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Restrictive antibiotic stewardship associated with reduced hospital mortality in gram-negative infection.

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Competing interest statement:

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Abstract:

Introduction: Antimicrobial stewardship has an important role in the control of *Clostridium difficile* infection (CDI) and antibiotic resistance. An important component of UK stewardship interventions is the restriction of broad-spectrum beta-lactam antibiotics and promotion of agents associated with a lower risk of CDI such as gentamicin. Whilst the introduction of restrictive antibiotic guidance has been associated with improvements in CDI and antimicrobial resistance evidence of the effect on outcome following severe infection is lacking.

Methods: In 2008, Glasgow hospitals introduced a restrictive antibiotic guideline. A retrospective before/after study assessed outcome following gram-negative bacteraemia in the 2-year period around implementation.

Results: Introduction of restrictive antibiotic guidelines was associated with a reduction in utilisation of ceftriaxone and co-amoxiclav and an increase in amoxicillin and gentamicin. 1593 episodes of bacteraemia were included in the study. The mortality over 1 year following gram-negative bacteraemia was lower in the period following guideline implementation (RR 0.852, P = 0.045). There was no evidence of a difference in secondary outcomes including ITU admission, length of stay, readmission, recurrence of bacteraemia and need for renal replacement therapy. There was a fall in CDI (RR 0.571, P = 0.014) and a reduction in bacterial resistance to ceftriaxone and co-amoxiclav but no evidence of an increase in gentamicin resistance after guideline implementation.

Conclusion: Restrictive antibiotic guidelines were associated with a reduction in CDI and bacterial resistance but no evidence of adverse outcomes following gram-negative bacteraemia. There was a small reduction in one year mortality.

1. Introduction

Delay in delivery of appropriate antibiotic therapy in severe bacterial infection is associated with poor outcome(1).The rising prevalence of antibiotic resistance(2) and the increasing incidence of *Clostridium difficile* infection (CDI)(3) have been associated with antibiotic prescribing,(4-6) and particularly with broad-spectrum agents such as cephalosporins and quinolones (6,7). Antimicrobial stewardship programmes aim to limit prescribing of broad-spectrum antibiotics to specific preserved indications where possible. A systematic review demonstrated that published stewardship strategies have been associated with significant reductions in CDI(8) and a positive impact on gram negative resistance have also been observed(9,10). Such strategies are now recommended by guidelines in the United Kingdom(11) and elsewhere(12). As in other parts of the UK (13), the Scottish stewardship strategy has focused on reducing use of '4C' antibiotics: cephalosporins, co-amoxiclav, ciprofloxacin (and other quinolones) and clindamycin(14).

NHS Greater Glasgow and Clyde (population 1.2 million) introduced a comprehensive "4C" restrictive antimicrobial guideline across the 9 acute adult hospitals from July to August 2008. Similar restrictive guidance were developed and rolled out across primary care in 2009. Changes were made primarily in response to concerns regarding CDI with reported rates of 2.04 per 1000 occupied bed days for those aged ≥ 65 years in 2006/2007

{<http://www.documents.hps.scot.nhs.uk/hai/sshaip/publications/cdad/2007->

12-20-ar-cdad.pdf.} Updated guidelines recommended gentamicin in combination with narrow-spectrum beta-lactams instead of broad-spectrum beta-lactams (principally ceftriaxone or co-amoxiclav) for suspected severe gram-negative infection (table 1). Gram-negative resistance to gentamicin in Glasgow at this time was lower than the agents it replaced and its use was perceived to be associated with a lower risk of CDI than '4C' antibiotics(15). At the time of guideline implementation, concerns around promoting a greatly expanded role for gentamicin were considered. Specific concerns included the potential for increased incidence of acute kidney injury and ototoxicity as well as the relative paucity of data supporting the use of gentamicin monotherapy in severe infection(16,17). In view of the potential for unintended harm, it was recommended that gentamicin was restricted to the empiric phase of therapy with a maximum duration of 4 days. Within the restrictive guidance the importance of early recognition and investigation of sepsis with prompt intravenous antibiotic therapy was emphasized. Updated guidance was made available through educational meetings, electronic communication and intranet, posters and via the Health Board's Therapeutics handbook. In order to assess the impact of the restrictive antimicrobial policy on outcome (including unintended consequences) of severe gram-negative infection following the introduction of the updated guidelines we designed a pragmatic before/after cohort study.

