Impetigo in General Practice

Sander Koning

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Hans Holbein (Augsburg, Germany, 1497/1498 – 1543, London, England).
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Impetigo in General Practice

Impetigo in de huisartspraktijk

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Manuscripts based on studies described in this thesis

1. Koning S, van Suijlekom-Smit LW, Nouwen JL, Verduin CM, Bernsen RM, Oranje AP, Thomas S, van der Wouden JC. Fusidic acid cream in the treatment of impetigo in general practice: double blind randomised placebo controlled trial. British Medical Journal 2002;324:203-6. *(Chapter 2)*

2. Koning S, van Belkum A, Snijders S, van Leeuwen W, Verbrugh H, Nouwen J, Op 't Veld M, van Suijlekom-Smit LW, van der Wouden JC, Verduin C. Severity of nonbullous Staphylococcus aureus impetigo in children is associated with strains harboring genetic markers for exfoliative toxin B, Panton-Valentine leukocidin, and the multidrug resistance plasmid pSK41. Journal of Clinical Microbiology 2003;41:3017-21. *(Chapter 3)*

3. Koning S, Verhagen AP, van Suijlekom-Smit LWA, Morris A, Butler CC, van der Wouden JC. Interventions for impetigo (Cochrane Review). In: The Cochrane Library, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd. *(Chapter 4)*

4. Koning S, Mohammedamin RSA, van der Wouden JC, van Suijlekom-Smit LWA, Schellevis FG, Thomas S. Impetigo: incidence and treatment in general practice in 1987 and 2001. Results from two national surveys. British Journal of Dermatology. [in press] *(Chapter 5)*

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6. Koning S, van der Wouden JC. Treatment for impetigo. British Medical Journal 2004;329:695-6. *(Chapter 7)*

1

Introduction

A. Impetigo, a common disease with important unanswered questions in general practice

Biology and symptoms

Impetigo or impetigo contagiosa is a contagious superficial bacterial skin infection, most frequently encountered in children. It is typically classified as either primary impetigo or secondary impetigo, where the infection is secondary to some other underlying skin disease, such as scabies or eczema. Impetigo is also classified as bullous or non-bullous impetigo. Bullous impetigo is characterised by larger bullae. Non-bullous impetigo is the most common form of impetigo.

Staphylococcus aureus is considered to be the main bacterium that causes non-bullous impetigo. However *Streptococcus pyogenes,* or both *S. pyogenes* and *S. aureus,* are sometimes isolated. Especially in warmer climates the streptococcal variety seems more common. (1)

The relative frequency of *S. aureus* infections in impetigo has also changed with time. (2) It was predominant in the 1940s and 1950s, after which Group A streptococci became more prevalent. In the past two decades, *S. aureus* has become more common again. Bullous impetigo is always caused by *S. aureus*. Complications of non-bullous impetigo are rare. Local and systemic spread of infection can occur which may result in cellulitis, lymphangitis or septicaemia. Non-infectious complications of *S. pyogenes* infection include scarlet fever and glomerulonephritis. This has always been an important rationale for antibiotic treatment. The incidence of acute glomerulonephritis in the developed world however has declined rapidly over the last few decades, parallel with increasing socio-economic circumstances. (3,4)

Epidemiology

In the Netherlands, most people with impetigo consult their general practitioner (GP) and approximately 1% of the cases are referred to a dermatologist. (5) It is the third most common skin disorder in children after dermatitis/eczema and viral warts. (5,6) In British general practice 2.8% of children aged 0 to 4 and 1.6% aged 5 to 15 consult their GP about impetigo each year. (7) In the Netherlands in the late 1980s the consultation rate was 2.2% of all children under 14 years. (5) In some tropical or developing countries the incidence of impetigo seems to be higher than elsewhere. (8,9)

The way by which impetigo develops and spreads as an infection is far from clear. The presence of *S. aureus* and a (minor) interruption of the skin barrier seem to be necessary for development of impetigo. Though 20-55% of the population are nasal carriers of S. aureus, (10,11,12) and superficial skin lesions are extremely common as well, most people usually do not develop impetigo. Other factors in both the host and in the bacterium therefore must also play a role.

Concerning the host factors, it is generally believed that several human risk factors are associated with the occurrence of impetigo. These include poor hygiene, lower social classes and crowding. (13) In developed countries, the incidence of impetigo seems to be declining because of increased socio-economic circumstances such as better hygiene and less crowding. Many authors have described a peak incidence of impetigo in summer and autumn and believe this is related to closer unprotected skin contact and/or because there are more skin injuries due to cuts or insect bites in summertime.
Factors at the other, causative side may also be involved. Are all strains of *S. aureus* capable of causing impetigo, or are there specific (genetic) characteristics that facilitate the emergence of impetigo and the likeliness of its spread within individual or to others? Also, growing resistance against antibiotics may hinder treatment as well as facilitate spread and, increasingly, reports suggest that nowadays there are more uncontrollable epidemics, caused by multiple resistant strains of *S. aureus*. (14,15,16)

Course

It is believed that spontaneous resolution may be expected within two to eight weeks without treatment in most cases, but that more prompt resolution occurs with adequate treatment. (13,17,18) However, there is very little research on the natural history of impetigo. The only data of the "untreated" course of impetigo may be found in placebo arms of RCTs: reported cure rates of placebo creams vary from 8% to 42% at 7 to 10 days. (19,20) In daily practice, GPs usually see an impetigo patient only once and therefore does not know how long the time to cure is.

Considerations for treatment

For the individual patient, impetigo is a minor disease as cure can be expected within weeks maybe even without treatment. There may be three reasons however, for which a patient will be treated. The patients' concerns and wish to get rid of the unsightly aspect of impetigo as soon as possible may be the strongest motive to start treatment. Traditionally, the wish to avoid serious complications such as acute glomerulonephritis has been another reason for doctors for prompt (systemic) treatment. Aside from curing the individual, the third rationale for treatment could be to reduce the time that a patient with impetigo can infect other patients, thus preventing further spread or epidemics. Especially schools are interested in this and may demand that a child is treated or even cured before it can return to school again. Guidelines from government health departments or other relevant bodies differ in this respect: some recommend exclusion, (21,22,23) but others state that there is no evidence to support exclusion as an effective measure towards the prevention of spread of impetigo. (24)

Choice of treatment

Management options for impetigo include the following:

1. no specific treatment, waiting for natural resolution and applying hygiene measures;
2. topical disinfectants;
3. topical antibiotics, and
4. systemic antibiotics.

Within these categories, there are many preparations to choose from, and sometimes a combination of therapies is employed.

An ideal treatment should be effective, cheap, easy to use, and accepted by people. It should be free from side effects, and should not contribute to bacterial resistance. For this reason antibiotics should not have an unnecessarily broad spectrum, (25,26) and when a topical antibiotic is used it should preferably not be one that may be needed for systemic use. (27, 26) An advantage of the use of topical antibiotics is that the drug can be applied where it is needed, avoiding side effects like gastrointestinal upsets. For this reason, compliance may be better. (28) Disinfectant measures do not have the disadvantage of contributing to resistance and are cheaper, which may be important especially in developing countries.

The evidence about the efficacy of different treatments is not abundant and sometimes contradictory. Because of the supposedly benign spontaneous course, some authors suggest that an expectant attitude with just topical cleansing and no antibiotic treatment would suffice in mild cases. (29,17,13) However, as stated before, there is little supporting evidence to assure a concerned patient with.

Some authors prefer topical antibiotic treatment, and others prefer oral therapy. In the Netherlands, a general practice guideline for the treatment of impetigo exists since 1999. (29) In summary, the advice is a basic disinfectant treatment with povidon-iodine or chlorhexidine, and additional zinc ointment in case of limited lesions or fusidic acid cream in case of more extensive lesions. The authors of the guideline report however that the scientific basis for these recommendations is limited.

In conclusion, many questions about impetigo are still open. Since impetigo is such a common disease in general practice, we were challenged to find answers to some of these questions. The general aim of this thesis is to establish epidemiological data about impetigo, to identify host- and bacterial factors that contribute to occurrence of impetigo and to collect evidence for all treatment options. This thesis describes the results of our investigations, which were all carried out in general practice.

B. Scope of this thesis and description of chapters

Fusidic acid is an antibiotic that is often advocated as a topical treatment of impetigo, for instance in the Dutch general practice guideline. Its efficacy was however never compared to placebo. In **chapter 2** we describe a placebo controlled trial that we conducted into the efficacy of fusidic acid cream in the treatment of impetigo in children.
In **chapter 3** we assess the presence or absence of toxin encoding genes in *S. aureus* strains derived from patients in the trial and investigate whether the virulence gene potential of the strains and staphylococcal nasal carriage are associated with severity and course of the impetigo.
In the systematic review described in **chapter 4**, we explore, value, and present an overview of all the available evidence of treatments for impetigo that have been studied in randomised controlled trials.
In **chapter 5** we investigate the course of impetigo from the perspective of the patient, in order to get insight into the development of impetigo in children before and after they consulted their GP.
In **chapter 6** we investigate the incidence of impetigo and the epidemiological factors that may be associated with the incidence of impetigo in Dutch general practice, and the treatment applied by Dutch GPs. We also describe trends in incidence and treatment between 1987 and 2001.
In **chapter 7** we summarise and discuss our results and come to implications for practice and recommendations for further research.

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2

Fusidic acid cream in the treatment of impetigo in general practice: doubleblind randomised placebo-controlled trial

Koning S, van Suijlekom-Smit LW, Nouwen JL, Verduin CM, Bernsen RM, Oranje AP, Thomas S, van der Wouden JC. Fusidic acid cream in the treatment of impetigo in general practice: double blind randomised placebo controlled trial. British Medical Journal 2002;324:203-6.

Abstract

Objectives

Impetigo is the most common skin infection in children. Treatment options include either systemic or topical antibiotic treatment, sometimes combined with disinfecting measures. Fusidic acid cream has never been compared with placebo. We tested the hypothesis that fusidic acid would not increase the treatment effect of disinfecting with povidon-iodine alone.

Design

Randomised placebo-controlled trial. All children were treated with povidon-iodine shampoo and randomly assigned to receive either fusidic acid cream or placebo cream. Study participants and staff were blinded until primary statistical analyses were completed.

Setting

General practices in Greater Rotterdam.

Participants

184 Children aged 0-12 years with impetigo were reported by general practitioners and visited by a research nurse. 160 were randomised. Evaluation took place at 7, 14 and 28 days. Four children (2 in each group) were lost to follow-up.

Main outcome measures

Clinical and bacterial cure after one week.

Results

After one week of treatment 55% of the patients in the fusidic acid group were clinically cured versus 13% in the placebo group (OR 12.6, 95% CI [5.0 – 31.5], number needed to treat 2.3). After 14 and 28 days, differences in cure rates between the two groups became smaller. More children in the placebo group were noncompliant and had extra antibiotic treatment. The placebo group reported more side effects. In 96% of the positive cultures *Staphylococcus aureus* was found. No strains were resistant to fusidic acid.

Conclusions

Fusidic acid proved to be far more effective in the treatment of impetigo than placebo, both in combination with povidon-iodine shampoo. The value of povidon-iodine in impetigo can be questioned.

Introduction

Impetigo is the most common skin infection in children (1,2) caused mainly by *Staphylococcus aureus* and sometimes by *Streptococcus pyogenes* (group A). Because of the supposedly benign spontaneous course, some authors suggest that an expectant attitude with just disinfection and no antibiotic treatment would suffice in mild cases. (3,4,5) Antiseptic therapy with chlorhexidine or povidon-iodine is often advocated as a useful adjunct to antibiotic treatment. (3, 5)

Immediate antibiotic treatment is advised for most cases to achieve a quick cure and prevent spread of the infection to others. (4,5,6) Oral antibiotic treatment has long been first choice, because of better treatment results and because topical antibiotic treatment is more likely to induce sensitisation and bacterial resistance. (7) In recent years, however, the resistance of staphylococci to oral antibiotics (such as erythromycin) has increased dramatically. (1,8,9,10,11) At the same time, topical antibiotic treatment with mupirocin showed to have equal or even better treatment results compared to oral treatment. (1,9,12,13) In general, compliance is better with topical administration than with oral administration, (13) and less systemic side effects occur. (8)

Fusidic acid is a long existing antibiotic that is mainly used topically. (14) It is recommended as first choice topical antibiotic in the Dutch General Practitioners guideline on the treatment of impetigo. (3) However, some authors discourage topical use of fusidic acid, because of its value in systemic treatment. (5,15) Conversely, others advise to reserve mupirocin for treatment of nasal carriage of *S. aureus* in specific patient groups. (3,16) In a meta-analysis of three randomised trials, (17) the overall clinical effect of fusidic acid cream in impetigo patients was equal to mupirocin, but its effectiveness has never been assessed in comparison with placebo. The cost of fusidic acid compares favourably with that of mupirocin.

The present study compares the effectiveness of fusidic acid cream and placebo cream, both superimposed on a disinfecting treatment with povidon-iodine, in the treatment of impetigo in children. Our hypothesis was that fusidic acid cream would not improve the treatment effect of povidon-iodine.

Methods

Participants

General practitioners (GPs) in the Greater Rotterdam area were asked to report patients aged 0-12 years with nonbullous impetigo presenting at their surgery. Exclusion criteria were: immunocompromised patients, patients with extensive lesions (estimated surface more than 5 hand palms of the child = 5% of the total skin surface), deeper skin

structure infections, temperature >38.5°C, use of topical or systemic antibiotics in the previous 48 hours, hypersensitivity to povidon-iodine, hyperthyroidism, and absence of informed consent.

The GP notified the research nurse, who visited the children at home for an inclusion visit, usually the same day. The following data were recorded: duration of impetigo, nature of the lesions (redness, crusts, pustules and painfulness), number of lesions, their localisation and estimated area, body temperature, presence of regional lymphadenopathy, recent use of antibiotics, demographic data, and pre-existence of eczema. After written informed consent, inclusion took place, a bacterial swab of the lesions was taken, and the treatment regimen was started. The Medical Ethics Committee of the Erasmus University Rotterdam and University Hospital Rotterdam approved the trial protocol.

Interventions

The lesions had to be washed gently with povidon-iodine shampoo, 75 mg/ml, (Betadine® shampoo, ASTA, Diemen, The Netherlands) twice daily, in the morning and the evening. The study cream had to be applied three times a day (after the disinfecting, and once in between at midday). The study cream was either 2% fusidic acid cream (Fucidin®, Leo Pharmaceutical Products BV, Weesp, The Netherlands), or placebo. The placebo cream contained 13.5 g vaseline-cetomacrogol cream, 8.25 g glycerol 85%, 0.03 g sorbic acid, and aqua destillata up to 30 g. Patients were advised to use the study cream for maximal 14 days, or until the lesions had disappeared. Common hygienic measures were advised (cutting nails short, use of personal towels).

Evaluation visits by the research nurse at the home were scheduled at 7, 14 and 28 days after the start of treatment. Data were recorded on clinical cure, compliance, use of co-medication, protocol violation, school absenteeism, and side effects. A swab for bacterial culture of the lesions was performed if still present. If GPs wanted to prescribe other medication such as oral antibiotics, because the impetigo worsened or did not improve, they were free to do so, but all were encouraged to comply with the study protocol for at least the first week. Whenever the patient withdrew from the protocol regimen, the evaluation visits were performed as planned.

Assignment and masking

The placebo cream, composed by the pharmacist, was tested and showed no difference in colour, smell, or consistency from the fusidic acid cream. An independent statistician provided a computer-generated list of random set numbers in permuted blocks of six. The hospital pharmacist packed the study medication in identical blank tubes with a code number according to the randomisation list. The patients were randomised blockwise and stratified for presence of pre-existent eczema at the site of the impetigo.

During the inclusion visit patients were allocated by the research nurse, who was unaware of the treatment allocation, to the first available number of study cream in the corresponding block. The code number list was kept in a sealed envelope by the pharmacist, who was not involved in outcome assessment or analysis. Unblinding took place after the primary statistical analysis had taken place.

Outcomes

Primary outcome measures were clinical cure, improvement, size of affected area and bacterial cure, after 7, 14 and 28 days, as assessed by the research nurse. Clinical cure was defined as the complete absence of lesions or the lesions having become completely dry and without crusts. Remaining local redness of intact skin was acceptable. In case of incomplete cure, number, localisation and size of the affected area of the persisting lesions were recorded. The size of the affected area was estimated by comparing the size of the actual lesions with a range of examples with different exactly measured areas on paper. Improvement was defined as a decline in area and/or number of lesions. Bacterial cure was defined as the elimination of the causative pathogen(s) in persisting lesions or the unavailability of a swab, in case lesions were cured. Adverse effects were secondary outcome measures. We considered baseline characteristics, causative pathogen and resistance of the pathogen to fusidic acid at baseline as possible confounders.

Microbiological procedures

Wound swabs specimens were obtained using sterile cotton-wool swabs (Transwab, Medical Wire & Equipment Co. Ltd., Corsham, UK). The largest five wound lesions were swabbed with one swab by gently rubbing the wound surface. The swabs were immediately placed in Stuart's transport medium and kept at 4°C until inoculation (within 24 hours). Swabs were cultured semi-quantitatively on Columbia blood agar plates, which were incubated anaerobically (CBA) (Becton-Dickinson BV, Etten-Leur, The Netherlands), phenol-red mannitol salt agar (PHMA) and phenol-red mannitol salt broth (PHMB). (18) Identification of bacteria was done according to accepted international standards, based upon colony morphology on the CBA and PHMA. (19) Suspected colonies were cultured overnight on CBA. A catalase test and a latex agglutination test (Staphaurex Plus®, Murex, Dartford, UK) were then performed. Antisera to the Lancefield groups A, B, C, F and G cell wall carbohydrates (PathoDx, Strep Grouping latex agglutination kit, DPC, Los Angeles, USA) were used to identify ß-haemolytic streptococci. All isolates were stored at –70°C in glycerol containing liquid media. Vitek II equipment (bioMerieux Vitek, Hazelwood, Mo., USA) was used for susceptibility testing of *S. aureus* isolates. Mupirocin susceptibility was tested using disk diffusion. (22) The panel of antibiotics for staphylococci consisted of erythromycin, fusidic acid and mupirocin. Strains were categorised as resistant (R), intermediately sensitive (I), or

sensitive (S) to the antibiotic used following the guidelines of the National Committee for Clinical Laboratory Standards.(20,21)

Statistical analysis

The results were analysed by both intention to treat and per protocol. Crude and adjusted odds ratios were calculated for dichotomous outcome measures by means of logistic regression analysis. Baseline characteristics which had at least a weak relation ($p<0.25$) with the outcome variable in univariate logistic regression analyses were considered as potentially adjusting variables. If continuous baseline characteristics appeared to have a non-linear relationship with the outcome variable, we transformed these into categorical variables with two or three levels. A forward selection procedure (Wald) determined which adjusting variables entered the final multivariate model. For the change in affected area, a continuous outcome, a similar procedure was performed by linear regression analysis with the logarithm of the ratio of the area of the lesions at three visits and the area at baseline as dependent variable. With a postulated spontaneous cure of 50% at 7 days, and a detectable absolute difference of 25% in the treatment group, with alpha 0.05 and beta 0.10, the planned study population was 85 children in each group.

Results

From February 1999 until November 2000, 58 GPs reported 184 cases of children with impetigo. After the inclusion visit of the research nurse, 160 children were included and randomised (Figure 1). The groups were comparable with respect to baseline characteristics (Table 1). Non-Dutch patients predominantly were from Turkish and Moroccan origin, reflecting the population distribution in the catchment area.

As the number of evaluation visits that was missing was very small and similar between both groups (Figure 1), we decided not to impute data but exclude these children from the analysis for that particular evaluation moment.

