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Where to from here? The treatment of impetigo in children as resistance to fusidic acid emerges

Alison Vogel, Diana Lennon, Emma Best, Alison Leversha

ABSTRACT
Admissions for skin and soft-tissue infections have been increasing steadily in children and in the general population. Concerns have been raised recently about the increasing widespread use of topical fusidic acid and concurrent increase of fusidic acid-resistant *Staphylococcus aureus*. Fusidic acid resistance and methicillin resistant *Staphylococcus aureus* (MRSA) are both more prevalent in youngest age group (<5 year-olds) and particularly in the North island. In New Zealand, fusidic acid is recommended for treatment of minor impetigo and is the only fully-funded topical antibiotic. The evidence base for alternative treatment strategies for mild impetigo is limited. Most children with impetigo in the current skin and sore throat schools programmes received care with wound management with only a few requiring escalation. An upcoming randomised controlled trial comparing topical hydrogen peroxide cream, topical fusidic acid and wound management only (clean and cover) will help provide evidence about the effectiveness of alternative treatments in the New Zealand setting.

Background
Hospitalisations due to *Staphylococcus aureus* (*S. aureus*) infections have been steadily increasing in New Zealand; a trend also recognised internationally. In New Zealand, admissions are predominantly due to community-onset, methicillin susceptible *S. aureus* (MSSA) skin and soft tissue infections (SSTI) with admission rates for staphylococcal SSTIs in New Zealand increasing approximately 5% per year from 2000 to 2011. SSTI admission rates are highest for preschool children, the elderly, Māori and Pacific populations, among those living in the most deprived deciles and in Northern and Central regions. It is estimated that for each hospital admission, up to 14 children may visit their general practice with an SSTI.

Impetigo has often been regarded as a minor skin complaint. However, the high burden and the possibility of more serious sequelae (serious skin sepsis leading to hospitalisation or post-streptococcal glomerulonephritis) is acknowledged. In addition, current guidance includes recommendations that children should not attend school or day-care until 24 hours after antibiotic treatment has been commenced. With recurrent and household re-infections, such measures can potentially result in significant time off school with consequent educational impact for children and impact on work for parents.

Current treatment advice for minor skin infections outlines a small number of indications for topical antibiotics including children with localised impetigo (no more than three areas of the body affected or <5cm; <5% of body surface area) with topical fusidic acid being the first choice. In addition it is the Pharmac-subsidised topical antimicrobial. The second-line topical antibiotic, mupirocin, which has additional methicillin resistant *S. aureus* (MRSA) activity, is reserved for small localised areas of infection resistant to fusidic acid with funding restricted to proven MRSA infection. For other infective skin conditions such as boils and carbuncles, treatment is incision and drainage without antibiotics and oral antibiotics are reserved for more extensive areas of infection, cellulitis or skin infection with systemic symptoms. However, increased resistance amongst *S. aureus* to fusidic acid is a concerning development and has
coincided with rising prescription rates for fusidic acid. Rates of prescribing are highest for preschool children followed by those age 75+ and 5–14 years. Dispensing rates are highest for Pacific and Māori, and in the Northern regions. Rates of mupirocin dispensing have fallen significantly, coincident with removal of the Pharmac subsidy. Concern about the increasing resistance to fusidic acid has led to calls to consider limiting access via prescriber and funding restrictions.

Fusidic acid resistance is important for three reasons. It may lead to ineffective treatment in SSTI. Fusidic acid resistance may be associated with other antimicrobial resistance and an increasing prevalence of MRSA. The gene conferring fusidic acid resistance (FusC) and the gene conferring methicillin resistance (MecA) are located on the same mobile genetic element. A specific fusidic acid-resistant community associated methicillin-resistant clone (AK3) has recently emerged to rapidly become the current dominant MRSA clone causing illness in New Zealand. Thirdly, fusidic acid is also available in oral and intravenous formulations with a limited role as part of combination adjunctive treatment for invasive infections, especially of bone and joints (including those caused by MRSA) and efficacy in these situations might be impacted.

Microbiology and resistance patterns

Impetigo has traditionally been considered due to Streptococcus pyogenes although the role of co-infection with S. aureus may be important. Most studies do not include phage typing which if done suggests S. aureus may only be a secondary invader and not require specific treatment. S. aureus is thought to be the more common causative impetigo pathogen in temperate climates while S. pyogenes may be more common in warmer, humid regions. There are no published New Zealand data describing the prevalence of S. aureus and S. pyogenes in impetigo in the community.

