that is expected to report in 2009. It will be interesting to see if the results of these two studies help resolve some of the uncertainties surrounding the effectiveness and safety of combined or alternating antipyretic regimens.

Future studies should avoid the limitations of previous studies by having large enough sample sizes to detect clinically significant differences between groups, as well as adverse effects; having concealed randomisation.
### Summary of studies assessing effectiveness of combined or alternating antipyretic interventions

<table>
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<tr>
<th>Study details</th>
<th>Subjects</th>
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<th>Outcomes</th>
<th>Validity</th>
<th>Conclusion</th>
<th>Quality (Jadad scale)</th>
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<tr>
<td><strong>Combined ibuprofen and paracetamol</strong></td>
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<tr>
<td>Erelwyn-Lajeunesse et al (2006)</td>
<td>N=123; aged 6 months to 10 years; tympanic temperature ≥38°C</td>
<td>Single dose 3 arm trial: 15 mg/kg paracetamol, 5 mg/kg ibuprofen, or both drugs given together at baseline</td>
<td>The combined regimen was similar to ibuprofen in temperature reduction at 1h (mean adjusted difference 0.25°C; 95% confidence interval −0.01 to 0.50) and marginally better than paracetamol (0.35°C; 0.10 to 0.60); more children in the combined group were admitted to hospital; no serious adverse events reported</td>
<td>Open label randomised trial; adequate randomisation and concealment; lack of information on withdrawals; analysis was more per protocol than ITT; no data beyond 2h</td>
<td>Combined ibuprofen and paracetamol was no better than ibuprofen alone</td>
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<tr>
<td>Hay et al (2008)</td>
<td>N=156; aged 6 months to 6 years; axillary temperature ≥37.8-41.0°C</td>
<td>Multiple dose 3 arm trial: 15 mg/kg paracetamol every 4-6 hours, maximum of 4 doses/day; 10 mg/kg ibuprofen every 6-8 hours, maximum of 3 doses/day; or both drugs given together</td>
<td>Combined treatment was similar to ibuprofen alone for less time with fever in the first 4h (adjusted difference 16 min; −7 to 39) but superior to paracetamol (35 min; 33 to 77); for less time with fever over 24h combined treatment was superior to ibuprofen (2.5h; 0.6 to 4.4) and to paracetamol (4.4h; 2.4 to 6.3); clearance of fever was similar for combined treatment and ibuprofen (mean difference −3 min; 18 to −24) and faster than for paracetamol (mean difference 23 min; 2 to 45); no benefit was seen for discomfort; no major adverse events reported</td>
<td>Randomised 3 arm trial, adequate randomisation and concealment; parents and outcome assessors not blinded to group allocation; analysed sample less than calculated sample size (low power); ITT analysis</td>
<td>Combined treatment was no better than ibuprofen alone</td>
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<tr>
<td><strong>Alternating ibuprofen and paracetamol</strong></td>
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<tr>
<td>Nabulsi et al (2006)</td>
<td>N=70; aged 6 months to 14 years; rectal temperature ≥38.8°C</td>
<td>Single dose parallel group trial: 10 mg/kg ibuprofen alternating with 15 mg/kg paracetamol at 4 hours × 10 mg/kg ibuprofen</td>
<td>Alternating treatment was superior to ibuprofen alone—significantly more subjects had a normal temperature at 6h, 7h, and 8h; time to fever recurrence was longer (mean 7.4 (SD 1.3) vs 5.7 (2.2) h); and reduction in temperature at 7h and 8h was greater; no major adverse events reported</td>
<td>Randomised double blind placebo controlled parallel group trial; adequate randomisation and concealment; ITT analysis; recruited sample size less than calculated size</td>
<td>Alternating treatment was superior to ibuprofen alone</td>
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<tr>
<td>Sarrell et al (2006)</td>
<td>N=480; aged 6-36 months; rectal temperature ≥38.4°C</td>
<td>Multiple dose 3 arm trial over 3 days: 12.5 mg/kg paracetamol every 6h, 5 mg/kg ibuprofen every 8h, or alternating similar doses of paracetamol and ibuprofen every 4h; subjects were initially loaded with either 25 mg/kg paracetamol or 10 mg/kg ibuprofen equally divided among the three groups</td>
<td>Alternating treatment was superior to ibuprofen or paracetamol alone with lower mean temperature, more rapid reduction in fever, lower intake of antipyretics by the third day, less stress, less absenteeism from day care or work (parents); no major adverse events reported</td>
<td>Adequate randomisation and concealment; no placebo control; double blind masking; carried out by the groups having different treatment schedules</td>
<td>Alternating treatment was more effective than monotherapy</td>
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<tr>
<td>Kramer et al (2008)</td>
<td>N=38; aged 6 months to 6 years; rectal or oral temperature ≥38.0°C</td>
<td>Single dose parallel group trial: 15 mg/kg paracetamol alternating with 10 mg/kg ibuprofen at 3 hours × 15 mg/kg paracetamol every 4 hours</td>
<td>Statistically significant, but clinically insignificant differences in the mean temperatures (0.6-0.8°C) in favour of the alternating regimen at 4 and 5 hours; no difference in parental perception of antipyretic efficacy; no major adverse events reported</td>
<td>Randomised double blind placebo controlled parallel group trial; adequate randomisation and concealment; ITT analysis; small sample size</td>
<td>Alternating treatment marginally superior to paracetamol monotherapy</td>
<td>5</td>
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**Provenance and peer review:** Not commissioned; externally peer reviewed.


