Sir,

Dr Piddock's leading article provides a useful summary of the various arguments and research on the complex subject of whether the use of antimicrobials in animal treatment can be linked to the undoubted, and worrying, rise of resistant organisms in human medicine. However, in attempting to put the available information into perspective, a number of unmentioned factors also need to be considered.

The first must be scale of use: detailed statistics are currently being compiled, but anecdotal evidence based on the sales value of antimicrobials in the UK indicates that use in human medicine could be as much as 20 times the amount used in all aspects of animal treatment—veterinary therapy for pets and farm animals as well as animal husbandry. Furthermore, although attention is often focused on the use of certain specified antimicrobials as 'growth promoters', their UK sales amount to only 15% of the total use in all types of animal treatment. Unlike the human sector, there is no animal equivalent of the National Health Service and so medicines have to be paid for out of the owner's pocket—a natural limitation for unnecessary use—whether for pets or livestock.

Secondly, as Dr Piddock rightly explains, since 1969 the Swann Committee guidelines have been followed in the UK, restricting the antimicrobials used in growth promotion to a small group not used in human medicine. Control of other classes of antimicrobials is equally stringent—all are available only on prescription, requiring the involvement of a veterinary surgeon, and most are for treatment of individual animals.

I am in a position to write with confidence only on the UK situation—the Swann Committee's principles have not been widely adopted in other countries; furthermore, few countries have the tradition of strict control which, in the UK, dates back to the 1968 Medicines Act, applying equal stringency to the licensing of both human and animal medicines. It may be significant that many of the papers cited by Dr Piddock originate from abroad.

Your readers can be assured that there is no complacency in the UK veterinary profession or the animal medicine industry. Bad practices, whether on farms or in the abattoir, are unacceptable. Regular monitoring of all medicine residues in food is not only carried out but, uniquely in Europe, the results are published. These results are most encouraging but a vigorous response occurs whenever a problem is discovered.

Overseas use does clearly demonstrate that serious resistance in the human sector can occur even when animal use is absent; in Europe the use of avoparcin in animals has been blamed for the appearance of vancomycin resistance in human pathogens. Vancomycin resistance is particularly prevalent in the USA, where vancomycin is widely used in hospitals. However, avoparcin has never been used in animal treatment in the USA.

Development of resistance is not the only point that needs to be considered if the full human picture is to be put into perspective; the use of antimicrobials on the farm is predominantly to treat disease in animals which ultimately provide human food. Without access to such products, the likelihood of our food coming from diseased animals would increase, with the prospect of widespread zoonotic infection of consumers. Of even greater significance when viewed on a worldwide scale, we live on a planet where too many are short of food. Denial of antimicrobials to treat livestock would undoubtedly reduce human food supplies due to the impact of death and disease. Both zoonotic infection and food shortages offer genuine threats to human health.

If the problem of antimicrobial resistance in human medicine is to be solved, then it can only be done by addressing the facts. There are concerns that, by focusing on use in animals, the greater probability of resistance arising as a result of high levels of medical use (possibly from poor practice in hospital wards and theatres), will be ignored.

Reference

Susceptibility testing of fastidious organisms


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Sir,

The NCCLS has published guidelines for the susceptibility testing of fastidious organisms. Following these guidelines for the assessment of a new trienem, sanfetrinem (GV 104326), against Neisseria spp. we obtained unexpectedly high MICs and therefore undertook a study to compare MICs obtained on a variety of media.

The media compared were as follows: medium A, Iso-Sensitest agar (Unipath, Basingstoke, UK) supplemented with 20 mg/L NAD (Sigma, Poole, UK) and 5% whole horse blood (E and O, Bonnybridge, UK); medium B, Mueller–Hinton agar (Unipath) supplemented with 20 mg/L NAD and 5% whole horse blood; medium C, Mueller–Hinton agar supplemented with 20 mg/L NAD and 2% (w/v) haemoglobin (Unipath); medium D, GC agar base (Unipath) supplemented according to NCCLS recommendations excluding L-cysteine; medium E, GC agar base supplemented with 2% (w/v) haemoglobin and Vitox (Unipath); medium F, GC agar base supplemented according to NCCLS recommendations including L-cysteine; medium G, Mueller–Hinton agar supplemented with 5% whole horse blood and Vitox.

