**The EPISA study: antimicrobial susceptibility of *Staphylococcus aureus* causing primary or secondary skin and soft tissue infections in the community in France, the UK and Ireland**

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**Objectives:** To provide information on the susceptibility of *Staphylococcus aureus* causing skin and soft tissue infections (SSTIs) in France, Ireland and the UK.

**Patients and methods:** One thousand three hundred and ninety patients attending their general practitioners for skin infections were recruited. Susceptibility to 11 antimicrobials using CLSI (formerly NCCLS) broth microdilution was determined for 646 *S. aureus* isolates detected in the evaluable patient population.

**Results:** Susceptibility results were similar in the UK and Ireland, but differed in France. The largest difference between countries was observed for erythromycin and fusidic acid. In France, 67.8% of isolates were susceptible to erythromycin when compared with 88.6% in Ireland and 92.8% in the UK. However, 93.7% of French isolates were susceptible to fusidic acid, compared with 68.6% in Ireland and 75.6% in the UK. A diagnosis of impetigo was associated with reduced fusidic acid susceptibility.

**Conclusions:** Differences in the prevalence of certain diagnoses, particularly impetigo, rather than differences in antibiotic consumption may explain some of the observed differences in susceptibility seen between these countries.

**Keywords:** skin infections, *S. aureus*, antibiotic susceptibility, SSTIs

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**Introduction**

Skin and soft tissue infections (SSTIs) are some of the most common conditions managed by general practitioners. Community-acquired SSTIs include impetigo, cellulitis, folliculitis, furunculosis, infected eczema and trauma-related wound infections. They are often caused by *Staphylococcus aureus* or *Streptococcus pyogenes*. Given the continued emergence of antibiotic resistance, including methicillin-resistant *S. aureus* (MRSA), it is important to establish an accurate picture of the antimicrobial susceptibility of *S. aureus* associated with community-acquired SSTIs. The aim of this study was to provide up-to-date information on the susceptibility of *S. aureus* in this setting.

**Patients and methods**

This study was performed in the UK, Ireland and France in 2003–04. The protocol was approved by National Health Authorities and by local Ethics Committees. Patients aged 2 years or more attending a general practice clinic in the community, with primary or secondary SSTIs where *S. aureus* was suspected, were eligible. Patients who had received an antibacterial treatment or had a SSTI or who had been hospitalized within the previous 4 weeks were excluded. Written informed consent was obtained from all patients (or the parents of young children). Enrolment sites were located throughout the countries with a wide geographic distribution. A swab was
taken from the skin lesion for microbiological assessment in a central laboratory (GR Micro, London, UK).

Skin swabs were placed in an enrichment broth (tryptone soya broth supplemented with 6.5% sodium chloride) and incubated at 35°C for 18 h before being cultured to determine the presence of \textit{S. aureus}.

For each \textit{S. aureus} isolate, in vitro susceptibility testing was performed using the microdilution broth method, according to CLSI (formerly NCCLS) recommendations. The following antibiotics were tested: penicillin, oxacillin, gentamicin, erythromycin, clindamycin, tetracycline, ciprofloxacin, rifampicin, vancomycin, fusidic acid and mupirocin. The results were reported both as MIC values and as ‘susceptible’ (S) or ‘resistant’ (R) using breakpoints recommended by CLSI when appropriate. As CLSI does not have breakpoint recommendations for fusidic acid or mupirocin, breakpoints from the BSAC were applied for those two antibiotics. In addition to the MIC determination, a penicillinase test was also conducted on all isolates. Penicillinase producers were reported as resistant to penicillin.

\textbf{Statistical methods}

The evaluable analysis set comprised enrolled patients who had \textit{S. aureus} cultured from their swab and who did not fail any of the eligibility criteria. The analysis was based on \textit{S. aureus} isolates. The effect of age groups was based on ICH guidelines (children, 2–11 years; adolescents, 12–17 years; adults, 18–65 years; elderly, above 65 years), and current diagnoses on the distribution of diagnoses. Patients recruited in France had the same in the three countries, some differences were noted in the UK and Ireland where susceptibility was 95.5% for the elderly when compared with 1.8% of UK isolates. With other antibiotics, there was more consistency in the results (Table 1). Across all three countries, 57 (8.8%) isolates were susceptible to all antibiotics. In the UK, no isolate was resistant to more than four antibiotics and in Ireland none was resistant to more than five.