**What should we do in the light of the uncertainty?**

In view of the uncertainty around the superiority or safety of antipyretic combination regimens compared with monotherapy, we should continue to use either paracetamol or ibuprofen. NICE guidelines recommend that paracetamol and ibuprofen should not routinely be given together or used in an alternating schedule. However, if the child fails to respond to one of these drugs, the alternative drug may be used. Attending to parental anxiety and fears about fever, and educating parents about the immunological usefulness of fever and the risks associated with antipyretic abuse, remain a priority.

**Funding:** No extra funding needed.

**Competing interests:** MN received a lecturing honorarium from Janssen (Vail Pharmaceutical Industries, United Arab Emirates), which manufactures ibuprofen and paracetamol.

And well masked treatments; using 15 mg/kg doses of paracetamol and 10 mg/kg doses of ibuprofen; monitoring adverse events objectively, including early detection of probable acute renal injury. 24

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“Surely it is unethical for the medical and pharmaceutical industries to promote the use of toxic drugs in children to treat anxiety in parents and doctors? They should be educated to allow a beneficial host response to take its natural course and for themselves to take a ‘chill pill’!”

Ron Law: risk and policy consultant, Auckland, New Zealand, in a rapid response
In most patients acute lower gastrointestinal bleeding resolves with conservative management, but when bleeding is especially severe, more invasive investigations and treatment may be needed.

An 81 year old woman presented to hospital with a 12 hour history of passing copious blood per rectum. She gave a history of ischaemic heart disease with previous coronary stent insertions and chronic obstructive pulmonary disease. She was taking regular aspirin but was not taking an anticoagulant. She had no other relevant medical history.

On examination she was pale with cool extremities. Her pulse was thready (very fine and scarcely perceptible) at 100 beats/min, and her blood pressure was 100/76 mm Hg. Examination of the abdomen was normal but active rectal bleeding was noted.

What is the next investigation?

Although the history is highly suggestive of bleeding from the lower gastrointestinal tract, about 10-15% of patients presenting in this way are bleeding from a source in the upper gastrointestinal tract. Upper gastrointestinal endoscopy should therefore be considered in the first instance. If the upper gastrointestinal tract has been excluded as the source, the bleeding is most likely to originate from the colon. The table gives the prevalence of the most common causes of acute colonic haemorrhage in patients aged over 50. In most (85-90%) patients in this age group with acute lower gastrointestinal haemorrhage, the bleeding will stop with conservative management.

<table>
<thead>
<tr>
<th>Causes</th>
<th>Prevalence (%)</th>
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<tbody>
<tr>
<td>Diverticular disease</td>
<td>40-50</td>
</tr>
<tr>
<td>Angiodysplasia</td>
<td>10-30</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>7-30</td>
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<tr>
<td>Ischaemic colitis</td>
<td>5-10</td>
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<tr>
<td>Haemorrhoids</td>
<td>5-10</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>&lt;5</td>
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<tr>
<td>Radiation enteropathy</td>
<td>&lt;5</td>
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</tbody>
</table>

In patients with haemorrhage of sufficient severity to cause haemodynamic instability either at presentation or after resuscitation, colonic investigation is indicated to localise the site and cause of the bleeding and to guide definitive treatment. Mortality is high in this group and may be up to 33% in those requiring surgery.

