A fusidic acid-resistant clone of *Staphylococcus aureus* associated with impetigo bullosa is spreading in Norway

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**Objective:** To investigate the possibility that the increased prevalence of fusidic acid-resistant *Staphylococcus aureus* in Norway is caused by clonal spread.

**Methods:** Fusidic acid-resistant and -susceptible clinical isolates of *S. aureus* from patients with skin infections in the Norwegian county of Telemark and fusidic acid-resistant isolates from other parts of Scandinavia were compared. MICs of fusidic acid for bacterial isolates and pulsed-field gel electrophoresis (PFGE) patterns were investigated. Prevalence data for fusidic acid-resistant *S. aureus* for the period 1992–2001 were obtained.

**Results:** The prevalence of fusidic acid resistance in *S. aureus* increased from 1992 to 2001. Eighty per cent of the resistant isolates investigated shared an identical PFGE pattern. The same pattern was found in fusidic acid-resistant isolates from other parts of Scandinavia. Fusidic acid-resistant *S. aureus* was typically found in impetigo bullosa-like skin disease in children mostly in the summer months.

**Conclusions:** Fusidic acid resistance among *S. aureus* is increasing in Norway and is predominantly caused by one clone of *S. aureus*. The clone may spread further to other countries, and dissemination may be facilitated by extensive use of topical fusidic acid.

Keywords: pulsed-field gel electrophoresis, MIC, clonal

**Introduction**

Fusidic acid is a narrow-spectrum bacteriostatic antibiotic, particularly active against staphylococci. Fusidic acid has been advocated for use against impetigo on the basis of the results of controlled trials.¹⁻³ The preparation is also effective against invasive *Staphylococcus aureus* infections, and some authors have advised against topical use because of its value in systemic treatment.²

Since the introduction of fusidic acid in the 1960s, there have been scattered reports of increased resistance,⁴,⁵ but the majority of studies have reported a low prevalence of fusidic acid resistance among *S. aureus* and therefore resistance has not been regarded as a present or potential problem.⁶ Recently, however, a number of groups have reported fusidic acid resistance to be on the increase.⁷,⁸ It is not yet known to what extent these increases represent widespread dissemination of resistant strains, spread of resistance genes or selection of fusidic acid-resistant variants locally.

In the Scandinavian countries, fusidic acid has been used extensively for topical treatment of superficial skin infections for many years, irrespective of the aetiology. Until recently, >90% of *S. aureus* isolates from Norway were susceptible to fusidic acid.⁹

In the summer and early autumn of 1999, we noticed a marked increase in enquiries to our laboratory concerning outbreaks of impetigo among children. ‘Impetigo’ encompasses two different clinical entities. Impetigo contagiosa is caused by *Streptococcus pyogenes*, but *S. aureus* can secondarily infect impetigo contagiosa lesions. Impetigo bullosa, a superficial cutaneous disorder occurring predominantly in children, is caused by *S. aureus*. In impetigo bullosa, an epidermal split caused by exfoliating toxins results in the formation of 1–2 cm bullae containing neutrophils and

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staphylococci. Bacteriological investigations from these impetigous lesions frequently showed the presence of S. aureus, a majority of which were resistant to fusidic acid. This pattern was repeated in the summer months of 2000 and 2001. Similar observations were reported from other parts of Norway and from Sweden.

The present study was undertaken to determine the prevalence of fusidic acid-resistant S. aureus in our region and to analyse the clonal relationship of such isolates by pulsed-field gel electrophoresis (PFGE).

Materials and methods

Resistance data

Resistance data for S. aureus from 1 January 1992 to 31 December 2001 were retrieved from our laboratory records.

Bacterial strains

Thirty consecutive isolates of fusidic acid-resistant S. aureus from outpatients with the clinical diagnosis of impetigo were collected in August in both 2000 and 2001. Thirty-three of these isolates were chosen randomly for further study. Three additional fusidic acid-resistant isolates, also associated with impetigo outbreaks, were obtained from Førde Central Hospital (Førde, Norway), St Olav’s Hospital (Trondheim, Norway) and Växjö Central Hospital (Växjö, Sweden). A fusidic acid-resistant MRSA isolate from Denmark was also included. Fusidic acid-susceptible isolates of S. aureus from ordinary wound infections (n = 10) and both susceptible and resistant isolates from blood cultures (n = 20) were included as controls.