For patients recruited in the UK and Ireland, there were statistically significant differences between the four age groups (children, adolescents, adults and elderly) with respect to fusidic acid susceptibility ($P < 0.001$ and $P = 0.011$, respectively). In the UK, susceptibility was 95.5% for the elderly when compared with 46.2% for adolescents and 71.1% and 79.7% for children and adults, respectively. In Ireland, it was 75.4% for adults when compared with 50.0% for children and 72.7% and 70.4% for adolescents and elderly, respectively. No significant differences were observed in France.

Although the target patient population was presumed to be the same in the three countries, some differences were noted in the distribution of diagnoses. Patients recruited in France had primary SSTIs in 52.8% of cases, whereas in the UK, they represented 69.0% of cases. This difference was mainly attributed to the number of impetigo patients (12.2% of the French patients

\textbf{Results}

A total of 1390 patients were enrolled across the three countries from 96 centres distributed throughout the UK, Ireland and France. From the 1374 patients with laboratory data, 656 \textit{S. aureus} isolates were obtained (47.7% detection rate). As some patients did not meet the inclusion/exclusion criteria, the evaluable analysis set contained 646 \textit{S. aureus} isolated from 631 patients (15 patients had two \textit{S. aureus}).

The susceptibility of \textit{S. aureus} to erythromycin and fusidic acid varied considerably between countries (Table 1). The lowest susceptibility to erythromycin was found in France (67.8%), compared with 88.6% in Ireland and 92.8% in the UK. This trend was the reverse for fusidic acid with 93.7% susceptibility in France versus 68.6% in Ireland and 75.6% in the UK. Clindamycin susceptibility was surprisingly high when compared with erythromycin susceptibility in the three countries. As the initial microdilution method was not appropriate to reveal inducible resistance, disc diffusion later showed that, with the exception of 10 strains, all erythromycin-resistant isolates were also resistant to clindamycin. Some differences were also noticed for ciprofloxacin with 90.7% of French isolates susceptible, compared with 96.8% in Ireland and 97.7% in the UK. The percentage of MRSA also varied between countries. Almost 6% of French isolates and 5% of Irish isolates were methicillin-resistant, compared with 1.8% of UK isolates. With other antibiotics, there was more consistency in the results (Table 1). Across all three countries, 57 (8.8%) isolates were susceptible to all antibiotics. In the UK, no isolate was resistant to more than four antibiotics and in Ireland none was resistant to more than five.

\textbf{Table 1. Susceptibility of \textit{S. aureus} isolated from SSTIs of outpatients during 2003–04}