The antibiotics studied were sanfetrinem (Glaxo–Wellcome, Greenford, UK), spectinomycin (Upjohn, Crawley, UK), meropenem (Zeneca, Macclesfield, UK), ciprofloxacin (Bayer AG, Wuppertal, Germany), cefixime (Cyanamid, Gosport, UK) and benzylpenicillin (Smith–Kline Beecham, Welwyn Garden City, UK). The organisms investigated were ten clinical strains of Neisseria gonorrhoeae and control strain NCTC 12700 (ATCC 49226) and five clinical strains of Neisseria meningitidis.

The methodology was that described in the NCCLS guidelines and in the Working Party Report of the BSAC. Briefly, the final inoculum was 10⁴ cfu/spot, incubation was at 35–37°C in 4–6% CO₂ in air for 20–24 h and the MIC was defined as the lowest concentration of antibiotic inhibiting growth, up to three colonies being ignored.

In the Figure are plotted the mode MICs for the 11 N. gonorrhoeae strains tested for each of the media investigated. The graph clearly illustrates a variation in results obtained depending on the medium used. The NCCLS recommends that a medium free of L-cysteine should be used when testing clavulanate and carbapenem antibiotics and the results were in agreement with this recommendation. MICs obtained were significantly raised with meropenem and sanfetrinem and to a lesser extent with benzylpenicillin when using media E, F and G (all containing cysteine).

When sanfetrinem MIC data for media with and without the addition of L-cysteine were compared statistically (paired t-test) a P value of <0.0001 was obtained, indicating that there was a significant statistical difference. When medium D (NCCLS reference medium) and medium A (BSAC Working Party recommendation) were compared there was no statistical difference in results (P = 0.4294). A similar pattern of results was obtained for N. meningitidis. It is also worthy of note that all strains grew on medium A, whereas one clinical isolate of N. gonorrhoeae failed to grow on the NCCLS recommended media (F and G).

These data suggest that Iso-Sensitest agar supplemented with 20 mg/L NAD and 5% whole horse blood would be appropriate for sensitivity testing compounds affected by the presence of L-cysteine. Previous data published from this department have also shown that this medium is suitable for testing other fastidious organisms such as Streptococcus pneumoniae and Haemophilus influenzae.

The results from a recent BSAC questionnaire have shown that there is a general consensus that there is a need to standardize the testing of fastidious organisms. These data suggest that supplemented Iso-Sensitest agar, the medium chosen by the BSAC Working Party on antibiotic sensitivity testing, would be appropriate and that MIC results obtained with this medium would be comparable to those obtained on the NCCLS recommended media.

References

Sir,

Antimicrobial therapy alone is generally ineffective in the treatment of abscesses, especially for large collections of pus. The failure of antibiotics has been suggested to be based upon (i) slower growth of bacteria within the abscess environment, (ii) low pH of pus which inactivates certain antibiotics or (iii) inability of the drug to penetrate abscess fluid. The pharmacokinetics and pharmacodynamics of antimicrobials in abscess fluid have not been well studied in humans. The degree and rapidity of antimicrobial penetration into abscess fluid may influence the identification of microbial pathogens and the optimal treatment of these infections. The following study characterizes the penetration of a third-generation cephalosporin, ceftizoxime, into abscess fluids in patients, including those with brain abscesses. The study was approved by the Committee on Human Research at the University of California San Francisco. Patients receiving intravenous ceftizoxime requiring either percutaneous or surgical drainage of abscess fluid were identified. Samples of abscess fluid were taken, and antimicrobial history (patients A–F all received concomitant metronidazole with ceftizoxime; patients G and H were treated with ceftizoxime monotherapy), blood chemistry and microbiology reports were documented. Once sampled, abscess fluid was stored at \(-70^\circ C\) until performance of the assay. Determination of ceftizoxime concentrations in abscess fluid was performed via reversed-phase high pressure liquid chromatography, as previously described. A aerobic and anaerobic bacteriological cultures were performed according to routine laboratory methods by the clinical microbiology laboratory.

