More recently, emergence of daptomycin heteroresistance was demonstrated for a vancomycin-heteroresistant *E. faecium* after exposure to vancomycin, suggesting the same underlying resistance mechanism.\(^{16}\) During therapy with daptomycin for *S. aureus* bacteraemia and endocarditis, 16% of the patients failed with a persistent or relapsing infection with increasing isolates MICs. Most of these failures were in deep-seated infections for which a necessary surgical intervention was not performed.\(^{17}\) In the case of *Enterococcus*, either a chronic indwelling line or persistent focus of infection was reported for all but two of the seven reported cases of daptomycin clinical treatment failures, and non-susceptibility developed on treatment after an average of 19 days.\(^{4–10}\)

The mechanisms of non-susceptibility to daptomycin are thus diverse and not completely understood. Increasing MICs in the setting of pre-exposure to either vancomycin or daptomycin and/or evidence of a persistent focus of infection seem to be a frequent occurrence for clinical failures among both *S. aureus* and *Enterococcus* species. Despite lack of experimental data, it is plausible that the mechanisms that explain enterococcal non-susceptibility parallel those for *S. aureus*. The use of daptomycin in patients with prior prolonged vancomycin or daptomycin therapy, or with a focus of infection that cannot be removed, should be undertaken with caution, as clinical failure can occur.

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**Transparency declarations**

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**References**


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**Severe hypokalaemia caused by flucloxacinill**

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Keywords: aldosterone, collecting duct, kaliuresis, solute diuresis, spironolactone, spondylodiscitis

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Sir,

Hypokalaemia has been reported during treatment with penicillin G and broad-spectrum penicillins.\(^1\) We report, to our knowledge, the first time, a case of severe hypokalaemia during treatment with yet another penicillin, namely sodium flucloxacillin (floxacillin). Our aim was to illustrate that hypokalaemia is a class-effect of penicillins, to reiterate the importance of penicillin-induced hypokalaemia and to further investigate its mechanism and potential treatment.

A 67-year-old woman (height 165 cm and weight 45 kg) was treated with flucloxacillin (2 g six times daily) for spondylodiscitis during two admissions. Spondylodiscitis had developed after an elective colectomy for diverticulosis, which was
complicated by an abscess in the rectouterine pouch and Staphylococcus aureus bacteraemia.

During both admissions, hypokalaemia developed after flucloxacillin was started (after 3 and 2 days, respectively) and resolved after it was stopped. Hypokalaemia was caused by renal potassium loss (Table 1). Other causes of renal potassium loss were absent, including diuretics, hypomagnesaemia, ketonuria, bicitarbonaturia, renal tubular acidosis (no acid–base disorder) and, finally, hyperaldosteronism (low-normal renin and aldosterone levels, Table 1). Moreover, dietary potassium intake was normal and no causes of a shift of potassium into the cell (e.g. alkalosis or insulin) or its loss from the gastrointestinal tract (e.g. diarrhoea or laxatives) were present.

Penicillin-induced hypokalaemia is thought to develop because a penicillin derivative acts as a non-reabsorbable anion, resulting in more sodium reabsorption in exchange for potassium. This effect is believed to be mediated by volume depletion, because this will increase aldosterone and decrease distal chloride delivery, thereby maintaining a lumen-negative gradient. In fact, a low urinary chloride concentration is considered a diagnostic feature of hypokalaemia due to a non-reabsorbable anion.