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Total $n = 646$</th>
<th>France $n = 205$</th>
<th>Ireland $n = 220$</th>
<th>UK $n = 221$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%S CI %</td>
<td>%S CI %</td>
<td>%S CI %</td>
<td>%S CI %</td>
</tr>
<tr>
<td>Penicillin</td>
<td>12.2 9.8–15.0</td>
<td>13.7 9.3–19.1</td>
<td>10.5 6.7–15.3</td>
<td>12.7 8.6–17.8</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>95.8 94.0–97.2</td>
<td>94.1 90.0–96.9</td>
<td>95.0 91.2–97.5</td>
<td>98.2 95.4–99.5</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>99.9 99.1–100.0</td>
<td>99.5 97.3–100.0</td>
<td>100.0 98.3–100.0</td>
<td>100.0 98.3–100.0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>83.4 80.3–86.2</td>
<td>67.8 60.9–74.1</td>
<td>88.6 83.7–92.5</td>
<td>92.8 88.5–95.8</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>98.8 97.6–99.5</td>
<td>96.6 93.1–98.6</td>
<td>99.5 97.5–100.0</td>
<td>100.0 98.3–100.0</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>95.7 93.8–97.1</td>
<td>94.1 90.0–96.9</td>
<td>96.8 93.6–98.7</td>
<td>95.9 92.4–98.1</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>95.2 93.3–96.7</td>
<td>90.7 85.9–94.3</td>
<td>96.8 93.6–98.7</td>
<td>97.7 94.8–99.3</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>100.0 99.4–100.0</td>
<td>100.0 98.2–100.0</td>
<td>100.0 98.3–100.0</td>
<td>100.0 98.3–100.0</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>100.0 99.4–100.0</td>
<td>100.0 98.2–100.0</td>
<td>100.0 98.3–100.0</td>
<td>100.0 98.3–100.0</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>79.0 75.6–82.0</td>
<td>93.7 89.4–96.6</td>
<td>68.6 62.1–74.7</td>
<td>75.6 69.4–81.1</td>
</tr>
<tr>
<td>Mupirocin</td>
<td>99.4 98.4–99.8</td>
<td>99.0 96.5–99.9</td>
<td>100.0 98.3–100.0</td>
<td>99.1 96.8–99.9</td>
</tr>
</tbody>
</table>
versus 33.3% of the patients in the UK). There was also a significant difference between diagnoses with respect to fusidic acid susceptibility ($P = 0.032$ and $P < 0.001$ for the UK and Ireland, respectively). The susceptibility rates ranged from 61.6% (UK) and 48.4% (Ireland) for impetigo to 100% for paronychia (both countries). Again, no such difference was observed in France.

**Discussion**

This study highlights significant differences in the antibiotic susceptibility of *S. aureus* causing community-acquired SSTIs in the UK, Ireland and France. Although there were lower levels of macrolide susceptibility in France when compared with the UK and Ireland, susceptibility rates to fusidic acid were higher. Not all of these differences can be simply explained in terms of different levels of antibiotic consumption. The recent European Surveillance of Antibiotic Consumption project highlighted that outpatient consumption of all classes of antibiotics was significantly higher in France when compared with the UK and Ireland. Further analysis revealed that consumption of macrolides in France was almost double than that of the UK and Ireland (4.85 DDD/1000 inhabitants/day in France compared with 2.31 in the UK and 2.84 in Ireland). Although higher consumption of these agents may contribute to the lower rates of macrolide susceptibility seen in France, this does not explain the lower rates of fusidic acid susceptibility observed in the UK and Ireland as sales of fusidic acid (topical/oral/iv) are also higher in France than in the UK and Ireland (LEO data on file).

There were several patients with a primary diagnosis of impetigo in the UK and Ireland, compared with France. Whether this reflects cultural differences in patients seeking medical assistance between these countries or a genuinely higher prevalence of impetigo at the time of the study is not known. There is a fusidic acid-resistant clone of *S. aureus* associated with impetigo, initially described in Scandinavia, which has latterly been observed in the UK and Ireland. Further epidemiological studies have confirmed that this clone was responsible for 72% of the impetigo cases in the UK and Ireland, but it was not found in France. The dissemination of this clone in the UK and Ireland is therefore likely to be responsible for the observed reduction in fusidic acid susceptibility seen in these countries. As impetigo is predominantly an infection of children and adolescents, this would also explain some of the observed age-associated differences in fusidic acid susceptibility. The role of topical fusidic acid prescribing in promoting and maintaining this clone remains unclear but warrants further study. In Sweden, a decline in sale of fusidic acid ointments preceded the decline of the clone in superficial SSTIs in primary care by 1 year. Although a logical conclusion, it is difficult to categorically state that the decrease in antibiotic pressure was the major reason for the gradual decline in the clone.

In conclusion, this large study of *S. aureus* associated with community SSTIs in France, Ireland and the UK revealed notable differences in antibiotic susceptibility between the three countries. Although some of this may relate to differences in antibiotic consumption, the relative reduction in susceptibility to fusidic acid in Ireland and the UK is more likely to reflect the presence of a clone of *S. aureus* associated with impetigo.

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**Transparency declarations**

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**References**