Ceftizoxime was found to penetrate readily into abscess fluid, with levels ranging from 2 to 30 mg/L (Table). The highest concentrations were noted in patients receiving 2.0 g doses (patients G and H) or associated with more long-term therapy (patients C, E, F and H). Penetration into abscess fluid was confirmed as early as 10–15 min after administration of a single iv dose. Immediate penetration similarly was seen in two patients with brain abscesses. One patient (patient G) had a level of 2.8 mg/L 0.5 h after a single dose, which increased to 30.1 mg/L 0.83 h after a single dose.

### Table. Penetration of ceftizoxime into abscess fluid

<table>
<thead>
<tr>
<th>Location of patient abscess</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Serum creatinine (mg/dL)</th>
<th>Intravenous dose</th>
<th>No. of doses</th>
<th>Time after dose (h)</th>
<th>Ceftizoxime concentration in abscess (mg/L)</th>
<th>Microbiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>A intraabdominal</td>
<td>61</td>
<td>81</td>
<td>1.4</td>
<td>1 g x 1</td>
<td>1</td>
<td>0.17</td>
<td>4.4</td>
<td>Bacteroides</td>
</tr>
<tr>
<td>B intraabdominal</td>
<td>50</td>
<td>62</td>
<td>1.4</td>
<td>1 g q12h</td>
<td>3</td>
<td>0.25</td>
<td>5.7</td>
<td>S. aureus (methicillin-resistant)</td>
</tr>
<tr>
<td>C intraabdominal</td>
<td>67</td>
<td>49</td>
<td>1.0</td>
<td>1 g q12h</td>
<td>20</td>
<td>5.0</td>
<td>28.1</td>
<td>Bacteroides</td>
</tr>
<tr>
<td>D intraabdominal</td>
<td>29</td>
<td>56</td>
<td>0.7</td>
<td>1 g q8h</td>
<td>3</td>
<td>7.0</td>
<td>2.2</td>
<td>Bacteroides</td>
</tr>
<tr>
<td>E gall bladder</td>
<td>83</td>
<td>68</td>
<td>1.5</td>
<td>1 g q8h</td>
<td>12</td>
<td>1.0</td>
<td>11.9</td>
<td>S. viridans</td>
</tr>
<tr>
<td>F subhepatic</td>
<td>41</td>
<td>68</td>
<td>0.9</td>
<td>1 g q8h</td>
<td>10</td>
<td>4.5</td>
<td>6.2</td>
<td>Enterococcus</td>
</tr>
<tr>
<td>G brain</td>
<td>48</td>
<td>61</td>
<td>1.3</td>
<td>2 g x 1</td>
<td>1</td>
<td>0.5, 0.83</td>
<td>2.8, 30.1</td>
<td>N. asteroides</td>
</tr>
<tr>
<td>H brain</td>
<td>14</td>
<td>45</td>
<td>0.8</td>
<td>2 g q6h</td>
<td>9</td>
<td>3.5</td>
<td>19.7</td>
<td>S. aureus (methicillin-susceptible)</td>
</tr>
</tbody>
</table>
h after the dose. The data in this patient suggest that the penetration of ceftizoxime is associated with a rapid distribution phase. Patient H had a brain abscess fluid level of 19.7 mg/L; however, this level was achieved at a dose of 180 mg/kg/day after nine 2.0 g doses had been administered.

In several instances the isolated microorganisms were resistant to third-generation cephalosporins (yeast, methicillin-resistant Staphylococcus aureus, enterococcus). The other abscesses were associated with β-lactamase-producing Bacteroides spp., Nocardia asteroides, Streptococci viridans, and methicillin-susceptible S. aureus, all organisms only moderately inhibited by ceftizoxime (MIC<sub>90</sub> 8–16 mg/L). Notably, no cultures were positive for aerobic Gram-negative bacteria, including Enterobacteriaceae, which are usually highly susceptible to third-generation cephalosporins with MIC<sub>90</sub> values of <0.1 mg/L.