Colonoscopy

Colonoscopy is a well established, widely available, and accurate technique for diagnosing the cause of rectal bleeding. Accuracy in the acute setting may be reduced owing to the technical challenges of an unprepared colon and an unstable patient. Nevertheless, when clinicians are highly experienced, high levels of success have been reported both in the identification of the source of haemorrhage and in using haemostatic techniques to control bleeding.

The small risk of perforation is increased when therapeutic techniques are used, and the requirement for sedation also increases risks.

Digital subtraction angiography

Digital subtraction angiography is usually performed via a femoral arterial approach. To visualise the arterial supply to the liver and lower gastrointestinal tract, shaped catheters are used to insert cannulas selectively into the inferior mesenteric artery, the superior mesenteric artery, and the celiac axis and angiography is performed. Superselective catheterisation of branch vessels is performed to enable maximal opacification of the distal vascular arcades. The examination may be performed under local anaesthetic and carries only minimal risks to the patient.

The technique may be tailored to identify active extravasation of contrast into the bowel lumen to guide further management. More subtle findings can be neovascularisation resulting from a tumour and early venous filling secondary to angiodysplasia. Hepatic angiography is important if haemobilia is suggested from upper gastrointestinal endoscopy.

In animal models angiography can detect bleeding at flow rates of as little as 0.5 ml/min, but most authors estimate that the flow rates detectable in vivo are a little higher.

Despite this, digital subtraction angiography is often negative, even in cases of severe haemorrhage, because of...
Computed tomography angiograms (axial, top; coronal, bottom) of the abdomen showing pooling of contrast material (arrows) in the proximal transverse colon, indicating the site of haemorrhage.

The intermittent nature and unpredictable timing of arterial bleeding. Reported sensitivity ranges from 10% to 40%. Nevertheless, if active haemorrhage is detected selective embolisation can be performed, which can obviate the need for major surgery—particularly important in elderly people, who often have substantial comorbidity.

Multidetector row computed tomography angiography

The superior speed of image acquisition of the scanners used for multidetector row computed tomography allows the entire abdomen to be scanned within five to six seconds. This allows accurate depiction of the mesenteric vasculature with excellent resolution and is fast enough to detect active extravasation of contrast into the bowel lumen. Kuhle and Sheiman found that the superior contrast resolution of computed tomograms compared with digital subtraction angiograms results in a higher sensitivity in the detection of active haemorrhage; they found that computed tomography was able to detect bleeding with a rate of 0.4 ml/min.

Nuclear scintigraphy

Technetium labelled red blood cell scintigraphy has been studied extensively as a means of localising the source of gastrointestinal haemorrhage. This is a non-invasive examination in which the patient’s red cells are labelled with an intravenous injection of radionuclide and images obtained over about an hour using a gamma camera. No major associated risks have been reported.

Although nuclear scintigraphy is reasonably effective in confirming the presence of ongoing haemorrhage, with reported sensitivity of up to 50%, the exact site and cause of bleeding are not reliably identified and scintigraphy influences clinical management in only a minority of cases.

Outcome

While being actively resuscitated, the patient was transferred for computed tomography angiography, which showed contrast extravasation from a site in the proximal transverse colon (figure). Diverticulosis was seen at this site, but no other cause for bleeding was seen.

The patient continued to bleed and remained unstable. After discussion between surgeons and radiologists, and in view of the lack of immediate availability of interventional radiology, she was taken to theatre and right hemicolectomy was performed. Examination of the resected specimen confirmed haemorrhage as a result of diverticular disease. Although she initially made a good recovery with no further blood loss, she died 10 days later from postoperative pneumonia and multiorgan failure.

Contributors: GFM had the original idea, and AJE selected the patient. Both authors searched the literature and wrote the paper. GFM is the guarantor.

Competing interests: None declared.

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent not required (patient anonymised, dead, or hypothetical).

7 Bonacker MJ, Begemann PG, Dieckmann C, Yekaebas E, Adam G. The role of angiography in the diagnosis and therapy of gastrointestinal haemorrhage. Rofo 2003;175:254-31. [In German.]
EASILY MISSED?
Ovarian cancer

William Hamilton,1 Usha Menon2

Ovarian cancer is the leading cause of death from gynaecological cancer in the United Kingdom. Around 4,400 deaths occur each year, and UK mortality figures are worse than comparable European ones.1

Why is it missed?
The vagueness and non-specific nature of the symptoms, lack of serious pain or physical disability, and lack of awareness cause women to dismiss the symptoms as being related to normal body changes, such as the menopause, or to stress.2 The initial symptoms are often suggestive of benign gastrointestinal or urinary conditions, which are also much more common than ovarian cancer. The predominance of gastrointestinal symptoms means that women are often misdiagnosed as having irritable bowel syndrome or gastritis.3 In women over 50, the new onset of irritable bowel syndrome-like symptoms should raise the possibility of serious disease, including ovarian cancer.

Even if cancer is considered, colorectal cancer is more common, and patients are often sent on the wrong investigative pathway. Current UK referral guidelines recommend urgent investigation only in the presence of abnormal vaginal bleeding or a palpable pelvic mass.4 Both are uncommon early features. Screening is not available—it is still being evaluated in large randomised controlled trials.

Why does this matter?
Ovarian cancer is staged by the International Federation of Obstetrics and Gynaecology (FIGO) system. Most women present with advanced stage disease (FIGO III and IV), which is associated with a five year survival of 25-30% compared with 80-90% in those diagnosed in early stages (FIGO I or II). The median time to diagnosis is reported as less than three months in 55% of women, but it was more than six months in 26% and more than a year in 11%.3 Women who ignored their symptoms or presented with gastrointestinal symptoms were significantly more likely to be diagnosed with advanced disease.3,5

How is it diagnosed?
Clinical diagnosis
Because the incidence of ovarian cancer is relatively low, positive predictive values for most symptoms are low (table).6,7 Abdominal distension is usually persistent and progressive, unlike bloating, which most clinicians use to mean intermittent distension. However, women have their own interpretation of these terms, so it is important to clarify what is meant.8

A symptom index of pelvic or abdominal pain, increased abdominal size or bloating, and difficulty eating or feeling full, when present for more than a year and occurring on more than 12 days a month, had a sensitivity of 56.7% for early stage disease and 79.5% for advanced stage disease. Specificity was 90% for women age over 50 in a US primary care setting and 86.7% for women under 50 years.9

In the UK, recent guidance urges doctors to look for ovarian cancer in patients with the above symptoms, especially if they are of recent onset and persistent.10 A similar awareness campaign is under way in the United States. Abdominal and pelvic examinations are important—almost half of women may have a palpable mass at
diagnosis. If the examination is negative, women should be encouraged to return if symptoms become more frequent or pronounced.

Investigations
Serum CA 125 and transvaginal ultrasound had a specificity of 95% and 92%, respectively, in a pilot study of symptomatic women over 45 years in primary care. Their sensitivity in symptomatic women in primary care is unknown, so a negative test cannot completely rule out cancer. The preferred investigation is a combination of CA 125 and pelvic (ideally transvaginal) ultrasound, which is more sensitive and more specific than either alone in distinguishing benign from malignant adnexal masses. A “risk of malignancy index”—which combines CA 125, menopausal status, and transvaginal ultrasound findings—is often used to differentiate malignant ovarian masses from benign ones.

How is it managed?
Surgery is the primary intervention in suspected ovarian cancer, both to obtain histological confirmation and stage as well as first line treatment. In women who have completed their families, this usually means laparotomy with removal of the uterus, fallopian tubes, ovaries, part of the omentum, and any relevant biopsies. If disease is advanced, “debulking” surgery is performed with the aim of leaving behind as little tumour as possible. Increasing evidence points to increasing operation success with paclitaxel added on an individual basis.

In developed countries, tetanus is uncommon and cases are usually diagnosed in elderly patients. Levels of tetanus antibodies are progressively lower with increasing age in groups over 50 or 60 years old. Acute injuries and chronic wounds can allow entrance of Clostridium tetani. We report the case of a non-immunised patient with generalised tetanus after biopsy of a chronic ulcerated skin lesion.

Case report
A 67 year old man was referred to the dermatology department with a two year history of skin lesions on his right leg. The patient was otherwise healthy and not taking any drugs. On physical examination he had painless subcutaneous nodules on the distal part of the right thigh (fig 1) and an asymptomatic eroded, scabbed, violaceous, well defined plaque on the upper side of the right ankle (fig 2). He had no signs of infection, arterial or venous disease, or history of trauma. Possible diagnoses included lupus vulgaris or other mycobacterioses, necrobiosis, and sarcoidosis. Biopsy specimens were taken from both lesions in the operating theatre under standard aseptic conditions. The results were not available so the patient was told to care for the wounds by daily washing with water and soap and applying a topical antiseptic until stitches were removed.

Three weeks after the biopsies, the patient presented to the emergency service with acute dysphagia, odynophagia, and trismus. Symptoms evolved to cervical hyperextension, rigidity of the scapular waist muscles, and finally opisthotonos. On admission, the lesion on the right ankle

**LESSON OF THE WEEK**

**Generalised tetanus in a patient with a chronic ulcerated skin lesion**

Beatriz Aranegui, Ángeles Flórez, Ignacio García-Doval, Aránzazu García-Cruz, Carlos de la Torre, Manuel Cruces

Chronic ulcerated skin lesions and lesions resulting from their biopsies should be considered as wounds prone to tetanus.

In developed countries, tetanus is uncommon and cases are usually diagnosed in elderly patients. Levels of tetanus antibodies are progressively lower with increasing age in groups over 50 or 60 years old. Acute injuries and chronic wounds can allow entrance of Clostridium tetani. We report the case of a non-immunised patient with generalised tetanus after biopsy of a chronic ulcerated skin lesion.

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**Contributors:** WH wrote the first draft, with revision by UM. Both authors are guarantors.

**Competing interests:** None declared.

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**Patient consent not required** (patient anonymised, dead, or hypothetical).


**REFERENCES**

had been dirty and necrotic (fig 3); the patient had not been vaccinated against tetanus and did gardening at home. A diagnosis of generalised tetanus was considered, and he was transferred to the intensive care unit, where he received tetanus immunoglobulin and antitetanus toxoid. He developed respiratory difficulties and signs of autonomic dysfunction and needed sedation, intubation, assisted ventilation and, later, tracheostomy, neuromuscular blocking agents, drugs to control autonomic nervous system dysfunction, and intravenous antibiotics. He developed a pneumothorax, a pleural effusion that required chest tube drainage, two episodes of pneumonia due to mechanical ventilation, and catheter related bloodstream infection. *Alcaligenes sp* and meticillin sensitive *Staphylococcus aureus* grew in cultures from the skin lesion on the right ankle. *C tetani* was not isolated, but tetanus (severity 3b) was diagnosed on clinical grounds.\(^1\)

The patient stayed in the intensive care unit for 49 days until he was successfully extubated; he was transferred to the internal medical floor and discharged two months after admission. Leg lesions were diagnosed as sarcoidosis with cutaneous and pulmonary involvement and were treated with corticosteroids.

**Discussion**

The annual incidence of tetanus has decreased dramatically in developed countries since the introduction of tetanus toxoid and is now 0.16 per million population in the United States.\(^1\) International prophylaxis recommendations\(^13\) may be modified by local directives.\(^14\)

In developed countries tetanus occurs mainly in elderly people, who have had irregular booster shots in adulthood.\(^1\) The concentration of tetanus antibodies reduces with age, so that in a serological analysis carried out in the US only 31% of 70 year olds, and 47% in Australia, had protective levels of tetanus antibodies, whereas in England and Wales 53% of people over 60 had protective levels.\(^3\)\(^7\)\(^8\) In Spain, a national seroprevalence survey in 1996 showed that only 55% of people born before 1966 had protective levels of antibodies.\(^14\)

The risk of developing tetanus through chronic ulcerated skin lesions tends to be overlooked, even though varicose ulcers, dermatosis, and necrosed tumours have been the point of entry in 11% to 14% of cases.\(^9\)\(^10\) In diabetic patients with foot ulcerations, tetanus enters through these wounds in up to 25% of cases.\(^15\) The death rate is higher in such cases than in cases related to acute trauma.\(^16\) Up to 47% of patients with chronic leg ulcers—which affect 3-5% of people over 65\(^17\)—have insufficient IgG concentrations for immunity, rising to 70% in patients aged over 80.\(^9\) Consequently, chronic ulcerated wounds should be considered as prone to tetanus, and recommendations highlight the importance of prophylaxis.\(^9\)\(^11\)\(^15\)\(^18\)

Tetanus after surgery is uncommon. Most cases develop within 24 hours after gastrointestinal or gynaecological surgery.\(^19\)\(^20\) Both exogenous and endogenous sources could be responsible, as spores of *C tetani* can be found in operating rooms or in the intestinal content of asymptomatic colonised patients.\(^9\)\(^19\) Giving IgG before gastrointestinal surgery has been proposed.\(^21\)

Our patient developed severe generalised tetanus three weeks after the biopsy of a chronic ulcerated skin lesion, and the port of entry was probably the lesion. This case is unlikely to be considered as postsurgical tetanus, but the biopsy wound could have opened a route. Wound cultures did not isolate *C tetani* (but cultures are positive in only 32-50% of patients\(^13\)) and a diagnosis of tetanus could be made on clinical grounds.\(^12\) Our patient had not been vaccinated. His long hospital stay with intensive care produced high risks and costs as a result of what is a preventable disease.
What can general practitioners do to prevent these cases?