2. Methods

Data were collected retrospectively from patients presenting to the 4 acute adult hospitals in North Glasgow (around 2600 beds). Blood cultures yielding gram-

negative organisms over the two-year period spanning guideline introduction (1/8/2007–31/7/2009) were screened for inclusion. Outcome data were collected from prospectively maintained databases held within our NHS board. Hospital associated infection (HAI) was defined as bacteraemia which occurred in a patient admitted to hospital more than two days prior to the blood culture or who had been discharged within 28 days(adapted from 18). Throughout the period of study, antimicrobial sensitivity testing was conducted using disk diffusion testing according to CLSI guidelines. Antimicrobial utilisation data is presented in defined daily doses per 10³ occupied bed days [DDD])(19).

Outcome definitions

Recurrence was defined as gram-negative bacteraemia detected more than 48 hours after the initial blood culture. The detection of *Clostridium difficile* toxin in diarrhoeal stool was considered diagnostic of CDI. Need for renal replacement therapy (RRT) was defined as commencement of haemofiltration or haemodialysis in a patient who had not received RRT within the prior 60 days and had not been diagnosed with end stage renal disease. Serum creatinine was retrieved at admission and on days 7, 30 and 60 as long as the patient remained in hospital. Renal function was assessed using the modification of diet in renal disease (MDRD) estimate of glomerular filtration rate (eGFR). Kidney injury was classified according to the RIFLE criteria(20).

Statistical Analysis

Survival and outcome analysis was conducted using Cox proportional hazard modeling. Modeling of the impact of CDI on survival during multivariate analysis was conducted via a step parameter to avoid immortal-time bias. Analysis of bacterial resistance was conducted using 2x2 contingency tables and Fisher's exact test.

Statistical analysis was conducted using R for OS X 3.0.2. Plots were generated using ggplot2 0.9.3 and Prism 6.0 (Graphpad).

Ethics and Funding Statement

The regional ethics committee scientific advisor gave advice that the study represented service evaluation and did not require formal ethical review. Permission to use patient identifiable information was obtained from the Cauldicott Guardian. The research study was designed by the authors and no funding was received to assist in conducting it.

3. Results

1593 episodes of bacteraemia were included from 2350 positive blood cultures screened (figure 1). 791 (49.7%) episodes of bacteraemia were from the period prior to the introduction of the new guidelines (period 1) whereas 802 (50.3%) occurred after the change (period 2). There was no change in the incidence of bacteraemia over the study period. There was no evidence of a difference in the baseline characteristics of the patients and organisms isolated (table 2).

There was a significant change in antibiotic requisitions throughout North Glasgow hospitals in association with the new guidelines (figure 2A) with increased use of amoxicillin (173 and 269 DDD) and gentamicin (27.4 and 45.1 DDD) but decreased use of ceftriaxone (46.3 and 13.2 DDD), co-amoxiclav (18.1 and 12.7 DDD) and ciprofloxacin (11.0 and 9.1 DDD) (all $P < 0.001$). There was no evidence of an increase in the use of meropenem (18.1 and 20.5 DDD, $P = 0.15$) or piperacillin/tazobactam (16.3 and 16.9 DDD, $P = 0.50$) although the power to detect small increases in use of antibiotics was limited by the number of data points available. There was a significant increase in gentamicin therapeutic drug monitoring (TDM) within a week of the positive blood culture in period 2 (30% to 59%, $P < 0.0001$, figure 2B).

Mortality in the gram-negative bacteraemia cohort at one year was lower in period 2 than in period 1 (RR 0.852, 95% CI 0.73 – 0.99, $P = 0.045$) (figure 3A). Lower mortality was observed in HAI (RR 0.808, 95% CI 0.67 – 0.98, $P = 0.027$) but not CAI (RR 0.950, 95% CI 0.72 – 1.26, $P = 0.72$) (figure 3B).

There was no difference in outcome between time periods in terms of ITU admission (RR 1.095, 95% CI 0.72 – 1.67, $P = 0.667$), length of stay (median 11 days in both groups, $P = 0.769$) or recurrence of gram-negative bacteraemia with either the same (HR = 1.19 [0.78 – 1.81], $P = 0.431$) or a different species (HR = 1.04 [0.74 – 1.45], $P = 0.835$). Patients in period 2 were significantly less likely to develop CDI (HR = 0.57 [0.37 – 0.89], $P = 0.014$) (figure 4).