These data suggest that ceftizoxime, in combination with surgical intervention, is of value in the treatment of abscesses. The rapid penetration into these fluids is particularly noteworthy and may affect the microbiological findings. As with our patient population, preoperative antibiotics are routinely administered before surgical drainage. Considering how quickly ceftizoxime penetrates abscess fluid, these results suggest that the presence of antibiotic in abscess fluid potentially complicates microbiological identification of the pathogen(s). While the presence of ceftizoxime did not appear to affect the isolation of organisms intermediate susceptible or resistant to third-generation cephalosporins, it may have influenced the isolation of more susceptible bacterial pathogens. Controlled investigations are necessary to clarify the influence of antimicrobial penetration on both the diagnosis and the treatment of abscesses.

**Acknowledgement**

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**References**


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**Teicoplanin resistance in Staphylococcus haemolyticus, developing during treatment**

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**Sir,**

Teicoplanin is an important agent in the treatment of staphylococcal infection. Resistance is rare, but is known to occur in Staphylococcus haemolyticus. We report a patient whose treatment failed when S. haemolyticus isolated from a Hickman line became resistant after a single course of teicoplanin.

A 34-year-old female had a Hickman line inserted for treatment of non-Hodgkin's lymphoma. One month later she had an episode of neutropenic sepsis, felt to be due to a line infection. A coagulase-negative staphylococcus (CoNS) isolated from blood cultures was initially treated with vancomycin. This was changed to teicoplanin 400 mg od after an apparent allergic reaction; the line was not removed. Teicoplanin was continued for one week and the patient remained well until her next cycle of chemotherapy when a CoNS, indistinguishable from the previous strain apart from resistance to teicoplanin by the Stokes method, was isolated from a Hickman line blood culture.

Parent and resistant strains were identified as S. haemolyticus by API Staph (bioMérieux, Lyon, France), with similar biochemical profiles (66165151 and 6616051, difference not significant). MICs of teicoplanin were determined using the Etest (AB Biodisk, Solna, Sweden) and confirmed by the PHLS Antibiogram Reference Laboratory, Colindale, who found the strains to be indistinguishable by pulsed-field gel electrophoresis.

In order to investigate further the mechanisms of resistance, both strains were cultured on antibiotic-free medium and in the presence of a 30 μg teicoplanin disc. A pellet of organisms was collected from the edge of the zone of inhibition and from the teicoplanin-free area. Ultrathin section electron microscopy was performed on parent and resistant strains under both conditions. The thickness of the cell wall was assessed by determining the
ratio of external to internal cell wall diameters using a method previously described for Staphylococcus aureus.\(^2\)

Cell wall thickness was significantly greater in the resistant strain (Table), but this change was expressed only when the organisms were exposed to teicoplanin. Abnormally thick cell walls have been reported previously in glycopeptide-resistant Staphylococcus epidermidis, though this was a permanent change, being expressed in the presence and absence of the antibiotics.\(^3\)

Whole cell protein profiles were determined by SDS-PAGE after lysostaphin treatment. The resulting profile showed that the resistant strain produced an increased amount of a protein of approximately 35 kDa. A 35 kDa protein has been reported previously in teicoplanin-resistant S. aureus and S. haemolyticus, though it is unclear whether this is directly related to resistance.\(^4\)

Previous studies of non-isogenic or laboratory-generated strains of CoNS have shown differences in protein profile and cell wall structure but their role in glycopeptide resistance remains unclear. In this case isolates before and after the development of resistance were available and provided a unique opportunity to study the mechanism. We suggest that units using teicoplanin frequently should monitor the susceptibility of their local flora.

### References


### Table

<table>
<thead>
<tr>
<th>Parent strain (teicoplanin MIC = 4 mg/L)</th>
<th>R resistant strain (teicoplanin MIC &gt; 128 mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>teicoplanin-free</td>
<td>teicoplanin-exposed</td>
</tr>
<tr>
<td><strong>Ratio of external/internal diameter (mean ± s.d.)</strong></td>
<td><strong>Ratio of external/internal diameter (mean ± s.d.)</strong></td>
</tr>
<tr>
<td>1.121 ± 0.02</td>
<td>1.121 ± 0.02</td>
</tr>
<tr>
<td>P value (unpaired t-test)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant.