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Antimicrobial treatment and clinical outcome for infections with carbapenem- and multiply-resistant *Acinetobacter baumannii* around London

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ABSTRACT

Carbapenem- and multiply-resistant *Acinetobacter baumannii* (C-MRAB) are challenging pathogens, often susceptible only to polymyxins and tigecycline. We reviewed clinical outcomes in relation to antibiotic treatment for 166 consecutive patients infected or colonised with these organisms at 18 hospitals around London, UK. Clinical data were obtained along with the isolates, which were typed by pulsed-field gel electrophoresis (PFGE). Outcomes were compared for colonised and infected patients and in relation to treatment, with associations examined by logistic regression. Most subjects (103/166; 62%) were in Intensive Care Units (ICUs) or high dependency units; 84 (50.6%) were judged to be infected and 73 (44.0%) were colonised, with 9 indeterminate. Among the 166 C-MRAB isolates, 141 belonged to OXA-23 clone 1, a European clone II lineage. Survival rates among infected and colonised patients were 68% and 67%, respectively ($P > 0.05$), indicating little attributable mortality. Univariate and multivariate analyses indicated poorer outcomes among ICU infected patients and those with pulmonary infection or bacteraemia, whereas trauma patients had significantly better outcomes than the generality. Outcomes varied with hospital, even in multivariate analysis, reflecting either differences in management or case mix. There was little association between outcome and therapy with colistin and/or tigecycline except that, among patients with respiratory infection, 12/15 treated with intravenous colistin alone had poor outcome compared with 1/8 whose therapy include nebulised colistin. This difference was significant ($P = 0.003$), although the patients receiving nebulised drug were mostly younger, were trauma cases and were at a hospital with good outcomes.

1. Introduction

Multiresistant *Acinetobacter baumannii* (MRAB) are frequent nosocomial opportunists, often spreading among severely ill patients. They can affect any body site [1] but are most important in ventilator-associated pneumonia (VAP). Until recently, imipenem and meropenem retained near universal activity [2], but carbapenem-resistant MRAB (C-MRAB) are now widespread, their resistance being caused by acquired OXA- or metallo-carbapenemases or by *IS_{Abal}*-mediated upregulation of the chromosomal OXA-51-like carbapenemase [3].

C-MRAB are widespread in Southeast England, with many isolates belonging to OXA-23 clone 1 [4] or the SE clone [5,6]. Both of these clones belong to European clone II, a major *A. baumannii* lineage associated with outbreaks worldwide since the 1980s [7,8]. OXA-23 clone 1, with OXA-23 carbapenemase, is recorded from over 58 UK hospitals and has caused outbreaks forcing Intensive Care Unit (ICU) closures at several [4]. It is usually susceptible only to tigecycline and polymyxins.

Several case series document good outcomes with intravenous (i.v.) polymyxins in C-MRAB infections [9,10], although results are disappointing in pneumonia, perhaps reflecting poor pulmonary penetration [9], a limitation that may be overcome by high dosage [11] or co-administration of nebulised colistin [11,12]. Data on tigecycline in *A. baumannii* infections are scanty and mixed: Schafer et al. [13] reported good outcomes in 18/22 VAP cases, but a Phase III trial found tigecycline inferior to imipenem in VAP with disappointing

results in a further case series [14]. This caution is reinforced by reports of emerging resistance [15].

To analyse current practice and outcomes, we audited 166 cases of C-MRAB infection or colonisation in and around London, UK.

2. Materials and methods

2.1. Setting and patients

Existing records were reviewed to determine the clinical outcomes for consecutive patients colonised or infected with C-MRAB. Collaborators at 29 hospitals in and around London prospectively identified patients and referred one isolate per patient to the Centre for Infections (London, UK).

2.2. Data collection

Clinical details were collected on a form recording (i) basic demographics, (ii) underlying condition, concurrent infections and severity of illness, (iii) ventilator status, (iv) peripheral and central lines and any indwelling catheter, (v) Acute Physiology and Chronic Health Evaluation (APACHE) II score if available and (vi) sites from which *Acinetobacter* spp. were recovered and whether the responsible clinician considered the patient to be colonised or infected at each site. Patients infected or colonised at multiple sites were assumed to have the same strain at each site and only one isolate was subjected to laboratory investigation. Antibiotic treatment was recorded, along with clinical outcome, categorised as: (i) died during hospitalisation; (ii)

unresolved; (iii) clinically improved; or (iv) fully resolved. Death was considered to be related to C-MRAB infection when persistent signs or symptoms of infection were present at the time of death and/or when death occurred within 1 week of initiation of antibiotic therapy without any other clear explanation. Clinical cure required the resolution of symptoms but not microbiological eradication.