There was a significant change in gram-negative bacterial resistance following the introduction of the updated guidelines. There was a significant reduction in resistance to ceftriaxone (-4.7%, $P = 0.020$) and co-amoxiclav (-5.8%, $P = 0.022$) and a trend towards less resistance to piperacillin/tazobactam (-2.3%, $P = 0.109$). There was no evidence of an increase in resistance to gentamicin (0.5%, $P = 0.735$). In each case, the reduction in antimicrobial resistance observed was principally seen in patients with HAI with smaller, non-significant changes in bacterial resistance in CAI (figure 5). The proportion of bacteria sensitive to the guideline antibiotic regimen for gram-negative sepsis at the time of the bacteraemia increased from 79.1% to 90.0% (+10.9% [7.4 – 14.5], $P < 0.0001$) although this increase was primarily due to the lower prevalence of gentamicin resistance relative to that of ceftriaxone rather than the change in the sensitivity pattern of the organisms.

Serum creatinine measurements were available for the duration of each patient's admission to hospital. No difference in baseline renal function was observed (Baseline Cr: 140 and 137 mmol/l, $P = 0.63$) and there was no evidence of a difference in renal function at any of the follow up time points ($P = 0.86$). We were concerned that patients presenting with abnormal renal function (Injury, Failure or Loss in the RIFLE classification) at baseline might be at risk from the new guidelines. After excluding patients with normal renal function at baseline, there was a statistically non-significant trend towards a slower renal recovery in period 2 ($P = 0.14$, figure 6) and more patients with abnormal renal function at baseline in period 2 had a worsening of renal function over the first week of admission (RR 1.50, $P = 0.02$). There was no evidence of a difference in median

length of stay or mortality in this group. We also analysed the same data categorically using the RIFLE classification in place of eGFR with similar results.

4. Discussion

The impact of restrictive antimicrobial guidelines on reducing the rate of CDI(8) and bacterial resistance(9,10) has been reported before and this study provides further evidence of benefit from stewardship. However, a Cochrane review of outcomes following restrictive antimicrobial stewardship interventions did not find any reports on clinical outcomes except CDI and resistance(21). This is particularly important in view of historic findings from randomized controlled trials of gentamicin efficacy. A meta-analysis of clinical trials involving gentamicin found similar outcomes to comparator antibiotics but only a small proportion of patients had sepsis(16). Another meta-analysis of heterogeneous studies in secondary peritonitis found lower rates of clinical cure in patients treated with clindamycin and gentamicin although mortality was not affected(17). Clinical outcome data following severe infection managed using restrictive guidelines are extremely limited. One study (published only in abstract) which examined the mortality from "septicaemia" using discharge coding, found a 21% reduction in mortality after the introduction of restrictive guidelines similar to those used in Glasgow(22). In another uncontrolled study, treatment failure following the introduction of restrictive guidelines was associated with failure to administer guidelines antibiotics(23). To our knowledge, the pragmatic before/after study we report here is the first controlled study to investigate survival following severe infection in association

with such guidelines. This is important since the primary goal of antimicrobial guidelines must be to assist clinicians in giving effective therapy for severe infection. The desire to limit antibiotic associated harm must not be at the expense of less effective therapy for sepsis. Although a lack of association between the increase in gentamicin prescribing across Glasgow hospitals and the need for RRT was previously demonstrated(24), a gentamicin based regime for orthopaedic surgical prophylaxis in some Scottish hospitals was associated with an increase in renal dysfunction(21,25). This reinforces the importance of vigilance for identification of unintended consequences when implementing antibiotic guidelines. An evidence base for stewardship programs is also important for acceptance; opposition from prescribing clinicians is frequently cited as an important barrier to success of stewardship interventions(26). In our experience, concern about the efficacy of narrow-spectrum alternatives is a commonly cited reason for opposition – this study was conducted partly in response to these concerns.

In this study we have shown that a restrictive antimicrobial stewardship policy applied across acute hospitals in North Glasgow was not associated with detectable worsening in the outcome following serious gram-negative infection. An overall reduction in mortality was observed and was, attributable to those with hospital-associated gram-negative bacteraemia. There was a significant reduction in CDI following the introduction of the restrictive guidelines and, since gentamicin resistance was less common in Glasgow than resistance to previously used first line agents, patients treated according to the guidelines were more likely to receive effective antibiotic therapy. Since CDI and infection

with resistant organisms are associated with poor outcome and are more common in patients with HAI, it may be that these factors contributed to the difference observed and this hypothesis was supported by multivariate analysis (data not shown). However, despite accounting for these factors, there was still no clear evidence of increased risk of adverse outcome in patients treated under the restrictive guidelines. The absence of an increased need for renal replacement therapy was also reassuring since gentamicin associated nephrotoxicity is a particular concern. A modified version of the Hartford nomogram (27) with an online dosing calculator based on a gentamicin dose of 5 mg/kg 24 or 48 hourly was developed and is used in Glasgow hospitals(28).