For the intention to treat analysis the proportion of children cured clinically at 1 week was 55% in the fusidic acid cream group and 13% in the placebo group, resulting in a number needed to treat of 2.3. At 2 weeks and 4 weeks, the results were still in favour of fusidic acid, but with smaller differences and no longer significant (Tables 2 and 3). The final multivariate model comprised, apart from treatment the size of the affected area (adjusted OR=12.6, (5.0-31.5)). Clinical improvement and cure combined yielded a crude OR of 5.2 (fusidic acid versus placebo); this hardly changed after adjustment. The mean affected area declined steadily in the fusidic acid group, whereas in the placebo

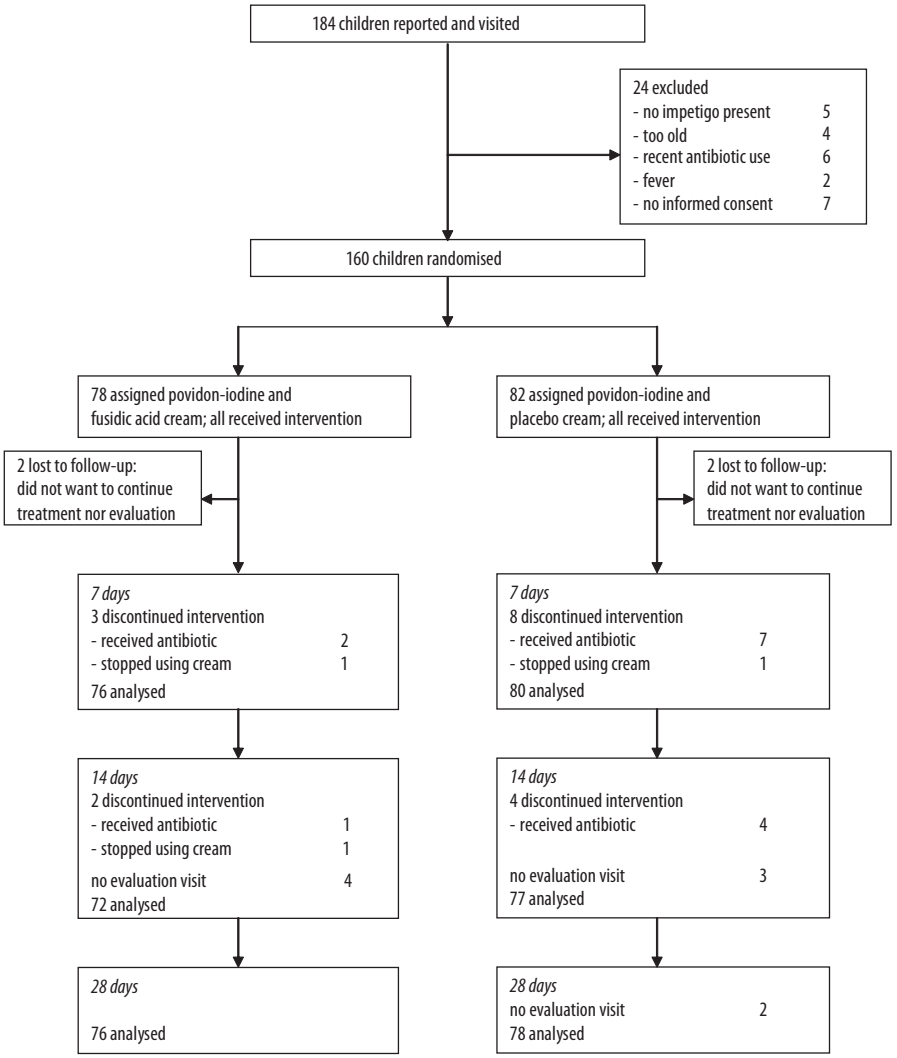

Figure 1. Participant flow and follow-up

group the mean affected area had increased after one week treatment (Table 4). No difference was found between children with and without eczema.

Non-compliance

In the first week, 3 patients in the fusidic acid cream group and 8 patients in the placebo group did not comply with the treatment protocol. Nine patients, of whom 7 in the placebo group, had received an antibiotic treatment from their GP and stopped using the study cream, in most cases because the impetigo had worsened or had not improved. Two patients, one in each group, had stopped using their study cream before

Table 1. Baseline characteristics of the study population (n=160)

	Fusidic acid cream (n=78)	**Placebo cream (n=82)**
mean age (years)	4.8 (sd 2.9)	5.1 (sd 2.7)
sex (male)	47 (60%)	51 (62%)
ethnicity (% Dutch)	47 (60%)	48 (59%)
attending daycare or school	59 (76%)	66 (80%)
mean number of lesions	11.4 (sd 13.3)	13.2 (sd 14.5)
mean affected area (cm^2)	5.6 (sd 7.3)	7.3 (sd 11.4)
mean body temperature (°C)	36.5 (sd 0.7)	36.6 (sd 0.7)
lymphadenopathy	32 (41%)	25 (30%)
mean duration of impetigo (days)	9.6 (sd 8.0)	9.2 (sd 10.2)
localisation		
head	61 (78%)	61 (74%)
trunk	22 (28%)	29 (35%)
limbs	36 (46%)	33 (40%)
preexistent eczema	10 (13%)	12 (15%)
pathogen isolated		
Staphylococcus aureus	66 (85%)	61 (74%)
Streptococcus pyogenes (A)	1 (1%)	4 (5%)
Both	1 (1%)	7 (9%)
None	10 (13%)	10 (12%)
fusidic acid resistance S. aureus		
resistant	0/67 (0%)	0/68 (0%)
intermediately sensitive	3/67 (4%)	7/68 (10%)
sensitive	64/67 (96%)	61/68 (90%)
mupirocin resistance S. aureus	1/67 (1%)	0/68 (0%)
erythromycin resistance S. aureus	6/67 (9%)	8/68 (12%)

the impetigo was cured but had not used any other treatment. Minor violations such as omission of a single iodine or study cream application were recorded in 14 cases (not in table). In the second week, another 5 patients had received extra antibiotic treatment: 4 in the placebo group and 1 in the fusidic acid group.

Side effects

Side effects were experienced in 26 cases; 7 occurred in the fusidic acid group and 19 in the placebo group. The most frequent side effects were pain (2 in the fusidic acid group versus 6 in placebo group) and burning (1 vs. 4) during administration of the povidon-iodine shampoo. Other side effects were redness (2 in each group), burning

Table 2. Clinical effect and bacterial cure (intention to treat analysis)

	Fusidic acid cream (n=76)	Placebo cream (n=80)
7 days Clinical effect		
- cure	42/76 (55%)	10/80 (13%)
- improvement	25/76 (32%)	37/80 (46%)
- failure	9/76 (11%)	33/80 (41%)
Bacterial cure	63/69 (91%)	23/72 (32%)
14 days Clinical effect		
- cure	53/72 (73%)	46/77 (60%)
- improvement	17/72 (23%)	20/77 (26%)
- failure	2/72 (3%)	11/77 (14%)
Bacterial cure	62/70 (89%)	52/70 (74%)
28 days Clinical effect		
- cure	70/76 (92%)	69/78 (88%)
- improvement	5/76 (7%)	7/78 (9%)
- failure	1/76 (1%)	2/78 (3%)
Bacterial cure	71/75 (95%)	70/75 (93%)

from the study cream (1 in placebo group), itching from both applications (2 in placebo group), pain and irritation from both applications (1 in each group).

Bacteriological results

For all baseline visits and 431 of the 459 follow-up visits (94%) swabs were available or lesions were cured. *S. aureus* was found in 135 of the 140 positive cultures at baseline (96%, Table 1), *S. pyogenes* and mixed infections were found in a minority of cases. Within the group of staphylococci, no strain was found resistant to fusidic acid. Ten of the 140 strains were intermediately sensitive to fusidic acid. At baseline, 20 (12.5%) of the 160 swab cultures showed no bacterial growth.

In the intention to treat analysis, the proportion of children with bacterial cure at 1 week was 91% in the fusidic acid group versus 32% in the placebo group (tables 2 and 3).

Discussion

This is the first study that compares fusidic acid cream to placebo in the treatment of impetigo. It demonstrates that application of fusidic acid cream in combination with povidon-iodine shampoo is far more effective than placebo cream combined with povidon-iodine shampoo.

The treatment effect of fusidic acid cream versus placebo is even larger after adjustment for confounders. After two and four weeks, the differences between the two treatments are smaller and no longer significant. Apart from the possibly spontaneous course of

Table 3. Results of logistic regression analyses

Clinical cure

Odds ratios (95%-CI*) fusidic acid cream (F) versus placebo (P)

	Intention to treat analysis		**Per protocol analysis**	
Outcome	**Cured**	**Cured or improved**	**Cured**	**Cured or improved**
7 days				
- crude	8.7 (3.9 - 19.3) 12.6 (5.0	5.3 (2.3 – 11.9)	8.5 (3.6 - 19.1) 3.0 (5.0	5.2 (2.2 - 12.4)
- adjusted	- 31.5)	5.5 (2.3 – 13.4)	- 33.8)	5.2 (2.2 - 12.4)
	(n=76/80) (F/P)		(n=73/72) (F/P)	
14 days				
- crude	1.9 (0.9 - 3.8)	5.8 (1.2 – 27.3)	1.8 (0.8 - 3.6)	4.6 (0.9 - 22.7)
- adjusted	1.9 (0.8 - 4.1)	5.2 (1.1 – 24.9)	1.9 (0.8 - 4.7)	4.1 (0.8 - 21.9)
	(n=72/77) (F/P)		(n=68/65) (F/P)	
28 days				
- crude	1.5 (0.5 - 4.5)	2.0 (0.2 – 22.2)	1.1 (0.3 – 3.5)	1.1 (0.1 - 17.6)
- adjusted	1.8 (0.5 - 5.9)	2.3 (0.1 – 50.5)	1.1 (0.3 – 3.7)	1.7 (0.0 - 26.6)
	(n=76/78) (F/P)		(n=71/66) (F/P)	

Bacterial cure

Odds ratios (95% CI*) fusidic acid cream versus placebo

	Intention to treat analysis	Per protocol analysis
7 days		
- crude	22.4 (8.5 – 59.2)	23.9 (8.4 – 68.0)
- adjusted	28.3 (9.5 – 84.7)	43.9 (13.1 – 147.1)
	(n=69/72) (F/P)	(n=70/63) (F/P)
14 days		
- crude	2.7 (1.1 – 6.7)	2.4 (0.9 – 6.6)
- adjusted	2.9 (1.1 – 7.8)	2.8 (0.9 – 8.1)
	(n=70/70) (F/P)	(n=66/58) (F/P)
28 days		
- crude	1.3 (0.3 – 4.9)	0.5 (0.1 – 3.1)
- adjusted	1.1 (0.3 – 4.4)	0.4 (0.1 – 2.7)
	(n=75/75) (F/P)	(n=70/63) (F/P)

*95% confidence interval

impetigo, this was probably caused by the fact that more patients in the placebo group had "crossover treatment" with antibiotics. Fourteen percent of the patients in the placebo group versus 4% in the fusidic acid group returned to their GP because of therapy failure and received an extra, usually oral, antibiotic treatment.

Table 4. Mean change in size of affected area

	fusidic acid cream	placebo cream	adjusted p-value (intention to treat analysis)
7 days	− 66%	+ 27%	<0.001
14 days	− 90%	− 38%	0.24
28 days	− 99%	− 95%	0.67

affected area at baseline = 100%

Our hypothesis that fusidic acid cream would not increase the treatment effect of disinfecting with povidon-iodine is firmly rejected. Conservative treatment with disinfecting alone finds no justification from these results.

Treatment with povidon-iodine combined with placebo cream had a very disappointing cure rate of 13% at 1 week. The mean affected area after one week of treatment was even larger than at the start of treatment. Also, the administration of the povidon-iodine more often caused pain and burning in the placebo group, which may be explained by prolonged healing of the lesions in this group. The relatively low cure rates in this study and the reported side effects raise questions about the value of povidon-iodine as an adjunctive therapy in the treatment of impetigo. Doubts have already been raised about the value of other disinfecting measures in the treatment of impetigo. (6,23,24) Future studies comparing povidon-iodine with placebo may provide more evidence.

At baseline, there was a small number of negative swab results (12.5%). Because the study object was the patient with a clinical diagnosis of impetigo, this was no reason to exclude these patients. *S. aureus* was the most frequently found pathogen, which is in accordance with other investigations showing that, in the last decades, the predominant organism in impetigo has changed from *S. pyogenes* to *S. aureus*.(1,11) Resistance against fusidic acid was not found in our study population, indicating that many years of use of topical fusidic acid has not resulted in significant resistance in staphylococci in the general population. The resistance against erythromycin in staphylococci was higher, in accordance with the international trend. Although in many countries oral antibiotics are used for impetigo, this latter finding provides an extra argument for topical treatment with fusidic acid cream.

Comparing fusidic acid and mupirocin, their effectiveness in the treatment of impetigo was shown to be equal in our previous meta-analysis;(17) however, the costs of fusidic acid are lower. As mentioned in the introduction, regional antibiotic policies may differ in restricting the use of one of the two. (3,5,16)

We conclude that topical fusidic acid cream is an effective treatment for impetigo, with very few side effects, and can be a first choice in the treatment of impetigo in general practice. The value of sole or adjunctive treatment with povidon-iodine can be questioned.

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3

Association of severity of impetigo in children with genetic markers in Staphylococcus aureus

Koning S, van Belkum A, Snijders S, van Leeuwen W, Verbrugh H, Nouwen J, Op 't Veld M, van Suijlekom-Smit LW, van der Wouden JC, Verduin C. Severity of nonbullous Staphylococcus aureus impetigo in children is associated with strains harboring genetic markers for exfoliative toxin B, Panton-Valentine leukocidin, and the multidrug resistance plasmid pSK41. Journal of Clinical Microbiology 2003;41:3017-21.

Abstract

Non-bullous impetigo is a common skin infection in children, frequently caused by *Staphylococcus aureus*. Staphylococcal toxins and especially exfoliative toxin A (ETA) are known mediators of bullous impetigo in children. It is not known whether this is also true for non-bullous impetigo. We set out to analyze clonality among clinical isolates of *S. aureus* from children with non-bullous impetigo, living in a restricted geographical area in The Netherlands. We investigated whether staphylococcal nasal carriage and the nature of the staphylococcal strains were associated with severity and course of impetigo. Bacterial isolates were obtained from the nose and wound of children suffering from impetigo. Strains were genetically characterized by pulsed field gel electrophoresis-mediated typing (PFGE) and binary typing which also assessed toxin gene content. In addition, a detailed clinical questionnaire was filled in by each of the participating patients. Staphylococcal nasal carriage seems to predispose to the development of impetigo and 34% of infections diagnosed in the Rotterdam area are caused by one clonal type of *S. aureus*. The *S. aureus* strains harbor the exfoliative toxin B (ETB) gene as a specific virulence factor. Especially the number ($p=0.002$) and size ($p<0.001$) of the lesions were increased in case of infection by an ETB-positive strain. Additional predictors for disease severity and development could be identified. The presence of a staphylococcal plasmid encoding multiple antibiotic resistance traits as detected by binary typing was associated with a reduction in cure rate. Our results recognize that a combination of staphylococcal virulence and resistance genes rather than a single gene determines the development and course of non-bullous impetigo. The identification of these microbial genetic markers, that are predictive for severity and course of the disease, will facilitate guided individualized anti-microbial therapy in the future.

Introduction

Over the past years the prevalence of streptococci as a leading cause of impetigo has dropped, whereas *Staphylococcus aureus* has become the most common causative microbial pathogen of this prevalent childhood disease [7, 8, 23]. Usually, *S. aureus* is encountered as nasal commensal, but the bacteria may ultimately induce a broad variety of skin infections. This suggests that staphylococcal carriage predisposes to the development of impetigo [14, 25]. Fortunately, the vast majority of these *S. aureus* strains is still broadly susceptible to antibiotics such as fusidic acid or mupirocin [15, 19, 26].

S. aureus toxins are considered to be the main effector molecules in a wide variety of childhood exanthemas. The clinical presentation is often due to the effect of various cytokines induced as a consequence of the infection process and a variety of disease mechanisms have been postulated [20, 22]. Recently, it was discovered that the staphylococcal exfoliative toxin A hydrolyses human desmoglein-1 [1]. The destruction of this important structural skin protein leads to the development of blisters below the stratum corneum, possibly facilitating bacterial proliferation beneath the physical skin barrier. Novel therapies may be based on these important findings. Consequently, there is a need for versatile laboratory systems enabling the direct or indirect detection of toxins and other virulence factors of clinical isolates of *S. aureus* [16]. However, one has to realize that the mere presence of a certain gene does not prove its causality in disease. Establishing the latter requires detailed clinical studies in addition to molecular diagnostics.

We recently performed a double blind, randomized, placebo-controlled trial into the clinical effectiveness of fusidic acid cream in the treatment of impetigo diagnosed among children in general practice [15]. It showed that fusidic acid cream treatment significantly accelerated to clinical and bacteriological cure of the infection and that the main cause of impetigo was *S. aureus*. In the present study we have set out to analyze gene and genome variability among the clinical isolates of *S. aureus* found at enrollment of the trial (before treatment), using pulsed field gel electrophoresis-mediated typing and a novel binary typing protocol. We assessed the presence or absence of toxin encoding genes in the strains and investigated whether the virulence gene potential of the staphylococcal strains involved and staphylococcal nasal carriage per se were associated with severity and course of the impetigo.

Materials and Methods

Bacterial isolates and clinical data collection

Koning *et al* described the isolation *S. aureus* strains from children affected by impetigo in the Rotterdam region (The Netherlands) [15]. Bacterial swabs were obtained from the nose, being the prime ecological niche for *S. aureus*, and from the impetigo wound. All samples were obtained at the inclusion home visit by a trained research nurse. Ninety eight *S. aureus* strains were analyzed by PFGE and extended binary typing (see below). For all patients (n=98) the following clinical parameters were recorded: number of lesions, location of the lesion, surface area of the lesion, temperature, lymphadenopathy (defined positive once palpable enlargement of the concerned regional lymph nodes was obvious), encrustation of the wound, presence of pustules, duration of infection and swimming habits. In addition, we recorded age, sex, ethnicity, quality of living environment and kindergarten attendance. We also investigated the relationship between virulence gene markers of the *S. aureus* strains and the course of impetigo, focussing on clinical and bacterial cure one week after inclusion and start of therapy. Clinical cure was defined as the complete absence of lesions or the lesions having become dry without crusts. Bacterial cure was defined as the absence of *S. aureus* strains at the lesion. The medical ethical committee of the Erasmus MC approved the trial protocol and informed consent was obtained from patients and parents. In case patients withdrew from the study protocol, evaluation visits were still carried out as scheduled.

PFGE analysis

PFGE analysis for *S. aureus* was performed according to established protocols [27]. The electrophoresis was performed in CHEF mappers (BioRad, Veenendaal, The Netherlands) using a 20-hour program consisting of two switching blocks (10 h 5-15 sec; 10 h 15-45 sec). The buffer system consisted of 1xTBE, whereas the temperature was kept constant at 14°C. DNA macro-restriction fragment-containing blocks were prepared by embedding *S. aureus* cells and treating these *in situ* with lysostaphin (Sigma, Steinheim, Germany), proteinase K (Sigma) and *Sma*I (Boehringer, Mannheim, Germany). For size determination, reference samples containing phage concatemeric DNA (BioRad) were included in all gels. After PFGE, gels were stained using ethidium bromide and photographed. Interpretation of the banding patterns was performed visually and types were assigned as suggested by Tenover *et al* [24]. In short, banding patterns differing in less than three band positions were assigned the same overall type, subtypes were identified by numbering.

Extended binary typing

Binary typing (BT) of the *S. aureus* strains was performed using the system as developed by Van Leeuwen *et al* [28]. Twelve strain-selective probes were immobilized on nylon strips and reversed hybridization with chemically labeled staphylococcal DNA was performed. Signals were recorded after staining and a 1 or 0 binary score was deduced for each of the probes, resulting in a twelve digit 1/0 genotype for each of the strains. This classical approach employs 12 BT probes (BIN 1-9, BIN11, BIN14 and BIN15), which are homologous to unknown regions in the staphylococcal genome (BIN 7), a hypothetical but not yet identified gene (BIN 2, 5, 8 and 15), the Panton-Valentine leukocidin gene (BIN 1), a repetitive motif (BIN 3), a pSK41-like multi-resistance encoding plasmid (BIN 4), the phiSLT bacteriophage (BIN 6), the intergenic region between a tRNA synthetase and an amino acid permease (BIN 9), the 3-hydrocyacyl-CoA dehydrogenase gene (BIN 11), and the acetyl-CoA synthetase gene (BIN 14). In addition, eleven toxin gene probes were included [18]. These included enterotoxin A,B,C,D and E (SEA, SEB, SEC, SED and SEE), exfoliative toxin A and B (ETA and ETB), toxic shock syndrome toxin (TSST) and hemolysins A, B and C (HLGA, HLGB and HLGC). All probes were generated by PCR. The validity of the results obtained with this approach was verified by including *S. aureus* strains with a phenotypically determined toxin production pattern as positive controls (results not shown). The latter strains were obtained from Drs. Max Heck and Wim Wannet (State Institute of Public Health and the Environment, Department of Infectious Disease Epidemiology, Bilthoven, The Netherlands)

Statistical analyses

For pair-wise comparisons, Fisher's exact tests were performed using 2x2 contingency tables. Two-sided p-values were considered significant once they were <0.05. Numerical analyses were performed using ANOVA. The relationship between gene markers and course of disease was tested both univariately and through step-wise logistic regression analysis. In the multivariate analysis, baseline characteristics and treatment modality (fusidic acid cream or placebo) were included in the analysis.