2.3. Microbiological methods

Isolates were assigned to *A. baumannii* clones by pulsed-field gel electrophoresis (PFGE) of *Apa1*-digested genomic DNA and detection of *bla_{OXA}* genes [4]. Antibiotic minimum inhibitory concentrations (MICs) were determined according to the British Society for Antimicrobial Chemotherapy (BSAC) method [16].

2.4. Statistical analysis

Associations were assessed by logistic regression analysis where the outcome was the binary variable of 'poor' (deceased or unresolved) or 'good' (resolved or clinically improved). Odds ratios (ORs) were median unbiased estimates from an exact logistic regression analysis performed using Stata 10 (StataCorp LP, College Station, TX).

3. Results

3.1. Patient and *Acinetobacter* populations

Of the 29 recruited hospitals, 18 submitted patient data and corresponding isolates, with 166 infected or colonised cases identified from August 2006 to April 2007; 103 were ICU or high dependency unit (HDU) patients. Five hospitals provided more than 10 patients each and accounted for 76.5% (127/166) of all patients, whereas eight hospitals provided only one to two subjects each (Table 1). Three of the five major contributors were teaching hospitals and two were acute general hospitals. The scarcity of C-MRAB at other hospitals should not be overinterpreted; three sites providing one to six patients had experienced major C-MRAB outbreaks in the preceding year, at least one with OXA-23 clone 1. APACHE II scores proved impossible to collect from most sites, but most patients had major underlying disease or injury: 53 had recent surgery, 33 had suffered physical trauma (mostly road traffic accidents), 28 had malignancy, 48 had underlying pulmonary disease, 33 had renal failure or disease, 23 had cardiovascular disease and 6 had liver disease. Among the 33 trauma victims, 21 were at hospital 001 specialising in emergency medicine.

PFGE revealed that most patients (141; 84.9%) had OXA-23 clone 1, recovered at 14 of the 18 contributing sites (Table 1). Twelve SE clone isolates were received from five hospitals, together with thirteen C-MRAB isolates belonging to various other strains. OXA-23 clone 1 accounted for virtually all isolates at four of the five major contributor sites; only site 003 had

greater diversity, with 5 SE clone isolates, 3 isolates of a local clone and 19 OXA-23 clone 1 isolates.

Only colistin and tigecycline retained good in vitro activity, with 99.4% and 81.9% of isolates susceptible, respectively, rising to 100% and 88.1% for OXA-23 clone 1 (Table 2). No other compound was active against more than 20% of isolates, and none against more than 10% of OXA-23 clone 1 isolates. Tigecycline MICs ranged up to 16 mg/L; none of the source patients for isolates with MICs in the range 4–16 mg/L was recorded as having received the drug.

Overall, 84 patients (50.6%) were assessed to be infected with C-MRAB in at least one body site (Table 3), whilst 73 (44.0%) were colonised, with insufficient details for the remaining 9 (5.4%). C-MRAB was often isolated at multiple sites, and obvious duplicates (e.g. blood and line tip, or sputum and throat) were counted as a single site. Following this correction, 62 of the 84 patients were judged to be infected at one site, 18 at two sites, 3 at three sites and 1 at four sites. The complexity of many of the patients is underscored by the fact that 53 'infected' cases had other certain or potential pathogens isolated concurrently: 22 had methicillin-resistant *Staphylococcus aureus* (MRSA) one or more body site and 21 had other bacteria or *Candida* spp. isolated from blood. The mean age of the infected patients was 57.1 years [range 17–95 years; standard deviation (S.D.) 20.5 years] with 64% males compared with a mean age of 59.4 years (range 7–98 years; S.D. 20.9 years) and 69% males among the colonised patients.