Renal failure is strongly associated with prolonged length of stay and mortality in many studies(29,30). Once daily dosing of aminoglycosides may be associated with decreased nephrotoxicity and improved clinical response compared with multiple daily dosing in some patient groups(31). Gentamicin nephrotoxicity has been associated with treatment duration(32,33); Glasgow guidelines recommend limiting gentamicin therapy duration to three or four days to reduce the risk of nephrotoxicity. Renal replacement therapy is an easily recorded outcome of renal failure, however it represents only the tip of the iceberg. There was no evidence of an impact of guideline change on renal function overall in our study. When the subgroup of patients with abnormal renal function at baseline was considered there was a trend towards delayed recovery of renal function. However, the trend effect was small and there was no evidence of impact on length of stay, nor need for renal replacement therapy or mortality.

An important limitation of this study is that individual prescribing data were not available. However, use of gentamicin TDM within the gram-negative bacteraemia cohort could be used as a surrogate for gentamicin therapy. It should be noted that despite the introduction of the updated guidelines, more than 40% of patients did not have gentamicin TDM. There are a number of potential reasons for this: a small number of patients may have received gentamicin but were switched to an alternative antibiotic or died prior to a TDM but the majority are likely to have received non-guideline antibiotics. This reflects the pragmatic nature of the guidelines, which encouraged discussion with infection specialists and did not impose procedural restraint on clinicians recommending non-guideline antibiotics. Patients with gram-negative sepsis are often among the most unwell patients and it is therefore not surprising that these patients are likely to receive individualised therapy. This study cannot purport to present evidence that gentamicin should be given to all unselected patients with suspected gram-negative sepsis. It does, however, provide significant reassurance that restrictive guidelines promoting the use of gentamicin, pragmatically applied, can be safely used as part of an antibiotic stewardship programme.

A general limitation of before/after studies is the difficulty in establishing causation of differences observed. The restrictive antimicrobial policy was introduced at a similar time to other linked interventions including an increased focus on infection control, health-care associated infection and prompt management of sepsis. The educational role out of the restrictive guidance in fact incorporated all these factors and particularly emphasized the importance of

prompt administration of parenteral antibiotic therapy in acutely unwell patients with infection. These and other unidentified factors may have significantly influenced outcome. Most successful strategies for reduction of CDI and antibiotic resistance incorporate interventions in both infection control and antibiotic stewardship; for this reason data assessing the impact of each in isolation are limited. Other experimental designs would be extremely difficult and costly to implement, so pragmatic before/after studies are likely to form the bulk of available data to guide practice.

In conclusion, the change to the empirical antibiotic guidelines in Glasgow hospitals was associated with a decrease in CDI, antibiotic resistance in gram-negative bacteraemia and a modest but significant reduction in mortality following Gram-negative bacteraemia but not with a significant increase in renal failure. This study provides evidence that restrictive antibiotic policies promoting the widespread use of empirical (short duration) gentamicin are effective.

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Contributors:

NDR designed the study and was responsible for co-ordinating data collection and analysis. He is guarantor. RAS led the development of the antibiotic guidance and its introduction and contributed to the design and interpretation of the study. AH, SCI and FR assisted with data collection and analysis in their specialist areas. BLJ contributed to the design and interpretation of the study. All the contributors were involved in drafting the manuscript and all contributors approved of its publication.

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Keywords:

Clostridium difficile; antibiotics; antimicrobial stewardship; aminoglycosides; gram negative; bacteremia

Figure 1.

Flowchart illustrating the identification of episodes of bacteraemia suitable for inclusion from the microbiology database.

Figure 2.

Antibiotic utilization data for period covering the introduction of restrictive antibiotic guidelines. Temporal trends in (A) pharmacy dispensing records and (B) gentamicin therapeutic drug monitoring within one week of detection of gram-negative bacteraemia. DDD: designated daily dose.

Figure 3.

Survival for 1 year following episode of bacteraemia before and after the introduction of restrictive antimicrobial guidelines. A. All patients. B. Stratified according to status of infection. CAI: community associated infection; HAI: hospital associated infection. P values shown are for log rank test.

Figure 4.

Analysis of pre-specified secondary end-points. Outcomes were assessed by univariate Cox proportional hazard model and represent relative risk of outcome except for length of stay which represents relative change in median time to

discharge. IQR: inter-quartile range; ITU: intensive care unit; CAI: community associated infection; HAI: hospital associated infection.