Susceptibility testing

Routine susceptibility testing was done with fusidic acid paper discs (10 µg) on Iso-sensitex medium (IST; Mast Laboratories, Merseyside, UK) with an inoculum of 0.5 McFarland Standard. Isolates growing with an inhibitory zone of <25 mm were defined as being resistant to fusidic acid.

MICs were determined using Etest (AB Biodisk, Solna, Sweden) on IST medium according to the manufacturer’s instructions.

Pulsed-field gel electrophoresis (PFGE)

PFGE using Smal was carried out as described in the Nordic PFGE protocol. Band patterns were compared visually and differences evaluated as described by Tenover et al.

Results

Figure 1 shows the prevalence of fusidic acid resistance in S. aureus among all outpatients. There was an increase from 3% in 1992 to 38% in 2001. Sixty per cent of the fusidic acid-resistant isolates included were from children below 12 years of age. In the last 3 years, we have also seen a marked seasonal fluctuation, with the highest prevalence in early autumn and a peak of 52% in August 2001.

Among the 33 fusidic acid-resistant isolates from suspected impetigo bullosa, PFGE identified one major DNA class (class A) containing 26 (78.8%) isolates. The remaining seven isolates belonged to five other DNA classes (Figure 2). The three isolates obtained from other Norwegian and Swedish laboratories were also of the predominant DNA class A.

PFGE of the 30 fusidic acid-susceptible control isolates showed a variety of DNA classes. A total of 17 different DNA classes were identified among the 20 invasive isolates, and the 10 skin isolates could be divided into eight DNA classes. One class of overproduction of nuclease was identified in one isolate from Trondheim, Norway. The fusidic acid-resistant MRSA isolate was also of DNA class A.
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Isolate shared the class A PFGE pattern: this was a fusidic acid-susceptible isolate from a wound infection.

Fusidic acid-resistant *S. aureus* having the PFGE class A pattern showed MICs ranging from 2 to 4 mg/L. MICs for fusidic acid-resistant *S. aureus* showing other PFGE patterns varied from 1 to >32 mg/L. All resistant isolates identified by disc diffusion were confirmed as resistant by MIC determination using Etest.

**Discussion**

From a low of 3% in 1992, the prevalence of fusidic acid resistance in *S. aureus* in our region has been increasing and in 2001 reached 36%. In the last 3 years, much of this increase seems to have been due to summer peaks of resistance, coinciding with outbreaks of impetigo among children. The seasonal variation may be explained by higher exposure of skin to trauma and increased skin contact between children during the summer months favouring the spread of the epidemic *S. aureus*.

Genetic typing with PFGE showed that ~80% of impetigo-associated fusidic acid-resistant *S. aureus* belonged to a single DNA class, and corresponding isolates from Sweden and other regions of Norway are of the same DNA class. In contrast, fusidic acid-susceptible isolates are genetically heterogeneous. We conclude, therefore, that the majority of impetigo-associated fusidic acid-resistant *S. aureus* isolates are closely related members of a single clone. Our results thus strongly suggest that a fusidic acid-resistant *S. aureus* clone has spread epidemically in Scandinavia in recent years. There is no reason to believe that this clone will respect national boundaries, and it may be the case that increasing fusidic acid resistance reported from North Yorkshire may be due to the clone spreading there from Scandinavia.

It remains to be determined to what extent this clone is confined to impetigo bullosa and to what extent the increase in fusidic acid resistance that is being observed now is due to the spread of clones, to transmissible resistance or to the accumulation of spontaneous resistance mutations in response to selective pressure. What is clear, however, is that fusidic acid resistance is on the increase and very probably spreading epidemically.

Excessive and indiscriminate use of fusidic acid is likely to exacerbate this situation. In the present epidemiological situation, we would remind clinicians that fusidic acid is only one of several antibiotic and antiseptic compounds suitable for topical treatment of *S. aureus* infections. We would also encourage microbiologists in countries outside Scandinavia to monitor the development of fusidic acid resistance in *S. aureus*, particularly in connection with outbreaks of impetigo bullosa.

Further work will focus on what mechanism of resistance is carried in this clone of *S. aureus*.

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**References**