3.2. Infection status and outcome

Outcome was identified for 129 subjects, including all 84 infected cases (Table 4) among whom 27 (32.1%) died compared with 15/45 (33.3%) colonised patients with a recorded outcome ($P = 0.891$). Bloodstream infection was associated with poor outcome [$P = 0.009$; OR = 3.3, 95% confidence interval (CI) 1.3–8.3], but the contribution of C-MRAB was not always easy to define. Thus, 16/34 patients with bacteraemia died, with C-MRAB infection noted as causative in 2 and contributory in 11; however 10 of these 13 patients had other infections and 5 had other organisms recovered from blood, including coagulase-negative staphylococci.

3.3. *Candida albicans* and *Pseudomonas aeruginosa*

Other factors associated with a poor outcome in the univariate analysis were: infection at two body sites ($P = 0.09$; OR = 2.3, 95% CI 0.86–6.0); infection at more than two sites ($P = 0.028$; OR = 5.3, 95% CI 1.2–23.7); being in an ICU when infected ($P = 0.008$; OR = 3.9, 95% CI 1.4–11.2); and the presence of a central venous line ($P = 0.05$; OR = 2.8, 95% CI 0.98–8.0). Respiratory infection came close to significance ($P = 0.074$; OR = 2.27, 95% CI 0.92–5.63), whereas urinary infection was negatively associated with poor outcomes ($P = 0.06$; OR = 0.28, 95% CI 0.075–1.1) as was being a trauma patient ($P = 0.009$; OR = 0.15, 95% CI 0.03–0.72). Factors found not to be significant included age ($P = 0.427$), sex ($P = 0.405$), wound infection ($P = 0.898$), infection at other sites besides blood, respiratory, wounds or urine (P

= 0.665), mechanical ventilation ($P = 0.372$), urinary catheterisation ($P = 0.674$), presence of an arterial line ($P = 0.18$) or peripheral i.v. lines ($P = 0.237$). It was assumed that all devices were in place prior to infection.

Factors remaining significantly associated with poor outcome, or nearly so, in the multivariate analysis were bacteraemia ($P = 0.056$; OR = 4.39, 95% CI 0.96–20.0), ICU location ($P = 0.052$; OR = 5.96, 95% CI 0.99–40.25) and pulmonary infection ($P = 0.034$; OR = 6.82, 95% CI 1.15–40.8), whilst a negative association remained between trauma and poor outcome ($P = 0.067$; OR = 0.15, 95% CI 0.18–1.14).

3.4. Treatment and outcome

Of the 84 infected patients, 37 received colistin alone (by any route), 5 tigecycline alone, 9 both colistin and tigecycline and 33 received neither agent (although 1 of these received minocycline, which was active against the particular isolate recovered). A further four 'colonised' patients were given colistin. Many patients received other antibiotics to which the C-MRAB isolates were resistant in vitro, perhaps for concurrent infections.

Among 52 infected patients given colistin and/or tigecycline or minocycline, 29 had good outcomes versus 20/32 given none of these agents ($P = 0.543$).

Good outcomes were achieved in 23/46 patients given colistin versus 26/38 patients not given this agent ($P = 0.13$; OR = 2.0, 95% CI 0.81–4.9);

corresponding proportions for tigecycline were 10/14 versus 39/70 ($P = 0.276$; OR = 0.5, 95% CI 0.14–1.8). Among 34 patients with bacteraemia, 12/25

receiving colistin and/or tigecycline had good outcomes versus 2/9 among those not doing so ($P = 0.178$); among those with *A. baumannii* OXA-23 clone 1, these proportions narrowed to 10/21 versus 2/6 ($P = 0.535$); among 25 patients with no pathogen besides C-MRAB, 7/13 (2/6 with bacteraemia) receiving colistin and/or tigecycline had good outcomes versus 8/12 (1/3 bacteraemia) not doing so ($P = 0.534$).

There was greater evidence of treatment modality influencing outcome among 41 patients with pulmonary infection. Among 15 who received i.v. but not nebulised colistin, 12 had poor outcomes and 9 died, with infection contributory or causal in 6. By contrast, there was only one poor outcome among eight patients who received nebulised colistin alone ($n = 4$) or combined with i.v. colistin ($n = 4$). Several patients in each arm received concurrent tigecycline. The difference in relation to nebulised colistin was significant ($P = 0.003$; estimated OR = 0.025, 95% CI 0.002–0.286), but there are several caveats. First, 4 of 15 patients receiving only i.v. colistin were bacteraemic compared with 1/8 receiving nebulised colistin. Second, five receiving the nebulised drug were at hospital 001, which specialises in trauma and which had generally good outcomes (see below), whereas only one patient given i.v. colistin alone was at this site. Third, although age was not a general risk factor, it is notable the mean age of the patients receiving nebulised colistin was 47.4 years (S.D. 16.8 years) versus 55.3 years (S.D. 20.9 years) for those receiving only the i.v. compound. When outcome was adjusted for bacteraemia, the statistical significance was not affected ($P = 0.005$; estimated OR 0.028, 95% CI 0.002–0.334); adjustment for both