National data for S. aureus antimicrobial resistance patterns and molecular epidemiology from community laboratory isolates for children with skin and soft tissue infections is available from a national survey of laboratory isolates performed in 2014 by ESR. (Table 1: reproduced with permission Helen Heffernan ESR). Almost half the isolates from pre-schoolers were fusidic acid resistant, and 20% of those from school age children. Fusidic acid resistance and methicillin resistant Staphylococcus aureus (MRSA) are both more prevalent in the youngest age group (<5 year olds) and particularly in the North Island.

The call to reduce fusidic acid use requires urgent reconsideration of the best strategies.

Table 1: Antimicrobial resistance for community acquired S. aureus skin and soft tissue infections in children by age: New Zealand 2014.

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MSSA</th>
<th>MRSA</th>
<th>All S. aureus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–4 y</td>
<td>5–14 y</td>
<td>0–4 y</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>36.8</td>
<td>16.7</td>
<td>93.7</td>
</tr>
<tr>
<td>Mupirocin</td>
<td>10.2</td>
<td>10.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>14.7</td>
<td>2.5</td>
<td>6.3</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

MSSA: methicillin-sensitive S. aureus
MRSA: methicillin-resistant S. aureus
Source: Heffernan et al 2015, ESR
for impetigo treatment relevant to current New Zealand pathogenesis and resistance patterns. Although inappropriate use of topical fusidic acid may also occur in other age groups, the large burden of SSTI, high use of fusidic acid and very high rates of resistance in young children means the problem needs to be addressed at this level.

**Treatment strategies for impetigo**

The basis of current recommendations for childhood impetigo treatment in New Zealand is a Cochrane review of treatment for impetigo, with local guidelines influenced by considerations of availability and funding. The Cochrane review is a meta-analysis of evidence from randomised controlled trials identified to July 2010.22 For this article we applied the search strategy from the Cochrane review to search for further relevant literature indexed in Medline or Embase from 2010 to March 2016, and reviewed abstracts to determine relevance.

**Topical antibiotics**

In New Zealand, fusidic acid and mupirocin are the two available topical antibiotics. Retapamulin is a newer alternative topical antibiotic available overseas. Mupirocin, fusidic acid or retapamulin are more effective compared with placebo cream in RCTs, although some of this evidence includes studies aged up to 30 years old.22,23 There is no difference in cure rates between fusidic acid and mupirocin22 or between retapamulin and fusidic acid.24

Prior to the year 2000, mupirocin was available as a pharmacy dispensed agent with no restrictions and was also subsidised on prescription. Community dispensing rates of mupirocin in the late 1990s were high and associated with higher rates of mupirocin resistance in *S. aureus*25 which has dropped following removal of Pharmac subsidy and restricted prescribing indications.17 Mupirocin remains useful for decontamination for MRSA and this, along with prior resistance in the face of high community use, means it is inappropriate to use in routine treatment of impetigo in the community. Resistance to retapamulin has also been reported (seen in almost 10% of *S. aureus* in a Texan study),26 again indicating that use of topical antibiotics is likely to lead to resistance in skin pathogen flora.

**Hygiene intervention:** “Clean, Cut, Cover”.

The simplest treatment strategy is using ‘Clean, Cut (finger nails), Cover’ advice without topical or oral agents.11,12 Nurse-led school clinics have been implemented since 2012 in 61 Counties Manukau schools as part of initiatives to address high rates of rheumatic fever and serious skin infection. In 2013 6,774 skin infections were treated and over 10,000 in the first nine months of 2014.27 Analysis of a sample shows that only 4% of those assessed with skin infections were prescribed antimicrobials, mostly topical fusidic acid or oral cephalexin.28 Therefore the vast majority were treated with the ‘Clean, Cut, Cover’ advice. The Cochrane review demonstrated studies with placebo cream found cure rates ranging from 8–42% at 7–10 days.22

**Antiseptic creams**

Antiseptic topical agents that have been used to treat impetigo include hydrogen peroxide, povidine iodine and chlorhexidine solution.29 There is an identified research gap in the evidence about the effectiveness of antiseptic agents.21 Evidence is summarised in the table below (Table 2).

**Table 2: Evidence for use of antiseptic creams.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence Type</th>
<th>Author, year</th>
<th>Site</th>
<th>Age</th>
<th>Comparison</th>
<th>Number</th>
<th>Outcomes measured</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen peroxide</td>
<td>RCT</td>
<td>Christensen 199430</td>
<td>UK, Sweden, Germany total 47 sites</td>
<td>2–74 yrs</td>
<td>Hydrogen peroxide vs fusidic acid, 2–3x daily to maximum 21 days</td>
<td>256</td>
<td>Healing; composite severity score, assessed 3, 7, 14, 21 days</td>
<td>HP 72% healed vs 82% fusidic acid NS</td>
<td>Composite report of three trials. Poor quality-in-adequate blinding.</td>
</tr>
<tr>
<td>Povidine iodine cream</td>
<td>No trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorhexidine cream</td>
<td>No trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HP: hydrogen peroxide
Importantly, reported resistance is much lower for topical antiseptics and mechanisms of resistance more complex for the organism. Antiseptics are also not related to antibiotics used for systemic treatment of infection therefore even if it does occur, development of resistance is less concerning. Reported resistance, adverse effects and current funding/availability are shown in Table 3.

### Table 3: Alternative antiseptic topical treatments in New Zealand.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Resistance</th>
<th>Adverse events</th>
<th>Funding in New Zealand</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen peroxide</td>
<td>Not reported</td>
<td>Short term burning Mild SE 11% HP vs 7% fusidic acid(^3)</td>
<td>Funded General sale</td>
<td>$8.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15g</td>
</tr>
<tr>
<td>Povidine iodine cream</td>
<td>Some</td>
<td>Sensitivity (rare) Interference with thyroid function tests Avoid if breastfeeding</td>
<td>Funded General sale</td>
<td>$3.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25g</td>
</tr>
<tr>
<td>Chlorhexidine cream</td>
<td>Some reports(^3)</td>
<td>Contact dermatitis, rare severe hypersensitivity (Medsafe warning)(^3)</td>
<td>General sale Cost??</td>
<td></td>
</tr>
</tbody>
</table>

Oral or intramuscular antibiotic treatment for impetigo

For moderate to severe impetigo, recommendations are for the use of oral antibiotics.\(^1\) The preferred options are flucloxacillin or cephalexin in children where palatability of flucloxacillin elixir is an issue.\(^3\) Erythromycin is indicated in penicillin allergy and co-trimoxazole for MRSA.\(^1\)

A recent rigorously performed randomised controlled trial in the Northern Territory of Australia raises pertinent questions for the management of impetigo in New Zealand.\(^3\) This non-inferiority trial enrolled 508 indigenous children aged three months to 13 years; 72% of whom had severe impetigo (as defined as two or more purulent or crusted sores, or five or more sores in total). Treatment with intramuscular benzathine penicillin was compared with the use of twice daily co-trimoxazole (4mg/kg plus 20mg/kg) for three days or once daily co-trimoxazole (8mg/kg plus 40mg/kg) for five days. Benzathine penicillin has been widely used in tropical settings to treat extensive impetigo although oral penicillin is not effective.\(^2\) Cotrimoxazole was used due to high community prevalence of MRSA being reported and isolated from impetigo lesions. The primary outcome was treatment success at day seven as measured by blinded assessment of photographs of the most severe lesion(s). Treatment was successful at 85% in each arm at seven days. S. aureus was identified from 81% of children, S. pyogenes from 90% and both from 74% pre-treatment. Ninety-percent of adverse events occurred in the benzathine penicillin group. The only independent predictor of treatment success was clearance of S. pyogenes. Clearance of S. aureus was not an independent predictor.\(^3\)

Important differences about health access mean that in remote communities where close supervision is difficult the use of long acting IM agents was justified, in contrast to New Zealand where close follow-up of high risk groups is usually possible via school-based clinics or primary care. The use of shorter courses of oral antibiotic treatment however is effective in severe lesions.

### Conclusion

The dual concerns of increasing rates of skin infection and increasing antibiotic resistance to fusidic acid require careful deliberation. Despite the prevalence of this problem there is insufficient evidence to guide informed treatment of childhood impetigo in the New Zealand context. The current large scale (population served 5–12 year-olds ~ n=30,000) community interventions to manage skin infections in school age children such as those occurring in Auckland offer an excellent opportunity to advance knowledge.\(^2\) These include studies to determine the relative frequency of S. aureus and S. pyogenes and of mixed
infections and ongoing surveillance of resistance patterns among isolates from skin infections. Shorter courses of oral antibiotics may be effective and could be subject to study. More pressingly, there is a need for well conducted trials of alternative treatments particularly the use of antiseptic creams. An upcoming funded randomised controlled trial (ACTRN 1261600356460p) of mild to moderate impetigo in school children comparing topical hydrogen peroxide cream, topical fusidic acid and local therapies only (clean and cover) should provide evidence about the effectiveness of alternative treatments. The school-based health services operating in low decile schools across the Auckland region provide an ideal opportunity for this to be examined.

Competing interests:
Nil.

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