**Table 1. Characteristics and laboratory analysis of hypokalaemia**

<table>
<thead>
<tr>
<th>Characteristics of hypokalaemia</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>number of measurements</td>
<td>21/38 (first admission), 10/30 (second admission)</td>
</tr>
<tr>
<td>&lt;3.5 mmol/L</td>
<td></td>
</tr>
<tr>
<td>lowest serum potassium</td>
<td>2.1 mmol/L (first admission), 2.4 mmol/L (second admission)</td>
</tr>
<tr>
<td>potassium supplementation</td>
<td>78 ± 43 mmol (oral and iv), (1.7 ± 0.9 mmol/kg)</td>
</tr>
<tr>
<td>symptoms of hypokalaemia</td>
<td>myalgia, paralytic ileus</td>
</tr>
<tr>
<td>Laboratory analyses*</td>
<td></td>
</tr>
<tr>
<td>glomerular filtration rate</td>
<td>70 mL/min</td>
</tr>
<tr>
<td>urine output</td>
<td>3100 ± 1211 mL (69 ± 27 mL/kg)</td>
</tr>
<tr>
<td>urine osmolality</td>
<td>482 ± 38 mOsm/kg</td>
</tr>
<tr>
<td>sodium, urine and fractional excretion</td>
<td>114 ± 35 mmol/L, 2.3 ± 3.6%</td>
</tr>
<tr>
<td>potassium, urine and fractional excretion</td>
<td>53 ± 19 mmol/L, 25.9 ± 21.1%</td>
</tr>
<tr>
<td>chloride, urine</td>
<td>140 ± 27 mmol/L</td>
</tr>
<tr>
<td>transtubular potassium gradient</td>
<td>8.3 ± 2.5</td>
</tr>
<tr>
<td>serum cortisol</td>
<td>360 mmol/L (reference: 150–700 mmol/L)</td>
</tr>
<tr>
<td>serum renin activity (supine)</td>
<td>0.1 ng/mL/h (reference: 0.1–1.7 ng/mL/h)</td>
</tr>
<tr>
<td>serum aldosterone (supine)</td>
<td>40 pmol/L (reference: 30–150 pmol/L)</td>
</tr>
</tbody>
</table>

*Averages based on the following number of measurements: urine output, 4 measurements; urine osmolality and transtubular potassium gradient, 7 measurements; urinary concentration and fractional excretions of sodium and potassium, 13 measurements; urinary chloride concentration, 4 measurements. Glomerular filtration rate was estimated using the Cockcroft–Gault equation, fractional excretions were calculated as $(U_K \times P_{\text{Cr}})/[P_K \times U_{\text{Cr}}] \times 100$ and the transtubular potassium gradient as $(U_K \times P_{\text{Osm}})/[P_K \times U_{\text{Osm}}]$. 

Surprisingly, the findings in our case contradicted the above. First, serum renin and aldosterone levels were low-normal and urinary chloride levels were high, both arguing against volume depletion (Table 1). However, aldosterone levels may have been higher early on and should also be interpreted in the context of hypokalaemia, which reduces aldosterone secretion. Secondly, treatment with intravenous fluids (2 L of 0.9% NaCl) and a 15 day trial of spironolactone (25 mg once daily) failed to prevent hypokalaemia, nor did it reduce kaliuresis. Triamterene (50 mg once daily), which was tried for 2 days, was also unable to decrease the renal potassium loss.

This calls into question the mechanism of penicillin-induced hypokalaemia. Given the large amounts of sodium administered with penicillin and intravenous fluids ($6 \times 2 + 2 \times 9 = 30$ g or 517 mmol), an alternative explanation could be the occurrence of a solute diuresis. A solute diuresis causes a high flow rate in the cortical collecting duct and subsequent potassium excretion, probably via the so-called BK channels. A number of additional observations support the presence of a solute diuresis: the majority of osmoles being sodium and potassium, the magnitude of their fractional excretions and the presence of polyuria (Table 1). We emphasize that a solute diuresis does not exclude a role for a non-reabsorbable anion. In fact, both mechanisms may act synergistically, because both can increase distal sodium delivery and therefore promote kaliuresis.

In summary, our case illustrates the class-effect of penicillins to cause hypokalaemia and its development in the absence of volume depletion, hyperaldosteronism and low distal chloride delivery. It also illustrates that low body mass index patients receiving high-dose penicillin therapy are at risk for developing severe hypokalaemia. The ineffectiveness of probenecid (reported in Mittal et al.), volume repletion and potassium-sparing diuretics (reported here) suggest an obligatory renal potassium loss that may exceed roughly 100 mmol/L. Thus, the mainstay of treatment remains aggressive potassium supplementation, for which special measures (potassium infusion pump, central venous catheter, intra-arterial line for monitoring) may be required.

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**References**


A review of vancomycin therapeutic drug monitoring recommendations in Scotland

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Keywords: glycopeptides, troughs, MRSA, treatment

Sir,

Confusion continues regarding the therapeutic monitoring of vancomycin. Most clinicians would agree that the analysis of peak concentrations is of limited value due to both the pharmacodynamic (time-dependency) and pharmacokinetic (multienzyme decline) properties of vancomycin.1 However, there is still a lack of uniformity with respect to trough concentrations. The historical recommendation of 5–10 mg/L was based on efficacy data from in vitro experiments, protein-binding information and early concerns about nephrotoxicity. However, recent evidence suggests that nephrotoxicity is rare with vancomycin monotherapy and that trough concentrations ≥15 mg/L may be safe and even desirable.2,3 Despite a lack of definitive evidence correlating greater clinical efficacy with higher vancomycin concentrations,1,2 there has been a trend towards recommending higher trough concentrations of vancomycin. This reflects a greater awareness of the need for adequate penetration into target tissues and concerns about vancomycin treatment failure in infections caused by methicillin-resistant Staphylococcus aureus (MRSA) strains that display heteroresistance to glycopeptides.4,5 Consequently, recent guidelines have recommended vancomycin trough concentrations of 10–15 mg/L for endocarditis and meningitis,6 and continuous infusions of vancomycin with target concentrations of 15–25 mg/L are increasingly being used, particularly in intensive care.6 The British National Formulary (BNF) now recommends aiming for vancomycin trough concentrations of 10–15 mg/L, rather than 5–10 mg/L. However, although the focus has changed to concerns about underdosing rather than toxicity, there has been little consideration of how this might influence dosage requirements. This audit examined current practice within Scotland with respect to vancomycin dosing and monitoring.

Seventeen microbiology laboratories serving all 14 NHS Health Boards within Scotland were contacted in October 2007, and a consultant microbiologist or clinical scientist was invited to answer the following questions: (i) What are the current targets for vancomycin trough concentrations reported by your laboratory? (ii) Do you measure peak concentrations? (iii) Are there plans to change the current targets for vancomycin monitoring and if so, to what? and (iv) If you have changed your monitoring recommendations, have you or do you plan to change your vancomycin dosing recommendations?

All 17 microbiology laboratories responded. Vancomycin concentrations are monitored during therapy within all 14 NHS Boards in Scotland. The analysis of peak vancomycin concentrations was discouraged in 13 laboratories, undertaken sometimes in 3 and routinely in 1. There was a wide range of recommended trough concentrations (Table 1). Of the six laboratories that recommended an upper limit of 10 mg/L, four accepted concentrations up to 15 or 20 mg/L for severe infections and were preparing to change their routinely recommended ranges upwards. Two laboratories did not report a lower limit for trough concentrations. Most laboratories recommending an upper limit of 15 mg/L had made this increase within the last 1–2 years. None of the laboratories with higher trough ranges had made changes to their dosing recommendations, although some had plans to address this.

Our results indicate that recommendations for vancomycin therapy in Scotland are in a state of flux. Laboratories have been moving away from target trough concentrations of 5–10 mg/L towards a variety of higher targets, up to and exceeding 15 mg/L. However, when changing recommendations for vancomycin trough concentrations, it would seem appropriate to consider whether dosage guidelines are in place to achieve these ranges. Current BNF dosage recommendations are 1000 mg twice daily, halved in patients over 65 years of age. However, to achieve these higher troughs, our clinical experience indicates that total daily doses of 2500–3000 mg (sometimes higher) are required by patients with normal renal function. The potential for underdosing these patients is of concern, especially in the first few days of therapy before vancomycin concentration results are available. A recent pharmacokinetic analysis suggested that up to a third of patients on standard doses of vancomycin could be receiving insufficient treatment2 and our own observations support this.

Table 1. Vancomycin trough concentration ranges recommended within Scottish microbiology laboratories

<table>
<thead>
<tr>
<th>Vancomycin trough concentration (mg/L)</th>
<th>No. of laboratories</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–10</td>
<td>1</td>
</tr>
<tr>
<td>5–10</td>
<td>5</td>
</tr>
<tr>
<td>0–15</td>
<td>1</td>
</tr>
<tr>
<td>5–15</td>
<td>4</td>
</tr>
<tr>
<td>10–15</td>
<td>5</td>
</tr>
<tr>
<td>15–25</td>
<td>1</td>
</tr>
</tbody>
</table>