bacteraemia and hospital site increased the P -value to 0.09, but the OR was little changed (OR = 0.066, 95% CI 0.003–1.54). It was not possible to include trauma as a further confounder in this model owing to small numbers; nevertheless, when the association between administration of nebulised colistin and outcome was adjusted for trauma, the P -value remained 0.009 (estimated OR = 0.019, 95% CI 0.001–0.368). It was possible to estimate significance adjusted for all three factors (bacteraemia, hospital and trauma) by exact logistic regression, and here the P -value rose to 0.25 (OR = 0.215, 95% CI 0.0–3.0). However, this model is extremely conservative and overall the analyses do support the view that nebulised colistin does result in improved outcomes.

There were 5 poor outcomes (all deaths) among 18 patients with respiratory ‘infection’ who received neither colistin nor tigecycline. This rate is better than among patients who received i.v. colistin but it may be that these ‘untreated infected’ patients were less seriously unwell than those given colistin and/or tigecycline.

One patient (Table 2) had a colistin-resistant *A. baumannii* isolate from sputum but was judged to be colonised and was not treated. He died from other causes 1 day after the isolate was recovered. All 14 patients given tigecycline had OXA-23 clone 1 isolates susceptible to this drug at ≤ 1 mg/L.

3.5. Hospital and outcome

There was a strong association between outcome and hospital (Table 5). At site 003, 12/14 patients (85.7%) had poor outcomes as did 9/16 (56.3%) at site 002 versus 2/16 (12.5%) at site 001. Outcome differences between sites were highly significant ($P = 0.0006$) in univariate analysis and remained so in multivariate analysis ($P = 0.05$) that controlled, for example, for the fact that all of the patients at site 003 were in the ICU and nine had C-MRAB bacteraemia (both risk factors for a poor outcome), whereas site 001 had an excess of trauma patients who generally had better outcomes. No obvious reasons were identified for the poor outcomes at site 003, although good outcomes at site 001 were probably because 8 of 16 C-MRAB-infected patients there were trauma victims, many from road traffic accidents, with a mean age of 39.9 years. Patients at the other sites had greater underlying pathology and were older, with mean ages at different sites ranging from 57.1 years to 64.0 years.

4. Discussion

C-MRAB strains are a major nuisance in ICU and HDU medicine, creating treatment and infection control problems. Although *A. baumannii* has low pathogenicity, it can cause disease in debilitated patients and was considered causative or contributory to death in 18 of 84 infections reviewed.

Nevertheless, no statistical differences in death or poor outcome rates were found between patients judged to be infected versus colonised. Whilst this points against significant attributable mortality, several caveats should be

noted: (i) the study lacked formal case–control (infected versus colonised) matching; (ii) the distinction between infection and colonisation is tenuous in patients with serious trauma or underlying disease; (iii) screening policies varied among sites, with some activity seeking to find colonisation and eradicate it; and (iv) some sites categorised patients as ‘infected’ only where specific therapy was given, whereas others included those the microbiologist thought should be treated irrespective of whether treatment was given.

A systematic review by Falagas et al. [17] recently highlighted the challenge of outcome analyses for *Acinetobacter* infections. Several reviewed studies attempted case–control matching based on APACHE II score, diagnosis at ICU admission and/or length of ICU stay, but others simply took patients concurrently on the same ICU as controls, irrespective of disease and severity. Meta-analysis proved impracticable, but Falagas et al. noted that all the studies indicated greater mortality among cases than controls, with the excess ranging from 7.8% to 23% for all patients and from 10% to 43% for ICU cases. The increase was least and lacked significance ($P = 0.056$ and 0.378) in two studies [18,19] that compared patients with *Acinetobacter* bacteraemia with non-bacteraemic controls who may nevertheless have been infected or colonised at other sites. A small excess mortality in bacteraemia is compatible with our results. Four studies [20–23] pooled infected and colonised ICU patients as ‘cases’, matching these to *Acinetobacter*-free ICU controls and finding 16–30% excess mortality ($P < 0.001$ to 0.046) in the colonised/infected group. Strikingly, 138/241 (57%) of the ‘cases’ in these studies were classed as colonised, not infected, and since true colonisation

cannot be harmful, the excess mortality can only be rationalised if: (i) infection has a very high excess mortality, which seems unlikely; (ii) the distinction between infection and colonisation is unreliable; or (iii) some factor not identified in the matching increased both mortality risk and vulnerability to colonisation by *A. baumannii*. The latter possibilities, if correct, have implications for the present study, which used 'colonised' patients as controls.

In general, we found that specific treatment had little effect on outcome, with 'poor' outcomes in 23/52 infected patients receiving colistin and/or tigecycline or, in one case only, minocycline, versus 12/32 among infected cases receiving neither ($P = 0.543$). Nevertheless, the effectiveness of treatment is difficult to assess since (i) the treated patients may have had the most severe infections and (ii) if there is little mortality associated with infection then treatment is unlikely to reduce mortality. Moreover, in the settings where the study did find an association between infection and outcome, i.e. bacteraemia and ICU-acquired infection, there is the issue of whether appropriate therapy was started quickly. Numerous studies have shown that delayed effective therapy is associated with increased mortality in severe infections [24], and limited data suggest that this applies with *Acinetobacter* [25]. If so, then a particular problem arises for C-MRAB since neither polymyxin nor tigecycline will be used empirically, and an audit at one participating site suggested that initiation of definitive therapy took up to 4 days. This introduces a contrast to the outcome analyses reviewed by Falagas et al. [25] dating from the mid 1990s when *A. baumannii* isolates were almost universally susceptible to carbapenems, which may have been used empirically.

Several case series describe the use of i.v. polymyxins in C-MRAB infections, reporting favourable outcomes in ca. 60% of non-pulmonary cases [9], although with less success among VAP patients [24]. The present data support this pattern: we observed 24/47 (51%) good outcomes and 29/47 (62%) survival overall among those given colistin, but only 3/15 (20%) good outcomes and 6/15 (40%) survival among those who received i.v (but not nebulised) colistin for pulmonary infection, perhaps reflecting poor lung penetration. This limitation might be overcome by co-administering the nebulised formulations, an approach described in many case reports, although not evaluated in formal trials [26]. The present results add support to this approach: there was only 1 poor outcome among 8 pneumonia patients receiving nebulised polymyxin versus 12/15 among patients receiving i.v. colistin, with several patients in each arm also receiving tigecycline. This difference is highly significant but subject to the caveats that (i) most patients receiving the inhaled drug were at site 001, which had generally good outcomes, (ii) they averaged a decade younger than the generality of patients and (iii) were mostly trauma victims without multiple underlying pathologies. Adjustment for these factors reduced, but did not obviate, the significance of the finding.

In summary, these data suggest that infections with OXA-23 clone 1 are not a significant independent cause of mortality, except in bacteraemic patients or those infected in an ICU. Nevertheless C-MRAB infections are often contributory to death in individual patients and are a considerable nuisance in

ICU medicine. Although tigecycline and colistin were generally active in vitro, their i.v. use had little clear effect on outcomes. Better outcomes were associated with nebulised colistin in pulmonary infections, although analysis was confounded by the fact that most of the patients receiving treatment by this route were at hospital 001 and were trauma victims, both factors associated with generally good outcomes.

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Competing interests

DML has spoken at and accepted hospitality/conference invites from Wyeth and Forest, who manufacture tigecycline and colistin, respectively. All other authors declare no competing interests.

Ethical approval

Not required; the Central Office of Research Ethics Committees defined this as an 'audit', confirming that neither Regional Ethics Committee review nor individual consent was required.