To ensure high population coverage of tetanus vaccination, every opportunity should be taken to offer boosters to adults. Acute wounds are not the only lesions that should be considered as tetanus prone. Chronic ulcerated lesions like pressure ulcers, venous stasis ulcers, necrosed tumours, or diabetic feet, which are common in elderly people, should also be considered, and such patients should receive tetanus prophylaxis according to local directives. Skin biopsy of these sort of lesions could be another opportunity to ensure the immunisation status of patients.

Contributors: BA identified and managed the case, performed the literature search, and wrote the article. AF identified and managed the case, performed the literature search and revised the article. IG-D had the idea for the article, performed the literature search and revised the article. AG-C and CNewaT performed the literature search, and wrote the article. MC identified and managed the case. PE revised the article. BA is guarantor.

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Competing interests: None declared.

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50 years ago: polio epidemics, immunisation, and politics

Efforts to develop a polio vaccine started in the United States in the early 1950s, with trials of the Salk vaccine taking place in 1954.1 In Hungary, the Salk vaccine was used after the 1957 epidemic. After a more severe epidemic in 1959, however, the need for a more effective prophylaxis became apparent.2 News emerged that AB Sabin, a US immunologist had developed an attenuated live virus vaccine given orally.

Learning that Mikhail Chumakov had given the “Sabin drops” to ten million children in the former Soviet Union caused a sensation. Chumakov, head of the Polio Research Institute in Moscow, had visited the United States and offered to cooperate with Sabin. After the death of Stalin, health affairs were a good field for collaboration. Sabin visited the country of his birth, Russia, and mass production of his live vaccine became apparent.

After agonising, we recommended the Sabin vaccine and kept quiet about the controversy. That year, 2.3 million children and 300 000 adults, aged 15-65 years, were vaccinated in some Baltic Republics and started work immediately, vaccinating in the rest of the country. After much discussion and debate, consent for large scale immunisation was refused. Further talks with the health ministers of individual Soviet Republics were satisfactory, consent for large scale immunisation was refused.

Chumakov then approached the health ministers of the individual Soviet Republics. As an acadecian from Moscow, he was permitted to vaccinate in some Baltic Republics and started work immediately, immunising 10 million people in a fortnight.

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All cases with the slightest suspicion of any complications were referred for assessment to my department. Dozens of children presented with a wide variety of diagnoses including muscular dystrophy, accidents, joint problems, tummy aches, diarrhoea, constipation, and ileus.

A Soviet-Hungarian conference on polio immunisation was organised in Budapest for the spring of 1960. Sabin attended, and we reviewed the 150 case notes of children referred. None of them were related to the immunisation. We were mortified.

In the Soviet Union, where all decisions stemmed from the decree of a party committee, individual initiatives were fiercely discouraged, particularly when they involved collaboration with an American scientist. Chumakov, however, received permission to test the vaccine in a few children’s homes. His status as a member of the Soviet Academy, and the fact that his wife was the daughter of Marshal Voroshilov, a Soviet war hero, must have helped. Although the results of the tests were satisfactory, consent for large scale immunisation was refused. Chumakov then approached the health ministers of individual Soviet Republics. As an acadecian from Moscow, he was permitted to vaccinate in some Baltic Republics and started work immediately, immunising 10 million people in a fortnight.

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All cases with the slightest suspicion of any complications were referred for assessment to my department. Dozens of children presented with a wide variety of diagnoses including muscular dystrophy, accidents, joint problems, tummy aches, diarrhoea, constipation, and ileus.

A Soviet-Hungarian conference on polio immunisation was organised in Budapest for the spring of 1960. Sabin attended, and we reviewed the 150 case notes of children referred. None of them were related to the immunisation.

No further polio epidemics occurred in Hungary after 1960. In that year, Albert Sabin was permitted to run vaccine trials in the United States,3 and he was granted a licence for its industrial production in 1962.4 In 1963, Mikhail Chumakov was awarded the “Lenin Prize”—the highest award in the former Soviet Union.5

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