Results

Genotyping of the bacterial isolates

Ninety eight *S. aureus* isolates from the wound of as many patients, obtained at their inclusion visit, were genetically characterized by PFGE and BT. A novel genotype was defined upon three or more band differences in the PFGE pattern, which was always accompanied by at least two differences in the BT outcome. Overall, among these strains, 67 different genotypes could be identified. Thirty-nine strains were identified

as belonging to one single clone identified by similarity in the PFGE banding patterns [24]. This clone was given the code 8. BT confirmed the existence of the clonal type as defined by PFGE and the binary probes BIN 1-4 identified most of the genetic heterogeneity between PFGE-type 8 and non-type 8 (diverse) strains. For all of the binary codes in the clone 8 group (except for those obtained by BIN2, BIN3 and BIN7) exceptions to the consensus code were found. This corroborates the genetic micro-heterogeneity already detected by PFGE and confirms that the BIN probes originate from intrinsically unstable regions in the *S. aureus* genome. We were unable to document significant geographic clustering of clones within the Rotterdam area (results not shown).

Toxin gene detection

The hemolysin A-C genes were present in essentially all of the *S. aureus* strains isolated during the Rotterdam impetigo study. The enterotoxin A, D and E genes, in contrast, were rare. Furthermore, not all of the clone 8 strains were identical with respect to their toxin gene potential. When clonal isolates were compared to the other (genetically diverse) strains, the presence of exfoliative toxin B and enterotoxin C and the absence of the toxic shock syndrome toxin appeared to be specific for the clonal isolates.

Nasal carriage and clinical characteristics

Out of the patients for whom nasal cultures were available, 79% showed nasal colonization by *S. aureus* during the inclusion visit. When strain identity was assessed pair-wise for each of the patients at the time of presentation, 75% had the same strain in the nose and the wound. The Table summarizes the data obtained by statistical comparison of bacterial and clinical characteristics. Presence of a given bacterial characteristic was not related to sex, ethnicity, occurrence of lesions on the head or the limbs, sensations of pain, frequency of impetigo, pre-existing eczema, or records of boils in the family (data not shown). The table highlights the characteristics that are statistically significant when the clinical signs are compared to strains harboring or lacking a given BT-probed gene. All 111 strains derived from wounds for which both BT and toxin detection was available were included in the survey, irrespective of their genotype (clone 8-related and genetically heterogeneous strains). In order to circumvent clone 8 induced bias, the same statistical exercise was repeated for the strains harboring non-clone 8 genotypes. The boxed figures in the table highlight those parameters that retained significance upon re-analysis. These will be discussed in more detail below.

A major marker for disease severity was the presence of the bacterial exfoliative toxin B gene (ETB) (see Table). Especially the number of lesions observed and the total surface size of the lesions were highly significantly associated with ETB presence. Also the BT probes BIN1 (homologous to the Panton-Valentine leukocidin gene) and BIN4 (pSK41-like multi-resistance encoding plasmid) seemed to be predictors for severity of

Table. Association between virulence gene markers of *Staphylococcus aureus* strains cultured at inclusion of patients in a randomized placebo controlled study on the efficacy of fusidic acid and clinical and demographic features of children suffering from impetigo.

	SEC	SED	SEE	ETA	ETB	TSST	BIN 1 (PVL)	BIN 2 (hyp. gene)	BIN 4 (pSK41)	BIN 8 (hyp. gene)
Age	<0.001 2.8-5.5 yr				<0.001 6.8-4.2 yr		0.001 6.1-4.3 yr		0.002 5.9-4.2 yr	
Duration at 1st visit						0.02 13.8-8.7days				
Number of lesions					0.002 17.7-9.9		0.03 15.4-10.1		0.003 15.9-8.8	
Surface of lesion					<0.001 11.6-3.9 cm^2		0.001 9.3-4.2cm^2		0.003 8.7-4.0 cm^2	
Lymphadenopathy		0.03 100-39%			0.003 20-53%	0.03 73-37%	0.04 30-51%			
Temperature (°C)				0.01 36.1-36.6°						
Encrustation										0.03 95-60%
Pustula	0.02 41-16%	0.02 75-18%					0.05 12-26%	0.03 50-17%		
Lesions on trunk					0.005 51-24%					0.04 31-80%
Familiy members or peers infected					0.005 35-12%					
Living in old house			0.03 100-34%							
Kindergarten attendance					0.005 5-27%		0.001 6-31%			
Kindergarten attendance and age >4 years	0.02 53-80%	0.04 25-78%			0.05 87-70%				0.02 85-66%	
Swimming habit					0.03 68-46%			0.03 27-57%	0.04 62-43%	

NB: N = 98 combinations of completely typed *S. aureus* strains together with a full complement of patient information. The pairs of figures listed indicate the average value of the parameters investigated for the patients harbouring strains including the markers versus those that do not. In case of the surface of lesions, for instance, the average lesion size was 11.6 square centimeters for patients infected with a ETB positive strains, whereas for patients infected with an ETB negative strain the surface of the lesion averaged 3.9 square centimeters. Only statistically significant figures were included in the table, no association with any of the listed disease parameters was found for the genes encoding SEA, SEB, HLGA, HLGB, HLGC and the BIN probes 2, 3, 5-7, 11, 14 and 15. Pairs of figures indicate the probe-positive (left) versus the probe negative (right) results. P values that are boxed retained significance upon exclusion of the clone-8 PFGE types of S. aureus. PVL = Panton-Valentine leukocidin; pSK41: multi resistance encoding plasmid pSK41; hyp. gene: hypothetical gene segment.

infection. Apparently, a strain harboring ETB, BIN1 and BIN4 showed strong disease inducing potential, probably due to the combined presence of virulence and antibiotic resistance genes. For ETB and BIN1 this finding was corroborated by absence of lymphadenopathy. The association between carriage of the ETB positive staphylococci and kindergarten attendance disappeared upon elimination of clonal type 8 strains from the analysis. Some additional conclusions can be drawn from the table. The presence of the genes encoding toxins SEC and SED predisposed to pustule formation. Strains harboring these genes did not seem to be spreading through kindergarten-associated infection. Furthermore, different age groups were colonized by different types of *S. aureus*. Finally, BIN8 associated with wound encrustation. Although the BIN8 nucleotide sequence corresponds to that of a currently ill-defined gene in the *S. aureus* chromosome to which a function has not yet been attributed, the observed association with impetigo implies that additional research into the precise nature of this potential virulence gene is warranted. BIN2, matching another hypothetical gene, seems to associate with pustule formation. Again, further studies into the nature of this gene are urgently required. Multivariate analysis showed that ETB was the clinically most relevant predictor of disease severity.

Relation with cure

None of the univariate relationships between gene markers and clinical cure after one week reached statistical significance, nor did nasal staphylococcal carriage. In stepwise multivariate logistic regression analysis, apart from treatment modality, only BIN4 contributed significantly ($\beta = -1.68$, $p = 0.005$), with a lower cure rate for patients that were infected by BIN4-positive strains. For bacterial cure after one week (data available for 88 patients) the presence of ETB and BIN8 positive strains turned out to be statistically related. When ETB was present, 40% of the patients were cured after one week, whereas in the absence of the gene 60% were cured ($\chi^2 = 5.25$, $df = 1$, $p = 0.03$). When strains were positive for BIN8 (which was the case in 84 out of 88 children) 60% cured within a week. Of the four patients with a BIN8 negative strain none were cured ($\chi^2 = 5.51$, $df = 1$, $p = 0.03$). In the regression analysis, apart from treatment modality, only BIN7 contributed to some extent, but this was not statistically significant.

Discussion

Nasal carriage of *S. aureus* is an important predisposing factor towards the development of staphylococcal infections [14]. The carriage rate of 79% in our impetigo patients exceeds the average carriage values found in many other studies, suggesting that *S. aureus* carriage predisposes to the development of impetigo. However, the ultimate

proof for this should be based upon prospective studies since our study design does not enable the distinction between cause and consequence. Based on the current data set it is not possible to definitely conclude that nasal carriage precedes skin infection. This would have required sequential bacterial cultivation prior to impetigo development. This is an impracticable approach.

The toxin gene repertoire of a given *S. aureus* strain has been suggested to be an important denominator for the strains' capacity to induce skin disease [3, 6, 17, 21]. Especially the antigenically distinct subtypes of the staphylococcal exfoliative toxins A and B are putatively involved in the development of bullous impetigo. Previous Japanese studies have demonstrated that approximately 70% of all clinical isolates produced either of these toxins, whereas among strains isolated from atopic dermatitis and furuncles these percentages were 3% and 0%, respectively [13]. In Japan the incidence for ETA was 57/144 (40%), for ETB 36/144 (25%) and both genes were present in 7/144 (5%) strains. Our figures were 12/98 (12%), 36/98 (37%) and 6/98 (6%), respectively. This may suggest geographical differences in gene incidence, but also that both ETA and ETB are important factors in the development and progression of impetigo. The fact that ETB may be plasmid borne probably contributes to its ease of dissemination [29]. Also in Italy, an association between exfoliative toxin gene content and impetigo was documented [4, 5]. It has to be emphasized that the figures mentioned above highlight the fact that not all *S. aureus* strains causing impetigo harbour, for instance, the ETB gene. This implies that additional factors, either or both host or pathogen derived, affect the development of impetigo. This suggests that impetigo is a multi-factorial syndrome, for which we provide evidence from at least the bacteriological viewpoint.

We here show that analogous to the already documented clinical importance of exfoliative toxin A in bullous impetigo, the structurally similar exfoliative toxin B contributes significantly to the development of non-bullous impetigo. Especially the surface and number of impetigo lesions were increased with ETB-positive infections. The epidemiological association between the presence of the bacterial gene and disease severity was very clear. Our study shows that clonal dissemination of certain bacterial genotypes is important in this respect, explaining a large proportion of disease cases. Additional clinical-microbiological markers were identified through binary typing. One of these, BIN4, displays sequence homology to one of the VRS plasmids belonging to the pSK41 family [2, 9]. How these multi-resistance encoding conjugative plasmids, harboring all requirements for gene transfer and various insertion elements, relate to severity of skin disease is currently unclear. However, its apparent relatedness with delay of cure is probably due to antibiotic resistance that is associated with this class of plasmids. For another important marker that we discovered, BIN1, the relation with disease severity is more obvious: this binary probe shares sequence homology with a Panton Valentine leukocidin located on the prophage phiPV8 [12]. The possible virulence effect of such a

molecule is obvious, as was also demonstrated in two recent studies showing increased leukocidin gene incidence among *S. aureus* strains isolated from impetigo patients [10] and general clinical isolates [11]. Moreover, Lina *et al* [17] demonstrated that this leukocidin appears to be specifically associated with necrotic lesions of the skin and mucous membranes.

In conclusion, we here show that impetigo among patients living in a geographic region of limited size can be caused both by clonally related and unrelated S. *aureus* strains. For the first time, a relation between virulence gene content and severity of impetigo has been demonstrated. Most particularly, we here demonstrate that various virulence factors are involved in impetigo and that severity of disease is most probably dependent upon the combined presence and activity of these variable factors. Independent of PFGE-defined staphylococcal clonality, bacterial toxin and virulence gene content are important in the severity and sometimes even in the course of the disease. Further improvement of microbial gene typing strategies as used here may result in prospective therapeutic intervention guided by molecular virulence assessment of the infectious agent.

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4

Interventions for impetigo
A systematic review

Koning S, Verhagen AP, van Suijlekom-Smit LWA, Morris A, Butler CC, van der Wouden JC. Interventions for impetigo (Cochrane Review). In: The Cochrane Library, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Abstract

Background

Impetigo is a common superficial bacterial skin infection, most frequently encountered in children. There is no standard therapy and guidelines for treatment differ widely. Treatment options include many different oral and topical antibiotics as well as disinfectants.

Objectives

To assess the effects of treatments for impetigo, including waiting for natural resolution.

Search strategy

We searched the Skin Group Specialised Trials Register (March 2002), Cochrane Central Register of Controlled Trials (CENTRAL, Issue 1 2002), the National Research Register (2002), MEDLINE (from 1966 to January 2003), EMBASE (from 1980 to March 2000) and LILACS (November 2001). We handsearched the Yearbook of Dermatology (1938-1966), the Yearbook of Drug Therapy (1949-1966), used reference lists of articles and contacted pharmaceutical companies.

Selection criteria

Randomised controlled trials of treatments for non-bullous and bullous, primary and secondary impetigo.

Data collection & analysis

All steps in data collection were done by two independent reviewers. We performed quality assessments and data collection in two separate stages.

Main results

We included 57 trials including 3533 participants in total which studied 20 different oral and 18 different topical treatments.

Cure or improvement

Topical antibiotics showed better cure rates than placebo (pooled odds ratio (OR) 6.49, 95% confidence interval (CI) 3.93 to 10.73), and no topical antibiotic was superior (pooled OR of mupirocin versus fusidic acid 1.76, 95% CI 0.69 to 2.16). Topical mupirocin was superior to oral erythromycin (pooled OR 1.22, 95% CI 1.05 to 2.97). In most other comparisons, topical and oral antibiotics did not show significantly different cure rates, nor did most trials comparing oral antibiotics. Penicillin was inferior to

erythromycin and cloxacillin and there is little evidence that using disinfectant solutions improves impetigo.

Side effects

The reported number of side effects was low. Oral antibiotic treatment caused more side effects, especially gastrointestinal ones, than topical treatment.

Reviewers' conclusions

Placebo controlled trials are scarce. There is little evidence about the value of disinfecting measures. There is good evidence that topical mupirocin and topical fusidic acid are equally, or more effective than oral treatment for people with limited disease. It is unclear if oral antibiotics are superior to topical antibiotics for people with extensive impetigo. Fusidic acid and mupirocin are of similar efficacy. Penicillin was not as effective as most other antibiotics. Resistance patterns against antibiotics change and should be taken into account in the choice of therapy.

Background

Biology and symptoms

Impetigo or impetigo contagiosa is a contagious superficial bacterial skin infection, most frequently encountered in children. It is typically classified as either primary impetigo or secondary impetigo. Impetigo is also classified as bullous or non-bullous impetigo. Bullous impetigo simply means that the skin eruption is characterised by bullae.

Non-bullous impetigo is the most common form of impetigo. The initial lesion is a thin-walled vesicle on previously normal skin that rapidly ruptures. It then leaves a superficial erosion covered with yellowish-brown or honey-coloured crusts. The crusts eventually dry, separate and disappear leaving a red mark that heals without scarring. The most frequently affected areas are the face and limbs. The lesions are sometimes painful. Usually, there are no systemic symptoms such as fever, malaise, or anorexia. Diagnostic confusion can occur with a variety of skin disorders including shingles, cold sores, cutaneous fungal infections and eczema (1,2).

Causes

Staphylococcus aureus is considered to be the main bacterium that causes non-bullous impetigo. However *Streptococcus pyogenes,* or both *S. pyogenes* and *S. aureus,* are sometimes isolated. In moderate climates, staphylococcal impetigo is more common, whereas in warmer and more humid climates, the streptococcal form predominates. The relative frequency of *S. aureus* infections has also changed with time (3). It was predominant in the 1940s and 1950s, after which Group A streptococci became more prevalent. In the past two decades, *S. aureus* has become more common again. Bullous impetigo is always caused by *S. aureus*.

Secondary impetigo may occur as a complication of many dermatological conditions, notably eczema. The eruption appears clinically similar to non-bullous impetigo. Usually *S. aureus* is involved. The underlying skin disease may improve with successful treatment of the impetigo and the converse may also be true.

Complications of non-bullous impetigo are rare. Local and systemic spread of infection can occur which may result in cellulitis, lymphangitis or septicaemia. Non-infectious complications of *S. pyogenes* infection include guttate psoriasis, scarlet fever and glomerulonephritis. It is thought that most cases of glomerulonephritis result from streptococcal impetigo rather than streptococcal throat infection and this has always been an important rationale for antibiotic treatment. The incidence of acute glomerulonephritis has declined rapidly over the last few decades. Baltimore stated that the risk of developing glomerulonephritis is not altered by treatment of impetigo (4); however, certain subtypes of Group A streptococci are associated with a much greater risk (5).

Epidemiology

In the Netherlands, most people with impetigo consult their general practitioner and approximately 1% of the cases are referred to a dermatologist (6). Although the incidence has declined slightly, impetigo is still a common disease, particularly in young children. In some tropical or developing countries the incidence of impetigo seems to be higher than elsewhere (7,8).

Treatment

Management options for impetigo include the following:

(1) no treatment, waiting for natural resolution, hygiene measures;
(2) topical disinfectants, such as saline, hexachlorophene, povidone-iodine and chlorhexidine;
(3) topical antibiotics, such as neomycin, bacitracin, polymyxin B, gentamycin, fusidic acid, mupirocin or topical steroid/antibiotic combination;
(4) systemic antibiotics, such as penicillin, (flu)cloxacillin, amoxicillin/clavulanic acid, erythromycin, cephalexin.

Rationale for the review

Guidelines concerning treatment vary widely. Some recommend oral antibiotic treatment, others local antibiotic treatment, or even just disinfection in mild cases (1,2,9), so doctors have many treatment options. The evidence on what works best is not clear. There is potential conflict between what is in the best interest of the individual patient, and what would best benefit the community in terms of cost and induction of antibiotic resistance.

Objectives

To assess the effects of treatments for impetigo, including waiting for natural resolution.

Criteria for considering studies for this review

Types of studies

Randomised trials.

Types of participants

People who have impetigo or impetigo contagiosa diagnosed by a doctor, and preferably confirmed by bacterial culture. The diagnosis could be either non-bullous or bullous impetigo. Studies on secondary impetigo or impetiginised dermatoses were included.

Types of interventions

Any program of topical or systemic (oral, intramuscular or intravenous) treatment, including antibiotics, disinfectants or any other intervention for impetigo, including awaiting natural response.

Primary outcome measures

(1) Cure as defined by clearance of crusts, blisters and redness as assessed by the investigator.
(2) Relief of symptoms such as pain, itching and soreness as assessed by participants.

Secondary outcomes

(1) Recurrence rate.
(2) Adverse effects such as pain, allergic sensitisation and complications.
(3) Development of bacterial resistance.

Search strategy and methods of the review

(1) Electronic databases

(a) The Cochrane Skin Group Specialised Register was searched (March 2002).
(b) The Cochrane Central Register of Controlled Trials (CENTRAL, Issue 1, 2002) and the National Research Register (2002) were both searched.
(c) MEDLINE was searched (from 1966 to January 2003).
(d) EMBASE was searched (from 1980 to March 2000).
(e) LILACS (November 2001) was searched.
(f) The *meta*Register of Controlled Trials on the Current Controlled Trials web site http://www.controlled-trials.com was searched.

We searched Medline (from 1966), Embase (from 1980), the Cochrane Controlled Trials Register (CCTR), the Cochrane Skin Register, the Meta Register of Controlled Trials on the Current Controlled Trials web site and the National Research register's MRC Clinical Trials Directory.

References from included studies including secondary review articles were checked for further studies. We searched unpublished, on-going trials, and grey literature via correspondence with authors and pharmaceutical companies. We applied no language restrictions. All randomised controlled trials comparing two different treatments were included. Blinding was not necessary. Primary outcome was cure as defined by clearance of crusts, blisters and redness as assessed by the investigator. Two reviewers

(JCvdW and SK) independently read all abstracts or citations of trials. If one of the reviewers thought the article might be relevant, a full copy of the article was acquired for further data collection. All full copy articles were independently screened by two reviewers (LvSS and SK). The articles were selected according to the earlier defined inclusion criteria. Two other independent reviewers assessed the methodological quality of the trials. In the assessment of methodological quality, the following items were addressed: randomisation procedure, allocation concealment, intention-to-treat analysis and baseline comparison of severity of disease.These criteria were applied using both the Jadad and the Delphi quality assessment lists (10,11). Studies that scored at least 50% of the maximum available scores on both lists were considered good. In those studies where the available data is sufficiently homogeneous and where a pooled estimate of the treatment effect makes sense, a meta-analysis was conducted by Peto's method (12). Odds ratios were used as effect measures for dichotomous outcomes. Two reviewers (ADM and CCB), using a pre-piloted data abstraction form, carried out the full data extraction.

Description of studies

Approximately 700 studies were identified, 221 of which were selected for full copy reading. One hundred and sixty-five of these studies did not meet the inclusion criteria. Fifty-six papers were eventually included, describing 57 trials. The studies had a total of 3533 evaluable participants, an average of 62 participants per study (see table 1). Most studied primary non-bullous impetigo. 25 trials studied patients with a range of infections, impetigo being one of them. We included these studies only if the main outcome measure was presented separately for the subgroup of impetigo patients.
Most trials were reported in the English language. Other languages included were Japanese (three), Korean, Thai, Portuguese, Spanish and Danish (one each). Some had abstracts and tables in English. Trials in Russian, German and French were among those that were excluded (not for language reasons). In instances where none of the reviewers were competent in the language of the paper, translators provided assistance.
The 57 trials evaluated 38 different treatments (20 oral treatments and 18 local treatments, both including placebo).

The most common type of comparison was between two different oral antibiotic treatments (25 studies). Cefalosporines (16 studies) and macrolide antibiotics, especially erythromycin and azithromycin (10 studies) were most often involved. A local antibiotic treatment was compared with an oral antibiotic treatment in 22 studies. Nineteen of these comparisons contained either erythromycin, mupirocin, or both. Only two trials

Table 1. Characteristics of included studies

Study	Methods	Participants	Interventions
Arata 1989a	Japan Range (13/265)	mainly S.aureus	cefdinir 100 mg, 3td cefaclor 250 mg, 3td
Arata 1989b	Japan Range (18/259)	mainly S.aureus (data for all participants)	lomefloxacin 200 mg, 3td norfloxacin 200 mg, 3td
Arredondo	Mexico city, Mexico Range (55/61)	S.aureus 67%	mupirocin ointment 2%, 3td dicloxacillin 250 mg, 4td
Barton 1987	Missouri USA only impetigo	S.aureus 35/65 Streptococcus 2/65 Both 30%	penicillin V 50 mg/kg/day in 4dd erythromycin 40 mg/kg/day in 4dd
Barton 1988	Missouri USA only impetigo	S. aureus 46/100, S. pyogenes 9/100, both 25/199.	erythromycin 40 mg/kg/day in 4dd dicloxacillin 25 mg/kg /day in 4dd
Barton 1989	Missouri USA only impetigo	S. aureus 80%	erythromycin 40 mg/kg/day in 3dd mupirocin ointment 2%, 3td
Bass	Honolulu, Hawaii only impetigo	S. aureus 41/48	Three arms: -cephalexin 50 mg/kg/day in 3 dd + placebo ointment -mupirocin ointment 2%, 3td + liquid oral placebo -bacitracin ointment 500 units/g, 3td + liquid oral placebo
Beitner	25 centres, Sweden Range (60/327)	S. aureus 86% of 327, Streptococcus 14% of 327 Included only participants who had bacteria sensitive to both drugs	cefradoxil 40 mg/kg/day, flucloxacillin tablets 750 mg, 2td, or susp 30-50 mg/kg/day in 2-3 dd
Blaszcyk	Multicenter; Europe, Latin America and Asia. Range (42/539)		clindamycin caps 150 mg, 4td clindamycin caps 300 mg, 2td dicloxacillin caps 250 mg, 4td
Britton	Portsmouth Virginia USA only impetigo	S. aureus 26/48	erythromycin 40 mg/kg/day in 4 dd + placebo cream mupirocin ointment 2%, 3td + placebo susp.
Christensen	Sweden, Germany, UK Outpatients (Germany) and GP (UK), both (Sweden) only impetigo	S.aureus 199/256, S.pyogenes 21/256, both 36/256	Hydrogen peroxide cream 1% (Microcid), 2-3 td Fusidic acid cream gel 2%, 2-3 td,
Dagan 1989	Negev region, Israel only impetigo	S. aureus 37/51, S. pyogenes 14/51	amoxicillin trihydrate syrup 40 mg/kg/day, in 3 dd amoxicillin/clavulanic acid syrup, 40+10 mg/kg/day, in 3 dd
Dagan 1992	Negev region, Israel only impetigo (bullous and non-bullous)	S. aureus 90/102, streptococci 1/3 of participants	erythromycin susp. 50 mg/kg/day 3td + placebo ointment mupirocin ointment 2% 3td + oral placebo susp.
Daniel 1991a	Belgium/France/FRG/ Netherlands/Norway/UK setting unclear Range (69/308)	All participants: S. aureus 195/308, streptococci 59/308	azithromycin 250 mg twice (day1),once daily (day2-5) erythromycin 500 mg 4td

Table 1. (Continued)

Study	Methods	Participants	Interventions
Daniel 1991b	Belgium/Germany/ Ireland/UK setting unclear Range (17/323)	All participants: S aureus 158/323, streptococci 41/323	azithromycin 250 mg twice (day1),once daily (day2-5) cloxacillin 500 mg, 4td
Demidovich	Honolulu, Hawaii only impetigo	S. aureus 45/73, GABHS 6/73, both 14/73,	penicillin V 40-50 mg/kg/day in 3 dd, cephalexin 40-50 mg/kg/day in 3 dd, erythromycin 30-40 mg/kg/day in 3 dd
Dillon	Alabama/USA only impetigo (bullous impetigo 57/70)	S. aureus: 64/70	cephalexin 50 mg/kg/day in 2 dd (>20 kg: 500mg 2td) dicloxacillin 15 mg/kg/day in 4 dd (>40 kg: 125 mg 4td)
Dux	Toronto, Canada setting unclear Range (36/149)	bacterial culture results unclear	mupirocin ointment 2%, 3 td eythromycin 250 mg, 4 td cloxacillin 250 mg, 4 td
Eells	Puerto Rico only impetigo	mainly S.aureus	mupirocin ointment 2%, 3td vehicle control, 3 td
Esterly	Milwaukee Wisconsin USA only impetigo	S.aureus 33% GABHS 12% both 41%.	mupirocin (dose NR) erythromycin (dose NR)
Fujita	Japan Range (10/204)		enoxacin 500 mg, 3td cephalexin 500 mg 2td (double dummy)
Gilbert	Quebec Canada Range (19/70)	S. aureus 41/70 Streptococci 22/70 (all pat.)	mupirocin ointment 2%, 3 td fusidic acid cream 2%, 3 td
Ginsburg	Dallas, Texas, USA only impetigo	S.aureus 78%, GABHS 64%, both 50%.	penicillin G 30 mg/kg/day in 4 dd, cefadroxil 45 mg/kg/day in 3 dd,
Goldfarb	Cleveland Ohio USA only impetigo	S.aureus 49/62, Streptococci 4/62, Both 9/62	mupirocin ointment 2%, 3td erythromycin 40 mg/kg/day in 4dd
Gonzalez	Florida USA only impetigo (bullous and non-bullous).	participants excluded if no S. aureus present	penicillin V potassium 50 mg/kg/day, in 4dd cloxacillin sodium 50 mg/kg/day, in 4 dd
Gould	Edinburgh UK general practice Range (39/107)	S. aureus 90/129, streptococci 32/129 (all participants)	mupirocin ointment 2%, once daily, placebo cream, once daily
Gratton	Montreal Quebec Canada Range (15/60)	S. aureus approx. 50%	mupirocin ointment 2%, 3 td erythromycin 250 mg, 4 td
Hains	Birmingham Alabama US only impetigo	S. aureus 35%, GABHS 12% both 54%	cefadroxil 30 mg/kg/day, max 1 g., in 1 dd cephalexin 30 mg/kg/day, max 1 g., in 2 dd
Jaffe 1985	Cleveland Ohio USA Range (32/42)	S. aureus 33/36, S. pyogenes 8/36	amoxicillin/clavulanic acid, eq. 20 mg/kg/day in 3 dd cefaclor 20 mg/kg/day in 3 dd.
Jaffe 1986	Multicenter, Wessex UK general practice Range (43/119)	S. aureus 16/34, S. pyogenes 5/34.	1% hydrocortisone+ 0.5% potassium hydroxyquinoline sulphate cream, 2td 1% hydrocortisone + 2% miconazole nitrate cream, 2td

Table 1. (Continued)

Study	Methods	Participants	Interventions
Kennedy	Bristol UK general practice only impetigo	S. aureus 23/34, S. pyogenes 10/34.	mupirocin ointment 2%, 2td neomycin ointment 1%, 2td
Kiani	multicentre USA (Southern States) admitted + outpatients Range (18/179)	S. aureus 152/179, S. pyogones 29/179 (all patients)	azithromycin 500 mg day 1, 250 mg, day 2-5 cephalexin 500 mg twice daily
Koning	Rotterdam, Netherlands general practice only impetigo	S. aureus 127/160, S. pyogenes 5/160, both 8/160, none 20/160	fusidic acid cream 2%, 3td + povidone-iodine shampoo, 2td placebo cream, 3td + povidone-iodine shampoo, 2td
Koranyi	Columbus, Ohio, USA only impetigo	S. aureus 22/30, S. pyogenes 10/30	bacitracin ointment 500 units/g, 4td + oral placebo erythromycin 250 mg 4td + placebo cream
McLinn	Scottsdale Arizona USA only impetigo	S. aureus 43/60, S. pyogenes 17/60	mupirocin ointment 2%, 3td, erythromycin 30-40/mg/kg/day in 3-4 doses
Mertz	San Juan Puerto Rico only impetigo	S. aureus 44/53, GABHS 37/53	mupirocin ointment 2%, 3td, erythromycin 30-50 mg/kg/day in 2 doses
Montero	Multicenter: Columbia Guatemala, Panama, S. Africa. Range (95/200)	S. aureus 109/200, S.pyogenes 39/200	azithromycin susp. 10 mg/kg/day once daily cefaclor susp. 20 mg/kg/day in 3 doses
Moraes Barbosa	Rio de Janeiro, Brasil only impetigo	S. aureus 100% (inclusion criterion)	Four arms: sodium fusidate ointment 2%, 3td chloramfenicol ointment, 3td, neomycin/ bacitracin ointment, 3td erythromycin oral 50 mg/kg/day, 4 dd
Morley	Plymouth/Bristol/UK general practice Range (89/354)	S. aureus 119/344, S. pyogenes 15/344, both 25/344 (all participants)	fusidic acid ointment 2%, 3td mupirocin ointment 2%, 3td
Nolting	Münster, Germany Range (66/80)	S.aureus 41/66, GABHS 8/66, both 17/66.	sulconazole nitrate cream 1%, 2td miconazole nitrate cream 2%, 2td
Park	Pusan / S-Korea only impetigo	S. aureus 90%	erythromycin 30-40 mg/kg/d fusidic acid cream 20-40 mg/kg/d cefuroxim 250 mg/day
Pruksachatkunakorn	Chiang Mai, Thailand only impetigo	S. aureus 77/110	penicillin V potassium 50 mg/kg/day in 4 dd cloxacillin sodium 50 mg/kg/day in 4 dd
Rice	Baltimore USA outpatients and general practice. Only impetigo	Culture done only in case of therapy failure.	erytromycin ethynyl succinate 40 mg/kg/day in 4 dd mupirocin ointment 2%, 3td
Rodriguez	Multicentre: Costa Rica, Guatemala, Panama, Venezuela. outpatients, Range (39/118)	S. aureus 69/118, S. pyogenes 9/118 (all participants)	Three arms: azithromycin 10 mg/kg/day (max. 500), once daily dicloxacillin12.5-25 mg/kg/day in 4 doses flucloxacillin 500-2000 mg/day in 4 doses

Table 1. (Continued)

Study	Methods	Participants	Interventions
Rojas	Dominican Republic only impetigo		mupirocin ointment 2%, 3td placebo/vehicle, 3td
Ruby	Dallas USA only impetigo	only GABHS 33/102, both S. aureus and GABHS 57/102	5 arms: phenoxymethyl penicillin 40-60,000 units/kg/day in 3 doses + HS phenoxymethyl penicillin 40-60,000 units/kg/day in 3 doses HS+ placebo placebo, 3td bacitracin ointment, 2td
Sutton	United Kingdom general practice (n=20) only impetigo (only facial)	S. aureus 68/177	fusidic acid cream 3td mupirocin ointment 3td
Tack 1997	multicentre US Range (225/394)	S. aureus 284/394 (all participants)	cefdinir 7 mg/kg/day , 2td, 10 days cephalexin 10 mg/kg/day, 4td, 10 days
Tack 1998	multicenter USA Range (62/952)	S. aureus 308/382 (all participants)	cefdinir caps 300 mg, 2td, 10 days cephalexin caps 500 mg, 4td, 10 days
Tamayo	Mexico only impetigo	S. aureus 18/30, S. pyogenes 4/30, both 1/30	rifamycin spray, 2td, 7 days mupirocin ointment 2%, 2td, 7 days
Tassler	Multicentre (Europe and S. America) hospital admitted and outpatients Range (42/172)	S. aureus 58% (all participants)	fleroxacin 400 mg, 1td, 7-21 days amoxicillin/clavulanic acid tablets 500/125 mg, 3td, 7-21 days
Vainer	Denmark general practice only impetigo	No bacterial culture done	fusidic acid cream 2% Tetracycline/polymyxin B ointment neomycin/bacitracin ointment
Wachs	multicenter USA only impetigo (secondary)	S. aureus 62/79	bethametasone valerate cream, 3td gentamycin cream, 3td bethametasone+gentamycin cream, 3td
Wainscott	London, United Kingdom outpatients and general practice Range (16/39)	S. aureus 31/48 (all participants)	mupirocin ointment 2%, 2td chlortetracycline cream 3%, 2td
Welsh	Monterrey, Mexico Range (15/60)	S. aureus 47/50	mupirocin ointment 2%, 3td ampicillin 50 mg, 4td
White	United Kingdom general practice Range (155/390)	S. aureus 43% (all participants)	mupirocin ointment 2%, 2td fusidic acid ointment 2%, 3td
Wilkinson	Quebec, Canada Range (10/50)	S. aureus 18/50 (all participants)	mupirocin 2%, 3td polymyxin B-neomycin (Neosporin), 3td

Setting: hospital outpatients, unless stated otherwise
all participants = data from all participants in the study, not just the impetigo participants;
approx = approximately;
GABHS=Group A beta Hemolytic Streptococcus;
HS=hexachlorophene scrubs;
range = study on range of skin infections, including impetigo (proportion impetigo patients of all participants);
td = times daily; m = months; yrs = years; dd=daily doses; ds = days

studied antiseptic or disinfecting treatments (Ruby; Christensen). Few placebo controlled trials were found (Eells, Gould, Koning, Rojas, Ruby). The latter is the only trial that compared an oral treatment with placebo.

Most studies were carried out in hospital out-patient clinics (paediatrics or dermatology, 49 studies), although some were carried out in general practice.
No study reported a predominantly streptococcal impetigo. The only studies not to report a preponderance of staphylococcal impetigo were Mertz 1989 and Ruby 1973 (carried out in Puerto Rico and Texas respectively).
Cure as assessed by investigator, our main outcome measure, was often not defined. Researchers sometimes combined the categories 'cured' and 'improved' and presented those participants as one group. The length of follow up varied widely and was sometimes not even specified, however we tried to retrieve the data for follow up as close as possible to seven days after the start of treatment. Bacterial resistance rate at baseline, or subsequent development of resistance was not often reported.

Methodological quality of included studies

The criteria that are used for the Delphi and Jadad quality scales are listed in Table 2. The scores given using these scales are shown in Table 3. Twelve of the 57 studies are considered "good" according to our predetermined criterion. (Bass; Blaszcyk; Britton; Dagan; Jaffe; Kiani; Koning; Koranyi; McLinn; Nolting; White).

Table 2. Quality Score: Content of Quality Score Lists

	Item
Delphi	
D1a	Was a method of randomisation performed?
D1b	Was the treatment allocation concealed?
D2	Were the groups similar at baseline concerning the most important prognostic characteristics?
D3	Were both inclusion and exclusion criteria specified?
D4	Was the outcome assessor blinded?
D5	Was the care provider blinded?
D6	Was the patient blinded?
D7	Were point estimates and measures of variability presented for primary outcome measures?
D8	Did the analysis include an intention-to-treat-analysis?
Jadad	
J1a	Was the study described as randomised?
J1b	Is the method appropriate?
J2a	Was the study described as double blind?
J2b	Is the method appropriate?
J3	Was there a description of withdrawals and drop-outs?

Table 3. Quality Score of Delphi and Jadad lists

Study	Delphi	Jadad	Study	Delphi	Jadad
Arata 1989 cef	2	2	Jaffe 1986	7	5
Arata 1989 lom	3	2	Kennedy 1984	6	2
Arredondo 1987	3	1	Kiani 1991	5	5
Barton 1987	3	4	Koning 2002	9	5
Barton 1988	3	3	Koranyi 1976	7	3
Barton 1989	2	1	McLinn 1988	5	3
Bass 1997	6	5	Mertz 1989	4	3
Beitner 1996	3	1	Montero 1996	4	2
Blaszcyk 1998	5	4	Moraes 1986	4	1
Britton 1990	8	4	Morley 1988	7	1
Christensen 1994	4	4	Nolting 1988	5	4
Dagan 1989	3	4	Park 1993	3	1
Dagan 1992	8	5	Pruksachat. 1993	3	1
Daniel 1991-1	3	3	Rice 1992	4	2
Daniel 1991-2	3	3	Rodriguez 1993	3	2
Demidovich 1990	6	1	Rojas 1985	3	1
Dillon 1983	3	3	Ruby 1973	3	3
Dux 1986	4	2	Sutton 1992	7	4
Eells 1986	3	4	Tack 1997	5	2
Esterly 1991	2	2	Tack 1998	4	4
Fujita 1984	5	3	Tamayo 1991	5	2
Gilbert 1989	4	2	Tassler 1993	4	2
Ginsburg 1978	3	1	Vainer 1986	5	2
Goldfarb 1988	3	2	Wachs 1976	5	2
Gonzalez 1989	5	2	Wainscott 1985	4	3
Gould 1984	3	4	Welsh 1987	4	2
Gratton 1987	2	1	White 1989	5	3
Hains 1989	3	2	Wilkinson 1988	3	2
Jaffe 1985	6	3			

Randomisation and selection bias

All included studies were described as randomised, as this was a selection criterion. However, most papers did not describe the method of the randomisation, so that the method could not be judged as appropriate (32 of 57). Of the papers that did describe the method, the method was usually considered appropriate (24 of 25). Only 18 of the 57 studies provided information on allocation concealment. In most cases (11 of 18), treatment allocation was not concealed.

Blinding of outcome assessment and detection bias

A minority of studies (23 of 57) was described as double blind. In only eight of these double-blinded studies, was the method considered appropriate. It was not always clear whether the patient, the care provider and the outcome assessor were all blinded.

Handling of losses and attrition bias

In some studies, high numbers lost to follow up were recorded. Only eight studies included an intention to treat analysis. For some other studies, an intention to treat analysis may be calculated from the data presented in the study. We did not construct intention to treat analyses ourselves.

Results

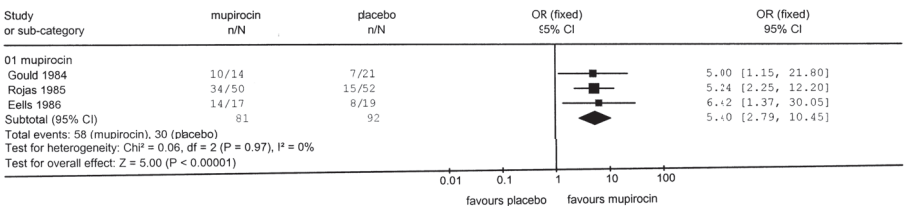
The first primary outcome was **clinical cure (or improvement)** at one week from commencement of treatment, as assessed by the investigator. The proportion of patients that were cured after one week in each study in shown in table 4.

(a) Non-bullous impetigo

(i) Topical antibiotics

Topical antibiotics versus placebo (5 studies)

Overall topical antibiotics showed better cure rates or more improvement than placebo (odds ratio (OR) 6.49, 95% confidence interval (CI) 3.93 to 10.73). This result was consistent for mupirocin (OR 5.40, 95% CI 2.79 to 10.45; 3 studies - Eells 1986; Gould 1984; Rojas 1985) (graph 1) and fusidic acid (OR 8.65, 95% CI 3.88 to 19.29; 1 study - Koning 2002). In one small study (Ruby 1973), bacitracin did not show a difference in cure rate compared with placebo (OR 3.97, 95% CI 0.15 to 104.18).



Graph 1. The squares represent the point estimates of the odds ratio of the comparison of treatment effects; the horizontal lines represent the 95% confidence intervals. The diamonds represent the pooled odds ratios and 95% confidence intervals of the studies together. When a horizontal line or diamond crosses the vertical line (odds ratio = 1), it means that the treatment effects do not differ significantly.

Topical antibiotic versus another topical antibiotic (12 studies)

No one topical antibiotic clearly showed superiority over another. There were ten different comparisons: four studies (Gilbert 1989; Morley 1988; Sutton 1992; White 1989) compared mupirocin with fusidic acid (OR 1.22, 95% CI 0.69 to 2.16, graph 2), and the remaining nine were all only represented by a single small study.

Table 4. Proportion of patients cured, of total, after one week of treatment (n/N)
2.01 Non-bullous impetigo: topical antibiotic versus placebo

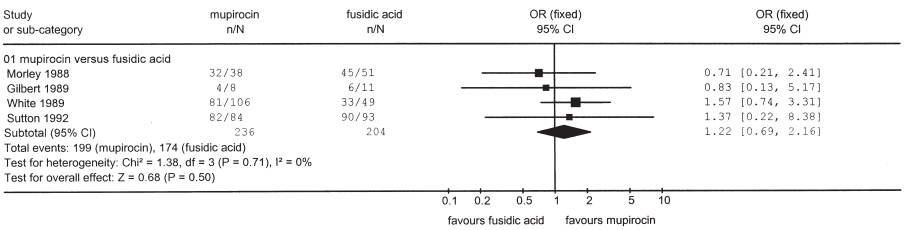
	mupirocin	placebo
Eells	14/17	8/19
Gould	10/14	7/21
Rojas	34/50	15/52

Koning	fusidic acid 42/76	placebo 10/80
Ruby	bacitracin 1/16	placebo 0/20

2.02 Non-bullous impetigo: topical antibiotic versus another topical antibiotic

	mupirocin	fusidic acid
Gilbert	4/8	6/11
Morley	32/38	45/51
Sutton	82/84	90/93
White	81/106	33/49

Tamayo	mupirocin 8/8	rifamycin 5/9
Kennedy	mupirocin 15/15	neomycin 13/17
Bass	mupirocin 6/7	bacitracin 3/9
Wainscott	mupirocin 6/6	chlortetracycline 7/8
Wilkinson	mupirocin 2/2	polymyxinB/neomycin 5/6
Vainer	fusidic acid 26/43	neomycin/bacitracin 27/41
Vainer	fusidic acid 26/43	tetracycline/polymyxin B 25/44
Nolting	sulcanozol 5/32	miconazol 1/34
Jaffe	hydrocortisone+ hydroxyquinoline 13/24	hydrocortisone +miconazole 5/19



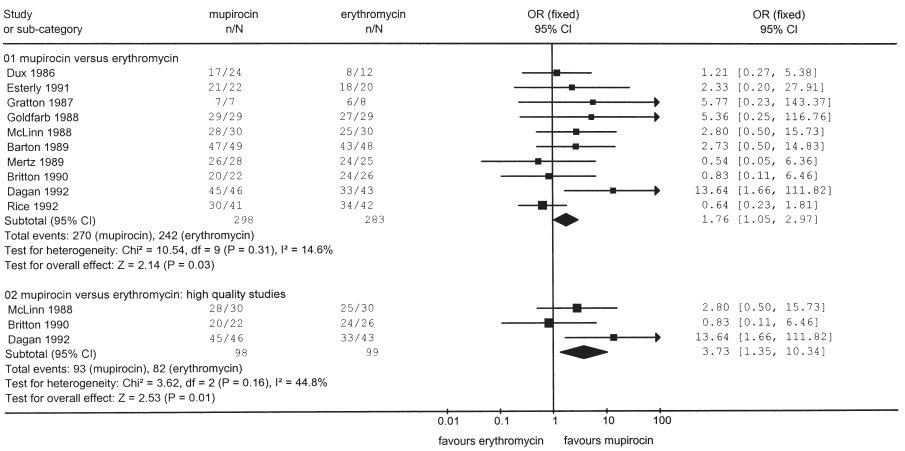
Graph 2

Topical antibiotics versus oral (systemic) antibiotics (16 studies)

Pooling of 10 studies which compared mupirocin with oral erythromycin showed significantly better cure rates or more improvement with mupirocin (OR 1.76, 95% CI 1.05 to 2.97, graph 3). However no significant differences were seen between mupirocin and dicloxacillin (Arredondo 1987), cephalexin (Bass 1997) or ampicillin (Welsh 1987). Fusidic acid was significantly better than erythromycin in one study (Park 1993), but no difference was seen between fusidic acid and cefuroxim in another arm of the same study. Bacitracin was significantly worse than oral cephalexin in one small study (Bass 1997), but no difference was seen between bacitracin and erythromycin (Koranyi 1976), or penicillin (Ruby 1973).

Table 4. (continued)
2.03 Non-bullous impetigo: topical antibiotic versus oral antibiotic

	mupirocin	**erythromycin**
Barton	47/49	43/48
Britton	20/22	24/26
Dagan 1992	45/46	33/43
Dux	17/24	8/12
Esterly	21/22	18/20
Goldfarb	29/29	27/29
Gratton	7/7	6/8
McLinn	28/30	25/30
Mertz	26/28	24/25
Rice	30/41	34/42
	topical antibiotic	**oral antibiotic**
Arredondo	mupirocin 26/26	dicloxacillin 26/27
Bass	mupirocin 6/7	cephalexin 9/10
Welsh	mupirocin 8/9	ampicillin 2/4
Park	fusidic acid 11/18	erythromycin 3/19
Park	fusidic acid 11/18	cefuroxim 12/22
Koranyi	bacitracin 5/15	erythromycin 10/15
Ruby	bacitracin 1/16	penicillin 3/18
Bass	bacitracin 3/9	cephalexin 9/10



Graph 3, 4

A sensitivity analysis on the influence of the quality score on the comparison mupirocin versus erythromycin (10 studies) revealed that there was no clear relation between the quality score of the study and the outcome. In meta-analysis, the three studies of good quality (Britton 1990; Dagan 1992; McLinn 1988) revealed a better cure rate of mupirocin compared to erythromycin (OR 3.73 95% CI 1.35 to 10.34, graph 4). The odds ratio for the overall analysis of ten studies also shows benefit for mupirocin, but not to such a degree as the three good quality studies.

Topical antibiotics versus disinfecting treatment (2 studies)

In one study (Ruby 1973), no statistically significant difference in cure/improvement

Table 4. (continued)

2.04 Non-bullous impetigo: topical antibiotics versus disinfecting treatments

	topical antibiotic	disinfecting treatment
Ruby	Bacitracin 1/16	Hexachlorophene 0/20
Christensen	Fusidic acid 105/128	Hydrogen peroxide 92/128

2.05 Non-bullous impetigo: oral antibiotics versus placebo

Ruby	Penicillin 3/18	Placebo 0/20

2.06 Non-bullous impetigo: oral antibiotic (cephalosporin) versus another oral antibiotic

	cephalosporin	other oral antibiotic
Demidovich	cephalexin 23/23	penicillin 19/25
Demidovich	cephalexin 23/23	erythromycin 24/25
Kiani	cephalexin 6/8	azithromycin 5/10
Montero	cefaclor 49/51	azithromycin 41/44
Jaffe 1985	cefaclor 13/16	amoxicillin/clavulanic acid 16/18
Ginsburg	cefradoxil 21/24	penicillin 23/26
Beitner	cefadroxil 25/33	flucloxacillin 25/27
Park	cefuroxim 12/22	erythromycin 3/19

2.07 Non-bullous impetigo: oral cephalosporin versus other oral cephalosporin

	cephalosporin	cephalosporin
Hains 1989	cephalexin 41/45	cefadroxil 47/51
Tack 1997	cephalexin 73/76	cefdinir 72/74
Tack 1998	cephalexin 11/17	cefdinir 15/18
Arata 1989a	cefaclor 2/4	cefdinir 7/9

2.08 Non-bullous impetigo: oral macrolide versus penicillin

	macrolide	penicillin
Barton 1987	erythromycin 14/14	penicillin V 11/15
Demidovich	erythromycin 24/25	penicillin V 19/25
Barton 1988	erythromycin 28/28	dicloxacillin 29/30
Daniel 1991b	azithromycin 7/10	cloxacillin 3/6
Rodriguez	azithromycin 18/25	lucloxacillin/dicloxacillin 12/14
Blaszcyk	clindamycin 23/26	dicloxacillin 14/16

2.09 Non-bullous impetigo: oral macrolide versus another oral macrolide

	azithromycin	erythromycin
Daniel 1991a	28/35	21/31

2.10 Non-bullous impetigo: oral penicillin versus other oral antibiotic (including penicillin)

	Oral penicillin	Other oral antibiotic
Dagan 1989	amoxicillin+clavulanic acid 21/22	amoxicillin 15/22
Tassler	amoxicillin+clavulanic acid 12/15	fleroxacin 19/27
Gonzalez	cloxacillin 33/33	penicillin 23/43
Pruksachatkunakorn	cloxacillin 42/45	penicillin 30/45

2.11 Non-bullous impetigo: other comparisons of oral antibiotics

Arata 1989b	lomefloxacin 6/10	norfloxacin 3/8

2.12 Non-bullous impetigo: oral antibiotics versus disinfecting treatments

Ruby	penicillin 3/18	hexachlorophene 0/20

Table 4. (continued)
2.13 Non-bullous impetigo: disinfecting treatments versus placebo

Ruby	hexachlorophene 0/20	placebo 0/20

2.14 Bullous impetigo

Moraes Barbosa	fusidic acid 10/12	chloramphenicol 2/12
Moraes Barbosa	neomycin/bacitracin 1/12	erythromycin 7/12
Dillon	cephalexin 26/28	dicloxacillin 23/29

2.15 Secondary impetigo

Wachs	betamethasone 15/27	gentamycin 8/27
Wachs	betamethasone+gentamycin 18/25	betamethasone 15/27
Fujita	cephalexin 2/4	enoxacin 4/6

was seen when bacitracin was compared to hexachlorophene (OR 3.97, 95% CI 0.15 to 104.18). In another study (Christensen 1994), there was a tendency for fusidic acid cream to be more effective than hydrogen peroxide, but this did not quite reach statistical significance (OR 1.79, 95% CI 0.99 to 3.25). When the two studies were pooled, topical antibiotics were significantly better than disinfecting treatments (OR 1.84, 95% CI 1.03 to 3.29).

(ii) Oral antibiotics

Oral antibiotics versus placebo (1 study)

A single study (Ruby 1973) was inconclusive, detecting no significant difference between oral penicillin and placebo (OR 9.26, 95% CI 0.44 to 192.72).

Oral antibiotic versus another oral antibiotic: cephalosporin versus another antibiotic (7 studies)

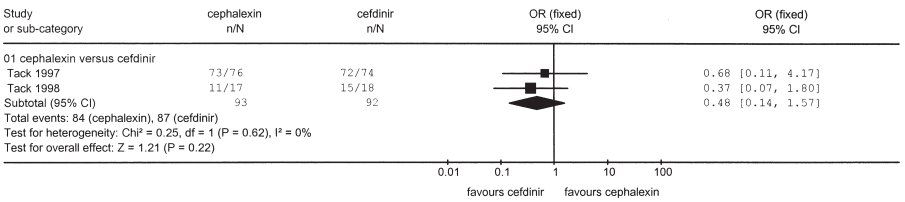
All comparisons consisted of single studies (or arms of a single study), with only one comparison (cefuroxim versus erythromycin) showing a signficant difference in favour of cefuroxim (OR 6.40, 95% CI 1.44 to 28.44; Park 1993).

Oral antibiotic versus another oral antibiotic: one cephalosporin versus another cephalosporin (4 studies)

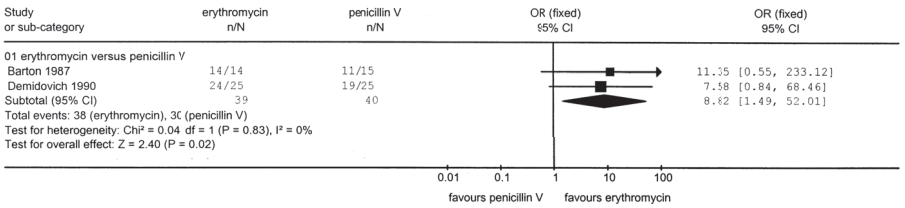
No significant differences were seen between cephalexin and cefadroxil (Hains 1989), or cefdinir (2 studies - Tack 1997; Tack 1998, graph 5); or between cefaclor and cefdinir (Arata 1989a).

Oral antibiotic versus another oral antibiotic: macrolide versus penicillin (6 studies)

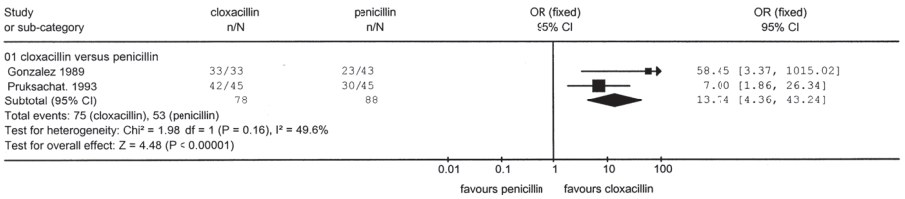
In two studies (Barton 1987; Demidovich 1990), erythromycin showed a better cure rate or more improvement than penicillin (OR 8.82, 95% CI 1.49 to 52.01, graph 6). The



Graph 5



Graph 6



Graph 7

other four comparisons consisted of single studies and did not show significant differences between macrolides and penicillins.

Oral antibiotic versus another oral antibiotic: macrolide versus another macrolide (1 study)

In a single study (Daniel 1991a), no difference in cure rate or improvement was seen between azithromycin and erythromycin (OR 1.90, 95% CI 0.62 to 5.83).

Oral antibiotic versus another oral antibiotic: penicillin versus other oral antibiotics (including other penicillins) (4 studies)

Amoxicillin plus clavulanic acid showed a better cure rate than amoxicillin alone in one study (Dagan 1989; OR 9.80, 95% CI 1.09 to 88.23), but when amoxicillin plus clavulanic acid was compared with fleroxacin in another study (Tassler 1993), no significant difference was seen (OR 1.68, 95% CI 0.37 to 7.63). Cloxacillin was significantly superior to penicillin in two studies (Gonzalez 1989; Pruksachatkunakorn. 1993: (pooled OR 13.74, 95% CI 4.36 to 43.24, graph 7).

Other comparisons of oral antibiotics (1 study)
In a single small study (Arata 1989b), no difference in cure rates/improvement could be detected between lomefloxacin and norfloxacin (OR 2.50, 95% CI 0.37 to 16.89).

Oral antibiotics versus disinfecting treatments (1 study)
In a single small study (Ruby 1973), no difference in cure rates/improvement could be detected between penicillin and hexachlorophene (OR 9.26, 95% CI 0.44 to 192.72).

(iii) Disinfecting treatments

Disinfecting treatments versus placebo (1 study)
In a single small study (Ruby 1973), no participants in either the hexachlorophene or placebo group showed cure or improvement.
Comparisons of disinfecting treatments with antibiotics are given above.

(b) Bullous impetigo

(i) Topical antibiotics

Topical antibiotics versus other topical antibiotics (1 study, 3 comparisons)
In a small study (Moraes Barbosa 1986), fusidic acid was significantly more effective than both neomycin/bacitracin (OR 55.00, 95% CI 4.30 to 703.43) and chloramphenicol (OR 25.00, 95% CI 2.92 to 213.99). In the same study no difference was detected between chloramphenicol and neomycin/bacitracin (OR 2.20, 95% CI 0.17 to 28.14).

Topical antibiotics versus oral antibiotics (1 study, 3 comparisons)
The same study (Moraes Barbosa 1986) showed that oral erythromycin was significantly more effective than both neomycin/bacitracin (OR 0.06, 95% CI 0.01 to 0.68) and chloramphenicol (OR 0.14, 95% CI 0.02 to 0.96). There was no significant difference between fusidic acid and erythromycin (OR 3.57, 95% CI 0.53 to 23.95).

(ii) Oral antibiotics

Oral antibiotic versus another oral antibiotic (1 study)
No significant difference was seen between cephalexin and dicloxacillin (Dillon 1983; OR 3.39, 95% CI 0.62 to 18.49)

(c) Secondary impetigo

(i) Topical antibiotics

Antibiotic versus steroid versus antibiotic plus steroid (1 study, 3 comparisons)

In a three-armed study (Wachs 1976), the combination of betamethasone and gentamycin cream was significantly more effective than gentamycin alone (OR 6.11, 95% CI 1.84 to 20.31). The comparisons of betamethasone with gentamycin alone or with betamethasone plus gentamycin did not show significant differences.

(ii) Oral antibiotics

In a very small study, no difference was detected between cephalexin and enoxacin (Fujita 1984).

The second primary outcome was *relief of symptoms*. This was recorded by only a few studies, and is therefore not reported here.

No relevant data were provided by any study for either the first (*recurrence rates*) or third (*development of bacterial resistance*) secondary outcome. The second secondary outcome was adverse effects

Adverse effects

(a) Disinfecting treatments

Eleven percent of the participants using hydrogen peroxide cream reported mild side effects (not specified) versus seven percent in the fusidic acid group (Christensen 1994). No patient was withdrawn from the study because of side effects. No adverse effects of scrubbing with hexachlorophene were recorded (Ruby 1973).

(b) Antibiotics

(i) Topical treatments

The trials included in this review usually reported few, if any, side effects from topical antibiotics. The studies comparing mupirocin, bacitracin and placebo reported none (Eells 1986; Ruby 1973) The study that compared fusidic acid to placebo recorded more side effects in the placebo group (Koning 2002). Three of four studies comparing mupirocin with fusidic acid recorded side effects: minor skin side effects were reported for mupirocin by 10 out of 368 (3%) participants and for fusidic acid by 4 out of 242 (2%) participants. Most other trials comparing topical antibiotics reported no side effects, or reported minor skin side effects in low numbers (less than 5% of participants).

(ii) Topical versus oral treatments

Of the ten trials comparing erythromycin with mupirocin, nine reported side effects. With the exception of two trials (Britton 1990: equally divided minor gastrointestinal side effects, Rice 1992: nil reported), all trials recorded more side effects from erythromycin. Gastrointestinal side effects (nausea, stomach ache, vomiting, diarrhoea) were recorded in 80 of 297 (27%) participants in the erythromycin groups versus 17 of 323 (5%) participants in the mupirocin groups. Skin side effects (itching, burning) were recorded in 5 out of 297 (2%) in the erythromycin groups versus 23 out of 323 (7%) in the mupirocin groups. Most other trials comparing topical and oral antibiotics did not record data on side effects.

(iii) Oral treatments

Eleven of the 26 trials comparing oral antibiotics did not report on side effects. Two of the five trials that studied erythromycin recorded side effects: only 1 of 54 (2%) participants reported gastrointestinal side effects. The other trials, usually making unique comparisons, mainly reported gastrointestinal side effects in small percentages. In four trials, a considerable difference in side effects was reported. Gastrointestinal complaints were recorded in 1 out of 113 (10%) in the enoxacin group compared to 4 out of 110 (4%) in cefalexin-treated participants (Fujita 1984). Fourteen of 327 (4%) of the cefadroxil-treated participants versus 2 of 234 (1%) of flucloxacillin participants had 'severe' side effects such as stomach ache, rash, fever, vomiting (Beitner 1996). Cefaclor caused more diarrhoea than amoxicillin plus clavulanic acid (5 out of 16, 31% versus 2 out of 18, 11%) (Jaffe 1985). Finally, the clindamycin group of participants reported more side effects (any side effect) than the dicloxacillin treated group (Blaszcyk 1998).

Industry sponsorship or organisation of the trial was declared to be present in 14 trials (25%) (Table 5).

We planned to do several sensitivity analyses. However, most trials were observer blind, took bacterial swabs, studied primary impetigo, and had staphylococcal predominance. Sensitivity analyses for these items were therefore not possible.

Discussion

The large number of treatments evaluated (36) supports the view that there is no standard therapy for impetigo. Most studies did not contribute to clear answers about the vast choice of treatment options. Many studies were under powered. This is partly due to the fact that many trials included several skin infections, impetigo being only one of them. These studies are directed at the drug rather than at the disease. In many cases,

Table 5. Declared sponsorship or funding

Study	Sponsor (product)
Barton 1987	Fleur de Lis Foundation
Barton 1988	Warner-Lambert Corporation
Barton 1989	Warner- Lambert Corporation
Beitner 1996	Bristol-Myers Squibb (cefadroxil)
Blaszcyk 1998	Pharmacia & Upjohn Asia (clindamycin)
Britton 1990	US Navy Bureau of Medicine and Surgery Clinical Investigation Program
Daniel, both studies	Pfizer Central Research (azithromycin)
Dillon 1983	Eli Lilly Research (cephalexin)
Goldfarb 1988	Beecham Laboratories (mupirocin)
Hains 1989	Bristol-Myers Squibb (cefadroxil)
Jaffe 1985	Beecham Laboratories (amoxicillin+clavulanic acid)
Koning 2002	Dutch College of General Practitioners
Mertz 1989	Beecham Laboratories (mupirocin)
Sutton 1992	Leo Laboratories (fusidic acid)
Tack 1997	Parke-Davis pharmaceutical research (cefdinir)
Tack 1998	Parke-Davis pharmaceutical research (cefdinir)
Wainscott 1985	Beecham Pharmaceuticals (mupirocin)
White 1989	Beecham Pharmaceuticals (mupirocin)

significant differences became insignificant when impetigo participants were considered after excluding participants with other sorts of infection. Another drawback of this type of study is that the age of participants is much higher than the typical impetigo patient (eg Blaszcyk 1998; Kiani 1991). The dosage of studied antibiotics may differ between studies, complicating the comparability of studies. However, the same doses were usually used (e.g. erythromycin 40 mg per kg per day). Cure rates of specific treatments can be different between studies, e.g. of fusidic acid and mupirocin (Sutton 1992; White 1989). This may explained by the fact that investigations were done in different regions and times, and that inclusion criteria differ.

Little is known about the 'natural history' of impetigo. Therefore, the scarcity of placebo controlled trials is striking, given that impetigo can be considered a minor disease. Only five placebo controlled studies have been conducted (Gould 1984; Eells 1986; Koning 2002; Rojas 1985; Ruby 1973). The seven-day cure rates of placebo groups in these studies vary but can be considerable (0 to 42%).

The disinfectant agents, such as povidone-iodine and chlorhexidine, recommended in some guidelines (Boukes 1999; Hay 1998; Resnick 2000), usually as supplementary treatment, have been inadequately studied, and have not been compared to placebo treatment. Hydrogen peroxide cream was not significantly less effective (cure rate 72% versus 82%) than fusidic acid in a relatively large trial (Christensen 1994). We judged that blinding in this trial was inadequate.

Topical mupirocin and fusidic acid can be considered as effective as, or more effective than oral antibiotics, and these topical agents have fewer side effects. This finding is in sharp contrast to the commonly held view that oral treatment is superior to topical treatment (Baltimore 1985; Tack 1998). Other topical antibiotics were generally inferior to mupirocin, fusidic acid, and oral antibiotics. The study by Vainer is an exception: no difference was seen between tetracyclin/bacitracin cream, neomycin/bacitracin cream and fusidic acid (Vainer 1986). Fusidic acid and mupirocin are the only topical antibiotics that have been compared to placebo (and shown to be more effective).

A striking finding is that the trials comparing erythromycin with mupirocin recorded more (gastrointestinal) side effects in the erythromycin group than the trials that compared erythromycin with other oral antibiotics.

None of the studies reported cases of acute (post streptococcal) glomerulonephritis. This complication has always been an important rationale for oral antibiotic treatment. The apparent absence of glomerulonephritis may reflect the reduced importance of streptococci in impetigo. It should be noted that study sizes are small and glomerulonephritis is rare.

There is a commonly accepted idea that more serious forms of impetigo (e.g. participants with extensive lesions, general illness, fever) need oral rather than topical treatment. This principle cannot be evaluated using the data included in our review, as trials that study local treatments usually exclude participants with more serious forms of impetigo.

Resistance patterns of staphylococci causing impetigo change over time. Outcomes of studies dating back more than 10 years, which form the majority of trials in this review, may not be applicable to the current prevalence of infecting agents. Also, resistance between regions and countries may vary considerably. Thus, up-to-date local characteristics and resistance patterns of the causative bacteria should always be taken into account when choosing antibiotic treatment. In addition, health authorities and other relevant bodies may advise against prescribing certain antibiotics for impetigo in order to restrict the development of bacterial resistance and reserve these drugs for more serious infections.

Reviewers' conclusions

Implications for practice

Implications for topical disinfectants in clinical practice

There is no evidence for the value of disinfecting measures in the treatment of impetigo, as sole or supplementary treatment.

Implications for topical antibiotics in clinical practice

There is good evidence that the topical antibiotics mupirocin and fusidic acid are equal to or possibly more effective than oral treatment for people with limited disease. Fusidic acid and mupirocin are probably equally effective, other topical antibiotics seem less effective. In general, oral antibiotics have more side effects than topical antibiotics, especially gastrointestinal side effects.

Implications for use of systemic antibiotics in clinical practice

There is good evidence that the topical antibiotics mupirocin and fusidic acid are equal to or possibly more effective than oral treatment. The only oral antibiotic that has been compared to placebo is penicillin, in an old study (Ruby 1973); there is no evidence that it is effective. Based on the available evidence on efficacy, no clear preference can be given for B-lactamase resistant narrow-spectrum penicillins such as cloxacillin, dicloxacillin and flucloxacillin, broad spectrum penicillins such ampicillin and amoxicillin plus clavulanic acid, cephalosporins, and macrolides. Other criteria such as price, (unnecessary) broadness of spectrum and wish to reserve a particular antibiotic can be decisive. Resistance rates against erythromycin seem to be rising. In general, oral antibiotics have more side effects, especially gastrointestinal ones. There is insufficient evidence to say whether oral antibiotics are better than topicals for more serious and extensive forms of impetigo. From a practical standpoint, oral antibiotics might be an easier option for people with very extensive impetigo.

Implications for research

Trials should compare treatments for a specific disease, rather than the effectiveness of a specific antibiotic on a variety of (skin) infections. As seen in this review, trials that study one treatment for several diseases, often show inconclusive results for specific diagnoses. Future research on impetigo should make a careful power calculation as most included studies were too small to be able to assess any difference in treatment effect.
Research trying to establish the natural course of impetigo would be useful. But although impetigo can be considered a minor ailment, studies with a non-intervention arm seem ethically impracticable.
The relative absence of data on the efficacy of topical disinfectants should urge future researchers to study these, since they do not contribute to antibiotic resistance and are cheap. This research may be of particular importance for developing countries.

A trial on impetigo should preferably:

- not combine data for several skin diseases, or both bullous and non-bullous impetigo, and primary and secondary impetigo.
- present results separately if it does study several diseases.
- report resistance rates of causative bacteria against the studied antibiotic and against reference antibiotics such as erythromycin, mupirocin and/or fusidic acid.
- use clear and objective outcome measures for cure and improvement of impetigo, instead of subjective judgements such as 'improved', 'satisfactory', 'good response'. Key elements defining clinical cure could be absence of crusts, dryness, intactness, and absence of redness of skin. A parameter of improvement could be 'size of affected surface'. Choosing 'standard' follow-up periods, i.e. 7, 14, 21 days will facilitate the comparison of studies.
- include a placebo group, or at least a 'gold standard' reference group. For topical treatments, mupirocin or fusidic acid could be considered 'gold standard'.

As part of the issue of antibiotic resistance, impetigo studies that establish the contribution of the studied treatment to the development of bacterial resistance are desirable.

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Potential conflict of interest

Three reviewers of this review are authors of one included trial (Sander Koning, Lisette WA van Suijlekom-Smit, Johannes C van der Wouden (Koning 2002)).

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5

Impetigo: incidence and treatment in general practice in 1987 and 2001. Results from two national surveys

Koning S, Mohammedamin RSA, van der Wouden JC, van Suijlekom-Smit LWA, Schellevis FG, Thomas S. Impetigo: incidence and treatment in Dutch general practice in 1987 and 2001. Results from two national surveys. British Journal of Dermatology. [in press]

Abstract

Objectives

Impetigo is a common skin infection in children. The epidemiology is relatively unknown, and the choice of treatment is subject for debate. The objective of our study was to determine the incidence and treatment of impetigo in Dutch general practice, and assess trends between 1987 and 2001.

Methods

We used data of the first (1987) and second (2001) Dutch national survey of general practice. All diagnoses, prescriptions and referrals were registered by participating general practitioners (GPs), 161 and 195 respectively.

Results

Incidence The incidence rate of impetigo increased from 16.5 (1987) to 20.5 (2001) per 1000 person years under 18 years old ($p< 0.01$). In both years, the incidence was significantly higher in summer, in rural areas and in the southern region of the Netherlands, compared to winter, urban areas and northern region respectively. Socio-economic status was not associated with the incidence rate.

Treatment From 1987 to 2001, there was a trend towards topical antibiotic treatment (from 40% to 64%), especially fusidic acid cream and mupirocin cream. Oral antibiotic treatment (from 29% to 14%), and disinfecting agents (from 11% to 3%) were less often prescribed.

Conclusions

Incidence We have shown an increased incidence of impetigo in the past decade, which may be the result of increased tendency to seek help, or increased antibiotic resistance and virulence of Staphylococcus aureus. Further microbiological research of the marked regional difference in incidence may contribute to understanding the factors that determine the spread of impetigo.

Treatment Trends in prescribing for impetigo generally follow evidence-based knowledge on the effectiveness of different therapies, rather than the national practice guideline.

Introduction

Impetigo or impetigo contagiosa is a contagious superficial skin infection. *Staphylococcus aureus* is currently the most common causative agent. For parents, a child with impetigo brings about concern and inconvenience, since children with impetigo are usually barred from schools and kindergartens. Although the incidence and population prevalence of impetigo seem to have decreased over the past decades, it is still a common disease, particularly in young children. (1,2,3)

Not much is known about the epidemiology. There is a general belief that good hygiene may prevent the occurrence of impetigo, (4) and that social factors such as crowding may increase the risk of developing of this disease. Regarding the level of the causative agent, specific characteristics of *S. aureus* have been identified, which affect the development and course of impetigo. (5,6,7)

There is debate about the treatment of impetigo. Are topical antibiotics effective? Should their use be promoted or discouraged because of rising resistance rates, especially against fusidic acid? (8,9) Since 1999, there is a guideline for Dutch general practitioners (GPs) on bacterial skin infections, issued by the Dutch College of General Practitioners. (10) In summary, the advice for impetigo is a basic treatment of disinfection, and additional zinc ointment in case of limited lesions or fusidic acid cream in case of more extensive lesions.

Against the background of changing social behaviour and changing resistance of the pathogen it is important to establish the occurrence and treatment of impetigo in daily practice. We investigated the incidence of impetigo and its management by GPs in the Netherlands, and tried to identify trends between 1987 and 2001. Our questions were:

- How often does the GP see children aged 0-17 with impetigo, and how is the incidence related to sex, age, season, region, urbanisation level and social economic status, and how did that change between 1987 and 2001?
- What is the treatment policy of the GP, and how did that change between 1987 and 2001?

Methods

We analysed data from the first and second Dutch national surveys of general practice, which were carried out by the Netherlands Institute for Health Services Research in 1987 and 2001, respectively. For this study, data from both surveys for children aged 0–17 years were analysed. In the Netherlands, general practices have a fixed list size, and all non-institutionalised inhabitants are listed in a general practice, and GPs have a gatekeeping role. Both surveys included a representative sample of the Dutch population.

First Dutch National Survey 1987

A non-proportionally stratified sample of 161 GPs was selected randomly to participate in the survey. The GPs were divided into four groups and each group registered data about all contacts between patient and practice on registration forms during one of four consecutive 3-month periods during 1987. The four registration periods covered one calendar year to correct for seasonal variability of morbidity. Data recorded from each consultation included patient characteristics (age, gender), diagnosis and prescription of drugs. Specially trained workers using the International Classification of Primary Care (ICPC) coded diagnoses made by the general practitioner afterwards. Other demographic patient characteristics were obtained by a questionnaire. Because of an underrepresentation of deprived areas, the population was weighted to the Dutch population of 1987. For further details about the first Dutch national survey, we refer to the book by Bruijnzeels. (1)

Second Dutch National Survey 2001

The second national survey was carried out in 2001. In short, 195 general practitioners in 104 practices registered data about all physician–patient contacts during 12 months. GPs registered all health problems presented within a consultation and coded diagnoses using the ICPC. Also, all prescriptions made by the GP were registered. Characteristics of participating practices such as settlement in rural or urban area were obtained by mailed questionnaire. Patient characteristics such as age and gender were derived from the GPs' computerized patient files. For further details about the second Dutch national survey, we refer to the article by Westert. (11) For this analysis, data from nine of the 104 practices were excluded for various reasons: five practices with inadequate registration of patient contacts or drug prescription were excluded after quality control. Four other practices were excluded because of software problems. When several contacts had taken place for impetigo, and there had been no cure between the contacts, we constructed an episode.

Statistical analyses

We defined incidence as number of first contacts for impetigo per 1000 person years. Differences between incidence rates were tested assuming a Poisson distribution with a significance level of 0.05 using STATA version 8.2.

Results

In the first National Survey (1987) and the second National Survey (2001), 86,577 and 82,053 children aged 0-17 participated respectively. In these groups, there were 380

(1987) and 1682 (2001) episodes of impetigo. These figures form the basis of the incidence rates.

Incidence

The incidence of impetigo in children under 18 was 16,5 per 1000 person years in 1987. In 2001, the incidence had risen to 20.5, an increase of 24% ($p < 0.01$). The incidence by age is represented in **figure 1**. It shows that especially children aged 6-11 years had impetigo more often in 2001 compared to 1987. Consequently, the peak age group for impetigo has widened and shifted to an older age. There was no sex difference in incidence in both surveys.

Table 1 shows the incidence of impetigo, related to type of insurance, urbanisation level, region, season and socio-economic status. Like in 1987, impetigo was more frequent in smaller towns and villages (< 30.000 inhabitants). This difference was statistically significant compared to all three other categories of urbanisation level. There was a geographic gradient in both surveys, stronger in 2001 than in 1987. In the south of the Netherlands, the incidence of impetigo was twice as high as in the north. In multivariate analysis, this proved to be independent of urbanization level. The seasonal peak in incidence in the summer was stronger in 2001 than in 1987. Socio-economic status appeared no significant factor in both surveys.

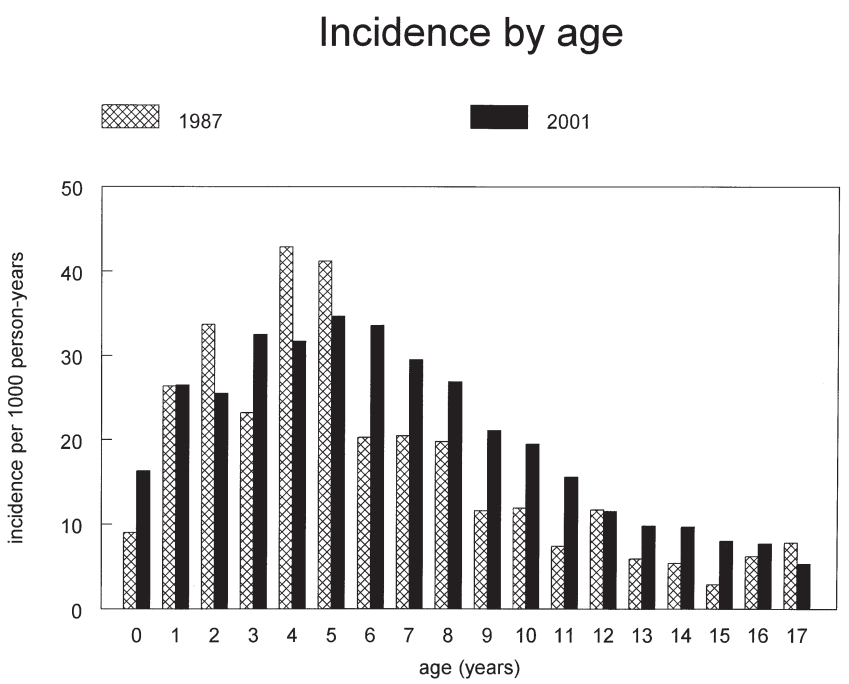

Figure 1

Table 1. Incidence of impetigo in 0-17 years olds
By insurance type, urbanisation level, region, season, and socio-economic group

	1987		2001	
	Incidence per 1000 person years (0-17)	**95% CI interval**	**Incidence per 1000 person years (0-17)**	**95% CI interval**
Insurance				
Sick fund	**18.3**	15.82 – 20.99	**21.7**	20.37 – 23.03
Private	**16.0**	13.44 – 18.94	**18.9**	17.49 – 20.44
Urbanisation level				
<30.000 inhabitants	**22.0**	18.75 – 25.59	**25.8**	24.13 – 27.52
30-50.000 inhabitants	**13.7**	11.27 – 16.59	**12.0**	10.33 –13.84
>50.000 inhabitants	**14.0**	10.69 – 17.96	**14.1**	12.65 – 15.57
Big cities [1]	**11.5**	7.21 – 17.41	**12.9**	10.04 – 16.33
Region				
North	**15.6**	11.07 – 21.46	**13.0**	11.05 – 15.25
Mid	**15.5**	13.53 – 17.74	**19.4**	18.19 – 20.74
South	**19.2**	15.68 – 23.34	**26.4**	24.35 – 28.55
Season				
Winter	**15.6**	12.27 – 19.56	**14.8**	13.20 – 16.61
Spring	**10.9**	8.53 – 13.83	**12.2**	10.72 – 13.81
Summer	**21.5**	17.38 – 26.26	**31.2**	28.78 – 33.66
Autumn	**18.6**	15.31 – 22.38	**23.0**	20.97 – 25.08
Socio- economic group [2]				
1 non-manual high	**17.4**	13.79 – 21.58	**19.5**	17.72 – 21.37
2 non-manual middle	**16.0**	11.62 – 21.47	**22.6**	20.37 – 25.01
3 non manual low & farmers	**15.0**	8.22 – 25.23	**23.5**	19.58 – 28.02
4 manual high/middle	**22.2**	17.63 – 27.67	**22.5**	18.34 – 27.41
5 manual low	**21.0**	16.09 – 26.90	**20.8**	17.41 – 24.62
Total	**16.5**	14.83 – 18.30	**20.5**	19.55 – 21.53

1 Amsterdam, Rotterdam, The Hague
2 according to education of the father

Prescriptions

The data are based on the prescriptions in the first contact of an episode, and are presented in **table 2**. Sixty nine percent of all prescriptions in 1987 were for an antibiotic; in 2001 this percentage was 78. In 2001, more topical antibiotics, especially fusidic acid cream and mupirocin cream, and less oral antibiotics were prescribed than in 1987. Other topical antibiotics were hardly used anymore. The number of prescriptions for disinfecting agents decreased from 11% to 3%. In a small minority of the consultations more than one prescription was issued.

Table 2. Prescriptions in the first contact of episode

	1987		2001	
	number	percentage	number	percentage
Total number of episodes	**380**	**100**	**1682**	**100**
Oral antibiotic	**109**	**29**	**242**	**14**
Amoxicillin and other penicillinase susceptible penicillins	82	22	78	5
Penicillinase resistant penicillins (flucloxacillin, amoxicillin + clavulanic acid)	15	4	89	5
Macrolides	4	1	60	4
Cefalosporins	1	0	14	1
Other	7	2	1	0
Topical antibiotic	**153**	**40**	**1078**	**64**
Fusidic acid	64	17	855	51
Mupirocin	-	0	210	12
Tetracyclin	54	14	3	0
Other	35	9	10	1
Antiseptic	**40**	**11**	**48**	**3**
Chloorhexidin	12	3	19	1
Povidon-iodine	17	4	29	2
Other	11	3	-	0
Other topical medication	**80**	**21**	**68**	**4**
No presciption	**35**	**9**	**240**	**14**

Discussion

Incidence: increase

We observe an increased incidence of impetigo seen in general practice over the past 14 years, which seems to be an upheaval after decades of decreasing incidence. (2) This increase may reflect a rising tendency of medical attention seeking and should not necessarily imply an increase at the population level. The unsightly aspect of (facial) impetigo may now be less acceptable to parents than before. Also, there seems to be more pressure from schools to undergo antibiotic treatment before the child can be permitted at school again. This may also explain the fact that the increase has mainly affected the age group 6-11 years. Possible explanations for an increased incidence at the population level are either a change in human behaviour, such as increased travelling or, on the other side, increasing virulence of the causative pathogen. Genetic characteristics of *S. aureus* are changing, and a selection of more virulent strains may

take place. (5) Also, a rise of antibiotic resistance in staphylococci has been reported. (8,9,12,13) Cure of impetigo may therefore last longer than before and patients may be contagious for a longer time. Reports of impetigo epidemics that are difficult to control, caused by multiple resistant staphylococci, are illustrative in this respect. (14,15)

Incidence: regional variance

The twofold higher incidence in the south compared to the north is a striking observation, especially for a small country like the Netherlands. Climatic differences within the country are small and seem to offer no explanation. The level of urbanisation and socio-economic scale turned out to be no factor either, shown by multivariate analysis. We propose that staphylococcal transfer from animal to man may explain the geographical gradient. Zoonoses in staphylococcal pyogenic skin infections have been proven before (16). In the Netherlands, there is a concentration of pig farming in the southern provinces, where approximately ten times as many pigs are bred as in the northern provinces. (17) It has been shown recently that pig farmers in France more frequently were nasal carriers of *S. aureus* than matched non-farmers, and that the *S. aureus* were more frequently macrolide resistant. (18) The same explanation may account for the twofold higher incidence of impetigo in rural areas versus other urbanisation levels. Research comparing genetic staphylococcal characteristics of specimens derived from different regions would be needed to test these hypotheses. The rise in incidence of impetigo does not seem to continue southwards, as data from Belgian GPs suggest that the incidence in Belgian general practice is lower than in the Netherlands. (Personal communication, Dr Stefaan Bartholomeeusen) The higher incidence of impetigo in the summer is not new and is consistent with many other reports. (2,19,20)

Treatment

There is a trend towards prescribing of topical antibiotics for impetigo, at the expense of oral antibiotics. The trebled increase of fusidic acid cream prescriptions from 1987 to 2001 may be influenced by the publication of the guideline on bacterial skin infections by the Dutch College of General Practitioners in 1999. (10) In this guideline, fusidic acid is the first choice antibiotic treatment. Contrarily, the number of prescriptions of mupirocin has also increased. Mupirocin cream, not available in 1987 yet, has proven efficacy in the treatment of impetigo, (21) but was not recommended in the 1999 guideline, considering that mupirocin should be reserved for treatment of nasal carriage of *S. aureus*. Many GPs did not follow the guideline in this respect. Furthermore, the guideline recommends disinfecting therapy with chlorhexidine or povidon-iodine as a basic treatment. This advice was even less often complied with in 2001 than in 1987. Possibly, disinfectants have been advised in some cases and were not registered because they are over-the-counter-medicines. However, a great proportion of GPs apparently has no

faith in the value of disinfecting treatments. The lack of evidence for the effectiveness of disinfectants may play a role. (21) In the group of oral antibiotics, a remarkable one third of all prescriptions are still penicillinase susceptible penicillins such as penicillin, amoxicillin and feneticillin, which are not indicated for the treatment of impetigo.

Limitations of this study

There are small differences in the design of the two national surveys, which might hinder the comparability of data. For example, in the first national survey, trained investigators coded diagnoses afterwards, whereas in the second national survey, the GPs coded the diagnoses themselves during the consultation. Furthermore, the participating GPs in the two national surveys may not be fully representative for the average GP in the Netherlands. This and the fact that their actions were recorded might distort our results.

In conclusion, we have shown an increased incidence of impetigo in the past decade, and marked regional differences in incidence. Further (microbiological) research of this observation may contribute to understanding the factors that determine the spread of impetigo. Secondly, we found a variety in the treatment of impetigo by GPs, which was incompatible with the national guideline.

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6

Treatment and course of impetigo. An observational study in Dutch general practice

Koning S, Molenbeek V, Op 't Veld-Mulders M, van Suijlekom-Smit LWA, Schellevis FG, Thomas S, van der Wouden JC. Treatment and course of impetigo. An observational study in Dutch General Practice. [Submitted]

Abstract

Background

Impetigo is a common skin infection in general practice. Treatment is subject to debate. We do not know much about the course of impetigo outside trials.

Aim

To establish the course of impetigo before and after consulting the GP, and the treatment advised by GPs and applied by patients.

Design

Observational study.

Setting

35 general practices in The Netherlands.

Methods

GPs requested children that presented with impetigo to participate in the study. The child or its parent filled in a questionnaire at home. We telephoned the (parent of the) child at two, four and 13 weeks after the consultation for follow-up data.

Results

We included sixty-three children with impetigo. The GP prescribed a topical antibiotic in 71% of the cases, usually fusidic acid cream and an oral antibiotic in 21% of the cases, usually erythromycin. The percentage of cured patients was 70% at two weeks and rose to 97% at 13 weeks. 11% of the patients had a recurrence of impetigo after initial cure. Half of the patients that were not cured or had a recurrence did not consult the GP again.

Conclusion

The course of impetigo in general practice is less favourable than the course in trials, and there is a relatively high recurrence rate. Dutch GPs apparently have no faith in the value of disinfectant cleansing and application of indifferent therapy with zinc ointment, as recommended in their national practice guideline. GPs should know that when the patient does not return, it does not mean he is cured.

Introduction

Impetigo is a contagious skin condition that mainly affects children, and is usually caused by *Staphylococcus aureus*. It is a common disease that is frequently seen by general practitioners (GPs). In the Netherlands, the incidence is 20.5 per 1000 children aged 0-17 years (1), corresponding with 10-12 cases seen per year by an average GP. We found one study reporting on the population prevalence of impetigo. This was carried out in a Portuguese village. The authors found a prevalence of 0.7%, (2) indicating that in a practice population of 2,400 seventeen patients had impetigo at the same time, and suggesting that a fraction of patients consult the GP.

There is debate about the choice of treatment. The main theme in the discussion is whether to promote treatment with topical antibiotics or not, regarding the development of bacterial resistance. (3,4) In the Netherlands, there is a guideline on bacterial skin infections, issued by the Dutch College of General Practitioners. (5) In summary, the advice for impetigo is a basic disinfectant treatment with povidon-iodine or chlorhexidine, and additional zinc ointment in case of limited lesions or fusidic acid cream in case of more extensive lesions. Many authors state that impetigo is a self-limiting disease. However, studies that evaluate a wait and see policy do not exist, so the natural course of impetigo is unknown. Evidence about the course of impetigo can be obtained from trials, but only few of these were placebo controlled. (6) No evidence exists about the course of impetigo outside trials. In daily practice, the GP usually sees patients only once during an episode of impetigo and consequently does not know the time needed to achieve cure. Moreover, the assumption that the disease has cured when the patient does not return may be false. We therefore performed an observational study on the course of impetigo in children who consulted their GP.

Our primary questions were:

What treatments for impetigo have been applied by doctors and patients, what was the course of impetigo prior and after the GP consultation, and was it related to the treatment?

Methods

This study was conducted among 35 practices that also participated in the second Dutch national survey of general practice, which was carried out by the Netherlands Institute for Health Services Research (NIVEL) in 2001. In short, 195 general practitioners in 104 practices registered data about all physician-patient contacts during 12 months. GPs registered all health problems presented within a consultation and coded diagnoses

using the ICPC. For further details about the second Dutch national survey, we refer to the article by Westert. (7)

For our purpose we selected the 35 practices (52 full time equivalent GPs) on the basis of the type of electronic registration system. The practices were located throughout the entire country, and they agreed to participate for twelve weeks. In some practices this period was extended. Research team members visited the practices for instruction. The distribution among single-handed practices and group practices was equal to that of all practices participating in the second national survey. There were differences however for the degree of urbanisation. Rural areas were over-represented (30% in present study versus 10% for the entire study, $\chi^2 = 10.1$, df = 4, p = .04).

The 35 practices agreed to request any child that presented with specific skin diseases to participate in our study. The inclusion period took place from August 2001 to February 2002. The electronic patient system was adapted to produce a notification to the GP as soon as an ICPC code of one of the skin disorders was entered. The age of the patients needed to be less than 18 years. After written consent of the patient or his parents, this was sent to the research team. The patient or his parents subsequently filled in an extensive questionnaire that we sent them at home. The questionnaire included patient characteristics such as age, sex, duration and other characteristics of the skin disorder, reason to visit the GP, (pre) used medications and over the counter medication and medication prescribed by the GP. For follow-up data, research assistants interviewed the (parents of) patients by telephone at two, four, and 13 weeks. Through tenacity and flexibility of our assistants we obtained 100% response.

Results

Response

Twenty practices (33 full time equivalent GPs) of the 35 practices effectively included impetigo patients. The number of included patients varied from one to 10 per practice. Among the 15 practices that did not include impetigo patients, nine included patients with other skin diseases, and six included no patients at all. This was partly caused by software problems. From the computer registration files, we were able to check if practices had registered impetigo patients that were not reported for the study. An exact calculation was not possible because the exact linking of the impetigo episode to the inclusion period of the practice was not possible. In the 20 including practices, approximately 110 children with impetigo had been registered during the inclusion period, of which 63 (57%) were actually included. The 15 practices that did not include patients had registered approximately 35 children with impetigo in their inclusion period.

Table 1. Characteristics of impetigo patients (n = 63) at first GP consultation

Age	Average	7.8 yrs
Sex	Male/Female	28/35 (44/56%)
Duration before consultation	Range	1 day-7 months
	Average	8 days †
Area of affected surface	Range	1-600 cm^2
	Average	12.5 cm^2 ‡
Number of lesions	Range	1-15
	Average	3.2
Location	Head/neck	41
	Trunk/limbs	53
Therapy applied before consultation	None	23
	Homoeopathic creams	9
	Other/cosmetic creams	8
	Cleansing with disinfectant	7
	Topical antibiotic cream	5
	Zinc-containing creams	5
	Plaster/bandage	3
	Antiviral cream, topical steroid, soak in detergent solution	1 each
Reasons for consultation	Ugly appearance	46 (73%)
	Concern for child	32 (51%)
	Concern to infect others	27 (43%)
	Lesions are itching	23 (37%)
	Lesions are painful	19 (30%)
	(Fear for) rapid increase	17 (27%)
	Other child has same disorder	7 (11%)

† calculated without outlier of 7 months
‡ calculated without outlier of 600 cm^2

In order to check whether the 20 including practices were different from the 75 other practices in the second national survey, we compared the electronically registered prescriptions patterns of the practices over the whole one-year registration period. The 20 including practices were just as likely as the other practices to prescribe fusidic acid cream and mupirocin cream. Within the oral antibiotic treatments however, they were less likely to prescribe amoxicillin+clavulanic acid and clarithromycin, and more likely to prescribe erythromycin than the other 75 practices.

Patients

Sixty-three patients with impetigo were included in total. The average child with impetigo presenting to the GP was eight years old and had three impetiginous lesions, with a total area of 12 cm^2, which existed since eight days. The lesions were located in the head-neck area and/or arms in most cases (see table 1). The age distribution of the impetigo patients did not differ from all children with impetigo registered in the second Dutch national survey. (1) Most patients had used some kind of treatment before consulting the GP, usually over the counter medication, but also prescribed medication such as topical antibiotic and steroid creams (see table 1). The most common reason for consultation was the ugly appearance of the lesions.

Table 2. Therapy by GP at first consultation (n = 63)

		single therapy	combined therapy	
			fusidic acid	other
oral antibiotic	Erythromycin	3	3	1 zinc
	Flucloxacillin	2	-	1 menthol
	Feneticillin	1	1	-
	Azithromycin	-	1	-
topical antibiotic	Fusidic acid	26	-	2 povidon-iodine 1 triamcinolon
	Mupirocin	10	-	-
	Tetracycline	1	-	-
other	Zinc products	5	-	-
	Povidon-iodine	1	-	-
	Other	4	-	-

Table 3. Number of patients cured (%) by type of treatment and time

	2 weeks		4 weeks		13 weeks	
All patients	44/63	(70)	59/63	(94)	61/63	(97)
Topical antibiotic	26/40	(65)	36/40	(90)	38/40	(95)
Oral antibiotic	6/7	(86)	7/7	(100)	7/7	(100)
Oral + topical	4/5	(80)	5/5	(100)	5/5	(100)
No antibiotic	8/11	(70)	11/11	(100)	11/11	(100)

Treatment

The treatment that patients received from the GPs was diverse (see table 2). Forty-five (71%) of the children had a prescription of a topical antibiotic, usually fusidic acid cream (34 times). In five of the 45 cases, this was combined with an oral antibiotic, in two cases with povidon-iodine and one case with triamcinolone cream. Thirteen (17%) children received an oral antibiotic (usually erythromycin, seven times), in five cases combined with a topical antibiotic (always fusidic acid cream). In 10 of the 63 cases (16%), no antibiotic was prescribed, but zinc containing creams, topical steroids and disinfectant creams. There were no children without any prescription. None of the children was referred to a specialist.

The patients reported in 23 cases (37%) to have received other than pharmaceutical advice from their GP. These were usually hygiene advices, or the recommendation to avoid physical contact with others.

The decision to prescribe an antibiotic appeared to be related to the surface area of the impetigo: children with more extensive lesions more often received oral antibiotics. Also the age of the child was of influence: younger children more often received oral antibiotic treatment than older children.

Table 4. No cure, recurrence, revisit to GP, and advice of GP (n=63)

	2 weeks	4 weeks	13 weeks
Absence of cure [a)]	19	4	2
Recurrence after cure [b)]	-	1	6
Patients that had consulted GP again	11	3	-
Advice of GP:			
-continue therapy	5	2	
-additional therapy	3		
-change therapy	3		
-stop therapy, no other therapy		1	

a) at moment of measurement
b) within period before measurement

The percentage of children cured increased from 70 percent after two weeks to 97 percent after 13 weeks. Children that received an oral antibiotic had slightly higher cure rates after two and four weeks than children with other treatments (see table 3). Eleven of the nineteen children whose impetigo had not cured in two weeks consulted the GP again. In five cases the GP advised to continue the treatment, six patients received another or a supplemental treatment (see table 4).
Seven children had a second episode of impetigo after initial cure. In one case the recurrence occurred within four weeks, in the other cases between four and 13 weeks. There seemed to be no relation between recurrence risk and previous therapy.

Discussion

This paper describes the treatment and the course of impetigo in Dutch general practice. However, we should recognise that the participating GPs in the national survey may not be representative for the Dutch GP in all respects. Also the fact that doctors know their actions are recorded might affect what they write down.

Non-response

Approximately 45% of the total number of children with impetigo seen by the participating GPs was included. Apart from software problems, we believe that reasons for the underreporting may be that the GP forgot or did not want to ask for willingness to participate, or think that the patients would not be suitable, or patients may have refused consent.

Treatment by GP

A minority of patients was treated with oral antibiotics. The choice for a topical antibiotic usually was fusidic acid. These choices are consistent with the national practice guideline for GPs. (5) Other recommendations in the guideline have been followed less soundly. Both disinfecting therapy, suggested as basic treatment in the guideline, and zinc ointment as first step therapy were not prescribed very often. Apparently the GPs do not have much faith in the value of these measures. The lack of evidence so far supports them. (6,8,9) The fact that the cure rates in the different treatment groups in this study are similar, may not lead to conclusions, since this is not a randomised study and the number of patients is small. Only three of the 13 prescribed courses of oral antibiotics were flucloxacillin, which is first choice in the guideline. The reason for this is probably that there is no suspension form of flucloxacillin available, whereas the alternative oxacillin suspension has not been available in the Netherlands since the year 2000. We do not have an explanation why younger children were more likely to receive oral treatment than older children.

Course

The average cure rate of impetigo after two weeks (70%) in this study is lower than those reported in RCTs. Depending on the study, the percentage of cured patients after one week is generally between 70% and 95%. (6) This may be explained by the fact that patients "in real life" do not receive follow-up or guidance as is common in RCTs. The fact that patients who did not receive antibiotics had equal cure rates is noteworthy, but the explanation could be that more serious cases received antibiotics more often. Regarding the total affected area, this actually was the case: more extensive forms of impetigo received oral antibiotic more frequently ("confounding by indication").

A substantial number of patients (approximately half) that had not achieved cure after two or four weeks did not contact the GP again. This was also true for the patients that had a recurrence of impetigo. This implies that the perspective of the GP is not sufficient to get insight in the course of impetigo: he/she simply is not aware that the condition is still there ("keyhole epidemiology"). Possibly, patients did not return to the GP because they were in a study and knew research staff would telephone them. However, we never gave any advice other than to return to the GP in case of problems or questions.

It should be noted that we did not study the natural history or "spontaneous course" of impetigo. This research has never been conducted to our knowledge, and would be interesting, but probably not feasible. Most patients will always ask some kind of treatment, with prescribed or over the counter medication.

In conclusion, we have shown that GPs choose a variety of treatments for impetigo. The chosen antibiotic therapy was largely in agreement of the recommendations, but

the absence of prescriptions for zinc ointment and disinfectant therapy was not. The course of impetigo after the consultation was less favourable than might be expected from trials, and when the patient does not return, it does not mean he is cured.

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7

Summary and general discussion

Summary

Impetigo is a common skin infection, usually caused by *Staphylococcus aureus* that mainly occurs in children. Patients with impetigo usually consult their general practitioner, who also treats the vast majority of cases. Impetigo is considered highly infectious, and consequently children are often barred from schools. Patients and doctors seek prompt treatment. Although we know the causative bacteria, we do not know what factors promote contagiousness or severity of impetigo. There are reports of epidemics, but we do not have recent incidence data. Many treatment options exist, but there has been much debate about which treatment is most effective.
The general aim of this thesis was to establish epidemiological data about impetigo, to identify host- and bacterial factors that contribute to occurrence of impetigo and to collect evidence for efficacy of all treatment options. We conducted a trial and other research ourselves, as well as analysed data collected by others. The setting of the research was always general practice as, in the Netherlands, impetigo is a typical disease seen and treated by general practitioners.

In **chapter 2**, we describe a randomised placebo controlled trial into the effectiveness of fusidic acid cream. We tested the hypothesis that fusidic acid would not increase the treatment effect of disinfecting with povidone-iodine alone in children with impetigo. 160 children aged 0-12 years with impetigo attending general practices in Greater Rotterdam were randomized. After one week of treatment 55% of the patients in the fusidic acid group were clinically cured compared with 13% in the placebo group (odds ratio 12.6, 95% confidence interval 5.0 to 31.5, number needed to treat 2.3). More children in the placebo group were non-compliant (12 v 5) and received extra antibiotic treatment (11 v 3). *S. aureus* was found in 96% of the positive cultures; no strains were resistant to fusidic acid. We concluded that fusidic acid is much more effective than placebo (when both are given in combination with povidone-iodine shampoo) in the treatment of impetigo. Because of the low rate of cure and high rate of adverse events in the placebo group, the value of povidone-iodine in impetigo can be questioned.

In **chapter 3** we investigated whether staphylococcal nasal carriage and the nature of the staphylococcal strains are associated with severity and course of impetigo. Staphylococcal toxins are known mediators of bullous impetigo in children. It is not known whether this is also true for non-bullous impetigo. We set out to analyze clonality among clinical isolates of *S. aureus* derived from the children with non-bullous impetigo in the trial described in the previous chapter. Bacterial isolates were obtained from the nose and impetigo lesions. Strains were genetically characterized by pulsed field gel electrophoresis-mediated typing and binary typing which also assessed toxin

gene content. Staphylococcal nasal carriage seems to predispose to the development of impetigo and 34% of infections diagnosed in the Rotterdam area were caused by one clonal type of *S. aureus*. The *S. aureus* strains harbored the exfoliative toxin B (ETB) gene as a specific virulence factor. Especially the number ($p=0.002$) and size ($p<0.001$) of the lesions were increased in case of infection by an ETB-positive strain. The presence of a staphylococcal plasmid encoding multiple antibiotic resistance traits was associated with a lower cure rate. Our results imply that a combination of staphylococcal virulence and resistance genes determines the development and course of non-bullous impetigo.

In **chapter 4**, we systematically reviewed the effects of treatments for impetigo, including waiting for natural resolution from randomised controlled trials of treatments for non-bullous and bullous, primary and secondary impetigo. We searched electronic databases such as the Cochrane Skin Group Specialised Trials Register, Cochrane Central Register of Controlled Trials, the National Research Register, MEDLINE, EMBASE and LILACS. We hand searched yearbooks and used reference lists of articles and contacted trialists and pharmaceutical companies.
We included 57 trials including 3533 participants in total which studied 20 different oral and 18 different topical treatments. Topical antibiotics showed better cure rates than placebo (pooled odds ratio (OR) 6.49, 95% confidence interval (CI) 3.93 to 10.73), and no topical antibiotic was superior (pooled OR of mupirocin versus fusidic acid 1.76, 95% CI 0.69 to 2.16). Topical mupirocin was superior to oral erythromycin (pooled OR 1.22, 95% CI 1.05 to 2.97). In most other comparisons, topical and oral antibiotics did not show significantly different cure rates, nor did most trials comparing oral antibiotics. Penicillin was inferior to erythromycin and cloxacillin and there is little evidence that using disinfectant solutions improves impetigo. The reported number of side effects was low. Oral antibiotic treatment caused more side effects, especially gastrointestinal ones, than topical treatment.
We conclude that placebo controlled trials are scarce. There is little evidence about the value of disinfecting measures. There is good evidence that topical mupirocin and topical fusidic acid are equally, or more effective than oral antibiotics for people with limited disease. It is unclear if oral antibiotics are superior to topical antibiotics for people with extensive impetigo. Fusidic acid and mupirocin are of similar efficacy. Penicillin was not as effective as most other antibiotics.

In **chapter 5** trends in incidence and treatment of impetigo between 1987 and 2001 are described, using data from two Dutch national surveys of general practice. The incidence rate of impetigo increased from 16.5 (1987) to 20.5 (2001) per 1000 person years under 18 years old ($p< 0.01$). In both years, the incidence was significantly higher

in summer, in rural areas and in the southern region of the Netherlands, compared to winter, urban areas and northern region respectively. Socio-economic status was not associated with the incidence rate. From 1987 to 2001, there was a trend towards prescribing topical antibiotic treatment (from 40% to 64%), especially fusidic acid cream and mupirocin cream.

In **chapter 6** we establish the course of impetigo before and after consulting the GP, and the treatment advised by GPs and applied by patients derived from a subset of 35 practices of the national survey. We included sixty-three children with impetigo. The GP prescribed a topical antibiotic in 71% of the cases, usually fusidic acid cream and an oral antibiotic in 21% of the cases, usually erythromycin. The percentage of cured patients was 70% at two weeks and rose to 97% at 13 weeks. 11% of the patients had a recurrence of impetigo after initial cure. Half of the patients that were not cured or had a recurrence did not consult the GP again.

General discussion

Epidemiology and bacteriology

In the Netherlands, impetigo cannot be considered as a condition in decline, as we show in this thesis. This observation is consistent with data from a continuous morbidity registration project in the Netherlands. (1) The increased incidence in 2001 versus 1987 may reflect an increased tendency to seek medical help. However, the general practice consultation rate for all diseases in children aged 0-17 years has decreased in the same period from 2.7 to 2.1 consultations per year, (2) and furthermore the consultation rate for other common skin diseases such as viral warts and eczema has also decreased considerably. The (disputable) custom to exclude impetigo patients from schools might specifically promote medical help seeking behaviour for this condition, but excluding children is advised for many other conditions as well. We therefore believe that we see a true increased incidence. This increase may be the result of changing host factors and/or changing bacterial factors. A traditionally recognised risk factor like lower social class was not confirmed as such by our study. We found no relationship between the incidence of impetigo and social class, although this may be different in developing countries (3). Other changing human behaviour such as increased travelling abroad may be an explanation. At the bacterial side, rising resistance rates or selection of more virulent strains may be determinants.

We have identified genetic staphylococcal markers, especially exfoliative toxin B, that determine the severity and duration of impetigo. We also showed that one clonal type of *S. aureus* was the cause of 34% of the cases of impetigo in our study among GP patients, which lasted for 20 months and took place in the greater Rotterdam area. This suggests that specific clones of *S. aureus* harbouring specific toxin genes are more likely to cause impetigo and cause more serious or more contagious infections. This observation has been confirmed in Sweden and Norway. (4,5)

The identification of these microbial genetic markers, that are predictive for severity and course of the disease, might facilitate the choice of anti-microbial therapy. Both the decision whether or not to treat an individual impetigo patient, and if so how, might be guided in the future by the characteristics of the *S. aureus*.

Treatment

For the clinician the choice of treatment will be based primarily on effectiveness and side effects and then on costs and convenience for the patient. A responsible doctor will also consider the problem of increasing bacterial resistance.

As shown by our trial and the systematic review of publishes randomised controlled trials, treatment with topical antibiotics with either mupirocin or fusidic acid can be considered at least as or even more effective than treatment with oral antibiotics. Topical

antibiotics other than mupirocin and fusidic acid can be considered inferior. Regarding oral antibiotic treatment, based on the available evidence on efficacy, no clear preference can be given for B-lactamase resistant narrow-spectrum penicillins such as cloxacillin, dicloxacillin and flucloxacillin, broad spectrum penicillins such ampicillin and amoxicillin plus clavulanic acid, cephalosporins, and macrolides. Oral penicillin was found to be inferior to most other orally administered antibiotics. In general, oral antibiotics have more side effects than topical antibiotics, especially gastrointestinal side effects. There is insufficient evidence to say whether oral antibiotics are better than topicals for more serious and extensive forms of impetigo. From a practical standpoint, oral antibiotics might be an easier option for people with very extensive impetigo.

We have no evidence to support the therapeutic use of disinfecting agents such as chlorhexidine or povidone-iodine as effective measures in the treatment of impetigo. Antibacterial soap did seem to be effective in the prevention of impetigo. (6)

According to the evidence the best choice for treatment of limited impetigo is either topical mupirocin or topical fusidic acid. We showed that Dutch general practitioners choose treatment according to this evidence, (chapter 5) instead of following their national practice guideline, which recommends zinc oxide cream and disinfectant therapy. (7) The trend in prescribing for impetigo apparently follows evidence-based knowledge on the effectiveness of different therapies, rather than the national practice guideline.

Recently, however, concern has been raised about the use of topical fusidic acid. The rising resistance rates of *S. aureus* against fusidic acid call for its prudent use. (8,9,10,11) In a Welsh study, the presence of fusidic resistance in *S. aureus* from impetigo patients was related to previous use of fusidic acid cream. (12) Although a link between prescribing antibiotics and resistance has been established at the level of the individual, (13) this relation is unclear at practice level or even group level. (14) Generally, higher prescription rates seem to be associated with higher resistance rates. Moreover, especially prolonged use of antibiotics in chronic conditions seems to be an important factor in the promotion of resistance. (15,16) A study in which impetiginized eczema was treated for two weeks did not result in resistance. (17) This means that a short antibiotic course of one to two weeks for acute primary impetigo should be relatively harmless. However more prolongued use, as is sometimes done on eczema patients, should be discouraged.

The effectiveness of any antibiotic is dependent on the susceptibility of the causative bacteria. In impetigo this is usually *S. aureus*. Resistance rates in staphylococci against fusidic acid vary considerably between regions and in time. (10,16) Therefore, treatment of impetigo should ideally be guided by susceptibility testing of a *S. aureus* isolate obtained from the patient. However, this time consuming procedure is hardly feasible in general practice and therefore is seldom done. Development of an easy and quick method of susceptibility testing for general practice would therefore be very helpful.

The final choice of treatment can be determined best by regional or national guideline developing bodies. Knowledge of local resistance patterns on the basis of surveillance of specimens derived from general practice should be incorporated in these documents. Furthermore, they may contain policies to reserve certain antibiotics for the treatment of other, more serious infections. For example, systemic fusidic acid is considered vital in the treatment of severe bone infections, and mupirocin is a cornerstone in eradication of methicillin resistant *S. aureus* carriage. Other criteria such as price and unnecessary broadness of spectrum may also be decisive. Frequently updated guidelines of this kind are not available yet in most parts of the world.

Limitations of this research

There is a commonly accepted idea that more serious forms of impetigo (e.g. participants with extensive lesions, general illness, fever) need oral rather than topical treatment. This principle cannot be evaluated using the data collected in this thesis, as trials that study local treatments usually exclude participants with more serious forms of impetigo.

None of the placebo controlled studies reported cases of acute (post streptococcal) glomerulonephritis. This complication has always been an important rationale for oral antibiotic treatment. The apparent absence of glomerulonephritis may reflect the reduced importance of streptococci in impetigo. It should be noted however that study sizes are small and glomerulonephritis is rare.

As our research has been conducted in general practice, the results may therefore not be applicable to referred patients and hospital admitted patients. Probably, these patients have more serious, therapy resistant impetigo, more co-morbidity and carry staphylococci that are more virulent and antibiotic resistant. This difference was not always acknowledged by other researchers and has led to surprise if not disbelief about the low resistance rate to fusidic acid we found in *S. aureus*. (18,9,10) Also the generally low rate of outpatients' use of antibiotics in the Netherlands may contribute to lower resistance rates than elsewhere. (19)

Many trials in the review however, were included that were carried out in hospital settings. Furthermore, regional and national differences may prevent applying data from one region to other regions. Especially resistance rates are known to differ enormously between countries and regions.

Recommendations for future research

More knowledge about the genetic characteristics of impetigo causing staphylococci, and the development of rapid test for these factors could eventually lead to an individual treatment approach, preventing both excessive (antibiotic) treatment but also under treatment, leading to epidemics.

As part of the issue of antibiotic resistance, more studies that establish the contribution of a given treatment for impetigo to the development of bacterial resistance, such as Ravenscroft (17), are desirable. Our hypothesis in chapter 5 that there may be causality in the association of the incidence of impetigo and the location of the pig farming industry in the Netherlands merits further study. This research would consist of bacteriological typing and comparison of staphylococcal strains derived from impetigo patients in different regions of the country and from pigs.

Other questions that need to be answered are whether prompt treatment of impetigo reduces contagiousness or prevents epidemics, and whether barring affected children from school is an effective measure towards prevention.

Research trying to establish the untreated course of impetigo would be very useful. But although impetigo can be considered a minor ailment, studies with a non-intervention arm seem ethically impracticable.

The relative absence of data from well designed randomised controlled trials on the efficacy of topical disinfectants should urge researchers to study these, since they do not contribute to antibiotic resistance and are cheap. This research may be of particular importance for developing countries, and will have to be financed by governmental bodies because there is no commercial imperative.

In order to make randomized clinical trials more easily comparable, trialists should preferably not combine data for several skin diseases, present results separately if they do study several diseases, use clear and objective outcome measures and standardization of moments for assessment of cure and improvement. Furthermore, they should report resistance rates and include a placebo group, or at least a 'gold standard' reference group. Future trials on impetigo should make careful power calculations, as most studies were too small to be able to assess clinically relevant differences in treatment effect.

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Samenvatting

Impetigo is een bij kinderen veel voorkomende huidinfectie, meestal veroorzaakt door de bacterie *Staphylococcus aureus*. Patiënten met impetigo consulteren vaak de huisarts, die het overgrote deel van de gevallen zelf behandelt. Impetigo wordt als zeer besmettelijk gezien, en daarom worden kinderen met impetigo veelal van scholen en crèches geweerd. Zowel patiënten als artsen willen graag een snelle en effectieve behandeling. Hoewel de verantwoordelijke bacterie bekend is, kennen we geen bacteriële factoren die de ernst van de impetigo bepalen. Er wordt regelmatig melding gemaakt van epidemieën, maar recente gegevens over het vóórkomen van impetigo ontbreken. Er bestaan vele behandelopties, maar er is altijd veel discussie geweest over de meest effectieve behandeling.

Het algemene doel van dit proefschrift was om epidemiologische gegevens over impetigo te verzamelen, om zowel bij de patiënt als bij de bacterie factoren te identificeren die bijdragen aan het ontstaan en de verspreiding van impetigo, en om bewijs te verzamelen voor de effectiviteit van alle mogelijke behandelingen van impetigo. Wij voerden zelf onderzoek uit, waaronder een trial, en analyseerden gegevens die door anderen zijn verzameld. De setting van ons eigen onderzoek was steeds de huisartspraktijk omdat, in ieder geval in Nederland, impetigo vooral een ziekte is die door huisartsen gezien en behandeld wordt.

In **hoofdstuk 2** beschrijven we een gerandomiseerd placebo gecontroleerd onderzoek naar de effectiviteit van fusidinezuurcrème. Wij testten de hypothese dat fusidinezuur het behandeleffect van alleen jodium niet zou vergroten. 160 kinderen van 0 tot 12 jaar met impetigo die daarvoor de huisarts bezochten in de regio Rotterdam werden gerandomiseerd. Na een week behandeling was 55% van de kinderen in de fusidinezuurgroep genezen, tegenover 13% van de kinderen in de placebo groep. Dit betekent dat de huisarts 2 à 3 kinderen die impetigo hebben met fusidinezuur moet behandelen om na een week één kind extra te genezen. In de placebo groep weken meer kinderen af van de voorgeschreven medicatie (12 versus 5) en kregen meer kinderen een extra antibioticum (11 versus 3). In 96% van de positieve kweken werd *S. aureus* gevonden; geen van de stammen was resistent voor fusidinezuur. Wij concludeerden dat bij de behandeling van impetigo fusidinezuur veel effectiever is dan placebo (wanneer beide gegeven worden in aanvulling op jodium). Vanwege het lage genezingspercentage en het hoge percentage bijwerkingen in de placebogroep, kunnen vraagtekens geplaatst worden bij de waarde van jodium.

In **hoofdstuk 3** onderzochten we of *S. aureus* neusdragerschap en de aard van de *S. aureus* stammen geassocieerd zijn met de ernst en het beloop van de impetigo.
Van stafylokokken toxinen is bekend dat zij van invloed zijn op impetigo bullosa bij kinderen. Het is onbekend of dit ook geldt voor impetigo vulgaris. Wij analyseerden klonale verwantschap bij stammen die verkregen waren van de impetigo-kinderen in de trial, beschreven in het vorige hoofdstuk. Van de neus en de impetigo plekken werden kweken afgenomen. Stammen werden genetisch gekarakteriseerd door middel van "pulsed field gel electrophorese typering", en binaire typering, waarmee ook het toxine gehalte werd vastgesteld. De aanwezigheid van *S. aureus* in de neus lijkt te predisponeren voor het ontstaan van impetigo, en 34% van de onderzochte impetigo-infecties in de regio Rotterdam bleek te worden veroorzaakt door één enkel klonaal type *S. aureus*. De *S. aureus* stammen bezitten het exfoliatieve toxine B (ETB) als specifieke virulentiefactor. Vooral het aantal en het oppervlak van de laesie was vergroot in geval van infectie met een ETB positieve stam. De aanwezigheid van een stafylokokkenplasmide dat codeert voor meervoudige antibioticaresistentie was geassocieerd met een lager genezingspercentage. Onze resultaten betekenen dat de aanwezigheid van een combinatie van verschillende virulentie- en resistentiegenen in *S. aureus* medebepalend zijn voor het ontstaan en het beloop van impetigo vulgaris bij kinderen.

In **hoofdstuk 4** hebben we in een literatuuroverzicht de effecten naast elkaar gezet van alle behandelingen van impetigo (inclusief wachten op spontane genezing) afkomstig van alle gerandomiseerde onderzoeken die zijn gedaan naar de behandeling van bulleuze, non-bulleuze, primaire en secundaire impetigo. Wij doorzochten elektronische databestanden zoals het Cochrane Skin Group Specialised Trials Register, het National Research Register, het Cochrane Central Register of Registered Trials, Medline, Embase, en Lilacs. Wij doorzochten jaarboeken en keken literatuurverwijzingen na, en namen contact op met onderzoekers en met farmaceutische bedrijven.
Wij vonden uiteindelijk 57 geschikte trials, die 20 verschillende orale en 18 verschillende lokale behandelingen onderzochten bij in totaal 3533 patiënten. Lokaal toegepaste antibiotica (crèmes) hadden betere genezingspercentages dan orale antibiotica, en de effectiviteit van fusidinezuur en mupirocine verschilde niet. Lokaal mupirocine was superieur ten opzichte van oraal erytromycine. Bij de meeste andere vergelijkingen tussen orale en lokale antibiotica werden geen significante verschillen in genezingspercentage gevonden, en ook niet bij vergelijkingen tussen verschillende orale antibiotica. Penicilline was inferieur aan erytromycine en cloxacilline. We vonden weinig bewijs dat het gebruik van desinfecterende middelen impetigo doet verbeteren. Placebo gecontroleerd bleek schaars. Het is onduidelijk of orale antibiotica beter zijn voor patiënten met zeer uitgebreide impetigo.

In **hoofdstuk 5** worden trends in incidentie en behandeling van impetigo beschreven tussen 1987 en 2001. Voor dit onderzoek werd gebruik gemaakt van de twee Nationale studies naar ziekten en verrichtingen in de huisartspraktijk. De incidentie van impetigo bij kinderen tot 18 jaar steeg van 16,5 (1987) naar 20,5 (2001) per 1000 persoonsjaren onder de leeftijd van 18 jaar. In beide jaren was de incidentie significant hoger in de zomer, op het platteland en in het zuiden van Nederland, vergeleken met respectievelijk de winter, de grote steden en de noordelijke regio. Sociaal economische status was, in tegenstelling tot wat vaak gedacht wordt, niet gerelateerd aan het vóórkomen van impetigo.

In **hoofdstuk 6** beschrijven wij het beloop van impetigo, zowel voordat de huisarts geconsulteerd wordt als daarna, de behandeling die door huisartsen geadviseerd wordt, en de behandeling die door patiënten wordt toegepast. Wij onderzochten dit bij patiënten van 35 praktijken die aan de nationale studie deelnamen. 63 kinderen met impetigo werden geïncludeerd. De huisarts schreef in 71% van de gevallen een lokaal antibioticum voor (meestal fusidinezuurcrème) en in 21% van de gevallen een oraal antibioticum, meestal erytromycine. Het percentage genezen patiënten was 70% na 2 weken en steeg tot 97% na 13 weken. 11% van de patiënten had na genezing een recidief van de impetigo. De helft van de patiënten die niet genazen of opnieuw impetigo kregen, ging niet opnieuw naar de huisarts.

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Met mijn opeenvolgende kamergenoten van de eerste jaren, Marjolein Tasche, Marco Blanker, Léonie Damen, Marjolein Berger en Herman Bueving, heb ik plezier gehad, en zij waren inspirerende voorbeelden. Corine, Arianne, Hanneke, Annet, Robbert, Elsbeth, Michiel, Sita en Bart zijn meer recent kamergenoten geweest. Ook de overige onderzoekers, zowel van de Westzeedijk als van wat tegenwoordig “de overkant” heet, dank ik voor hun gezelligheid en collegialiteit.

De deelnemende huisartsen aan de trial, aan de nationale studie en aan de beloopstudie hebben gezorgd voor het onderzoeksmateriaal. Dat waren de kinderen met

krentenbaard, zoals mijn overbuurmeisje Mirre. De andere kinderen zijn de anonieme helden van dit verhaal.

Curriculum Vitae

Sander Koning werd op 1 februari 1967 in Utrecht geboren. In 1985 behaalde hij het gymnasiumdiploma aan de Rijksscholengemeenschap "Schoonoord" in Zeist. Hij volgde kortdurend colleges scheikunde te Utrecht alvorens te starten met de geneeskundestudie aan de Erasmus Universiteit Rotterdam. Binnen de onderzoeksstage ondernam hij studies naar wratten en molluscum contagiosum, en hij legde in 1993 het artsexamen af. Na een jaar als dienstplichtig militair arts in Weert te hebben gewerkt, volgde hij van 1994 tot 1997 de huisartsopleiding in Rotterdam. Hiervan waren stages huisartsgeneeskunde te Vlaardingen (opleider F.B.M. Kuis) en Putte (opleider W.J.C.A.L. de Graaf) en interne geneeskunde in Breda (opleider dr. P.J. Stijnen) onderdeel. Na een waarneemperiode van anderhalf jaar in diverse praktijken, voert hij sinds 1999 een duo-huisartspraktijk te Vlaardingen. Tegelijkertijd was hij verbonden aan de afdeling huisartsgeneeskunde van het Erasmus MC, waar hij aan de in dit proefschrift beschreven onderzoeken heeft gewerkt. Hij is in Vlaardingen bestuurslid van het transmuraal medisch centrum en lid van de kwaliteitscommissie van de centrale huisartsenpost. Sander Koning woont samen met Siska van Heerwaarden.