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Table 1

Numbers of subjects by hospital

| Hospital and type ^a | No. of cases | % of all cases | ICU + HDU | Colonised | Infected | Uncertain | No. OXA- 23 clone 1 |
|--------------------------------------|-----------------|----------------------|-----------------|-----------|----------|-----------|------------------------------|
| 001 (T) | 43 | 25.9 | 19 | 26 | 16 | 1 | 43 |
| 002 (M) | 29 | 17.5 | 17 | 12 | 16 | 1 | 29 |
| 003 (T) | 27 | 16.3 | 22 | 10 | 14 | 3 | 19 |
| 004 (T) | 17 | 10.2 | 14 | 6 | 9 | 2 | 17 |
| 005 (M) | 11 | 6.6 | 6 | 7 | 3 | 1 | 10 |
| 006 (M) | 9 | 5.4 | 7 | 0 | 9 | 0 | 9 |
| 007 (T) | 6 | 3.6 | 1 | 1 | 4 | 1 | 3 |
| 008 (M) | 5 | 3.0 | 3 | 5 | 0 | 0 | 1 |
| 009 (M) | 4 | 2.4 | 4 | 3 | 1 | 0 | 4 |
| 010 (T) | 4 | 2.4 | 4 | 0 | 4 | 0 | 2 |
| 011 (M) | 2 | 1.2 | 0 | 0 | 2 | 0 | 0 |
| 012 | 2 | 1.2 | 2 | 0 | 2 | 0 | 0 |
| 013 (Sp) | 2 | 1.2 | 1 | 1 | 1 | 0 | 0 |
| 014 (T) | 1 | 0.6 | 0 | 0 | 1 | 0 | 1 |
| 015 (M) | 1 | 0.6 | 0 | 0 | 1 | 0 | 1 |
| 016 (M) | 1 | 0.6 | 1 | 1 | 0 | 0 | 1 |
| 017 (M) | 1 | 0.6 | 1 | 0 | 1 | 0 | 1 |
| 018 (T) | 1 | 0.6 | 1 | 1 | 0 | 0 | 0 |
| Total | 166 | 100.0 | 103 | 73 | 84 | 9 | 141 |

ICU, Intensive Care Units; HDU, high dependency unit.

^a Based on Department of Health classification: T, teaching; M, Acute Trust;

Sp, specialist.

Table 2

Antimicrobial susceptibility of *Acinetobacter baumannii* isolates collected

| Antimicrobial agent | MIC (mg/L) | | | | | | | | | | | %S |
|----------------------------------|-----------------|------------------|----|----|----------------|---|------------------|----|------------------|------------------|------------------|-------------------|
| | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | 128 | 256 | |
| All isolates (<i>n</i> = 166) | | | | | | | | | | | | |
| Amikacin | | 4 | 7 | 10 | 2 | 2 | 1 | | 2 | | 138 ^a | 15.5 ^b |
| Gentamicin | | 3 | 1 | 1 | 3 | 2 | 3 | 8 | 145 ^a | | | 4.9 |
| Tobramycin | | 13 | 8 | 2 | | 2 | 3 | | 138 ^a | | | 13.9 ^b |
| PIP/TAZ | | | | | | | 3 | | | 163 ^a | | 1.8 |
| Ceftazidime | | | | | 3 | 4 | 1 | 4 | 84 | 51 | 19 ^a | 4.2 ^b |
| Imipenem | | | | | 6 ^c | 7 | 47 | 93 | 13 ^a | | | 0 |
| Meropenem | | | | | 1 | 3 | 51 | 99 | 12 ^a | | | 0 |
| Ciprofloxacin | | 1 | 1 | | 2 | 1 | 161 ^a | | | | | 1.2 |
| Tigecycline ^d | 65 ^e | 55 | 16 | 5 | 13 | 5 | 2 | | | | | 81.9 |
| Colistin | | 123 ^e | 42 | | | | | 1 | | | | 99.4 |
| OXA-23 clone 1 (<i>n</i> = 141) | | | | | | | | | | | | |
| Amikacin | | 2 | 3 | 4 | | 1 | 1 | | 1 | 129 ^a | | 7.7 ^b |
| Gentamicin | | 2 | 1 | 1 | 3 | | 2 | 3 | 129 ^a | | | 2.8 |
| Tobramycin | | 4 | 2 | | | | 3 | | 132 ^a | | | 4.9 ^b |

| | | | | | | | | | | | |
|--------------------------|-----------------|-------------------|---|----|----|---|----|------------------|-----|-----------------|------------------|
| PIP/TAZ | | | | | | 1 | | 140 ^a | 0.7 | | |
| Ceftazidime | | | 2 | 2 | | | 4 | 73 | 47 | 13 ^a | 2.8 ^b |
| Imipenem | | | | 4 | 40 | | 85 | 12 ^a | | | 0 |
| Meropenem | | | | 2 | 43 | | 88 | 8 ^a | | | 0 |
| Ciprofloxacin | | | | | 1 | | | 139 ^a | | | 0.7 |
| Tigecycline ^d | 63 ^e | 51 | | 10 | 1 | 8 | 4 | | | | 88.1 |
| Colistin | | 1046 ^e | | 37 | | | | | | | 100.0 |

MIC, minimum inhibitory concentration; %S, percent susceptible; PIP/TAZ, piperacillin/tazobactam.

^a MICs equal to or greater than the stated value, based on growth with highest drug concentration tested.

^b British Society for Antimicrobial Chemotherapy (BSAC) breakpoints for *Pseudomonas aeruginosa* used in the absence of values for *Acinetobacter* spp.

^c These isolates count as susceptible to imipenem, but are included on the basis of meropenem resistance; they belonged to clones other than OXA-23 clone 1.

^d Five isolates, four of them belonging to OXA-23 clone 1, were not tested with tigecycline.

^e MICs equal to or lower than the stated value, as no growth at lowest drug concentration tested.

Table 3Isolation sites for carbapenem- and multiply-resistant *Acinetobacter**baumannii*

| | Infected | Colonised | Uncertain | Total |
|----------|-----------------|-----------------|----------------|------------------|
| Sputum | 41 | 41 | 4 | 86 |
| Wound | 10 | 25 | 6 | 41 |
| Blood | 34 | 0 | 1 | 35 |
| Urine | 11 | 16 | 1 | 28 |
| Other | 15 ^a | 40 | 3 | 58 |
| Any site | 85 ^b | 74 ^b | 9 ^b | 166 ^b |

^a Lines or line tips, 7; fluids or aspirates, 5 (with 1 patient yielding cultures from both a line-tip and an aspirate); cerebrospinal fluid, 2; skin swabs, 2.

^b These figures do not equal the total of the values above since some subjects had infection or colonisation at multiple sites.

Table 4

Outcome by infection status and appropriateness of treatment received

| Outcome | Among infected ($n = 84$), received agent active in vitro ^a | | Among bacteraemic ($n = 34$ ^b), received agent active in vitro ^a | |
|---|--|----|--|----|
| | Yes | No | Yes | No |
| Resolved | 17 | 14 | 7 | 2 |
| Clinically improved | 12 | 6 | 5 | 0 |
| Deceased (C-MRAB causative or contributory) | 12 | 6 | 9 | 4 |
| Unresolved | 5 | 3 | 2 | 2 |
| Deceased (contribution of C-MRAB 'uncertain') | 6 | 3 | 2 | 1 |
| Outcome unknown | – | – | – | – |
| Total | 52 | 32 | 25 | 9 |

C-MRAB, carbapenem- and multiply-resistant *Acinetobacter baumannii*.

^a Colistin or tigecycline in the case of OXA-23 clone 1; otherwise any agent found to be active in vitro.

^b Excludes one bacteraemic patient whose infection status was uncertain.

Table 5

Comparison of outcome rates between hospitals

| Hospital | Proportion of infected patients with poor outcome | Estimated OR | 95% CI | Proportion of infected patients receiving colistin or tigecycline | Patient age (mean \pm S.D.) (years) |
|------------------------|---|--------------|---------------|---|---------------------------------------|
| 001 | 2/16 | Ref. | Ref. | 16/16 | 39.9 \pm 16.5 |
| 002 | 9/16 | 6.56 | 0.67– 63.9 | 8/16 | 62.0 \pm 17.1 |
| 003 | 12/14 | 38.9 | 3.1– 488 | 11/14 | 57.1 \pm 21.6 |
| 004 | 3/9 | 1.80 | 0.16– 20.0 | 5/9 | 61.1 \pm 20.3 |
| 006 | 2/9 | 1.30 | 0.1– 15.9 | 5/9 | 58.3 \pm 13.0 |
| Other hospitals pooled | 7/20 | 5.04 | 0.48– 52.1 | 8/20 | 64.0 \pm 17.3 |

OR, odds ratio; CI, confidence interval; S.D., standard deviation; Ref., referent.