Figure 5.

Change in rate of bacterial resistance to commonly used antibiotics between period 1 and period 2 and stratified according to hospital or community associated infection. Bars represent change in resistance with error bars showing 95% confidence intervals. CAI: community associated infection; HAI: hospital associated infection.

Figure 6.

Change in serum creatinine after detection of gram-negative bacteraemia in patients treated in period 1 and period 2 stratified according to RIFLE classification at baseline. Line represents mean serum creatinine at each time point with 95% confidence interval denoted by error bar.

Source of sepsis	Period to July 2008	Period after July 2008
Undifferentiated	Ceftriaxone ± gentamicin	Benzylpenicillin + flucloxacillin + gentamicin
Urinary tract	Ceftriaxone or co-amoxiclav ± gentamicin	Amoxicillin + gentamicin
Intra-abdominal	Ceftriaxone + metronidazole ± gentamicin	Amoxicillin + gentamicin + metronidazole

Table i. Guideline antibiotic therapy for patients presenting with sepsis syndrome likely to be caused by gram-negative organisms before and after the introduction of revised guidelines.

Characteristic		2007/2008	2008/2009	P value
Median age (IQR)		69.9 (56.6-79.2)	69.3 (54.6-79.7)	0.50
Male sex (%)		387 (48.6%)	384 (47.3%)	0.61
Source dept.	Medicine	324 (40.7%)	369 (45.5%)	0.21
	Surgery	201 (25.3%)	201 (24.8%)	
	Emergency	151 (19.0%)	132 (16.2%)	
	Other	119 (15.0%)	109 (13.4%)	
Hospital assoc.		449 (56.4)	452 (55.7)	0.80
Causative organism	E. coli	415 (52.2%)	457 (56.4%)	0.38
	Other coliforms	242 (30.4%)	225 (27.7%)	
	Pseudomonas sp.	33 (4.2%)	28 (3.4%)	
	Others	105 (13.2%)	100 (12.3%)	

Table ii. Baseline characteristics of patients with gram-negative bacteraemia and microbiological identification of isolates.

Abbreviations

CDI	Clostridium difficile infection
DDD	Defined daily dose/10 ³ occupied bed days
RRT	Renal replacement therapy
MDRD	modification of diet in renal disease eGFR
TDM	Therapeutic drug monitoring
HAI	Hospital acquired infection
CAI	Community acquired infection
eGFR	Estimated glomerular filtration rate

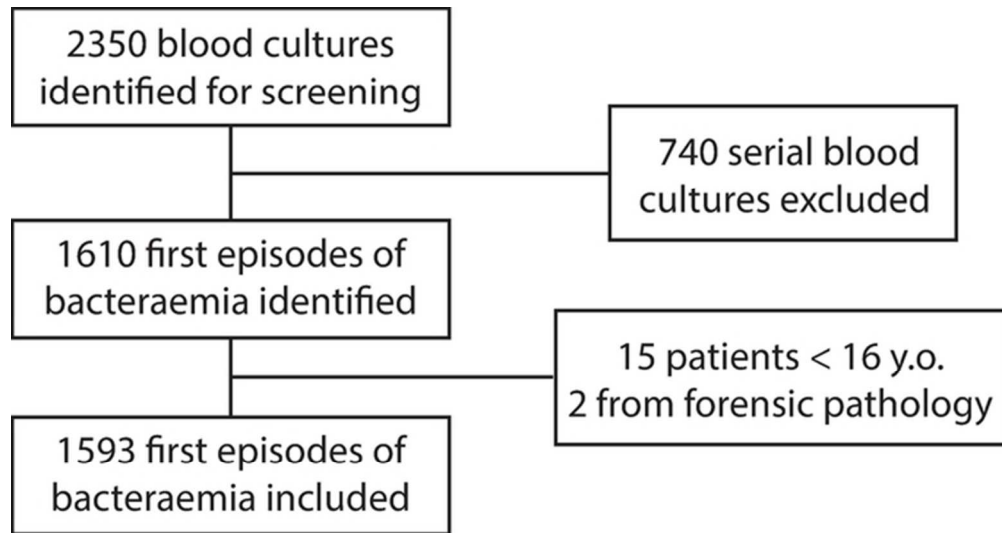


Figure 1. Flowchart illustrating the identification of episodes of bacteraemia suitable for inclusion from the microbiology database.

figure 1
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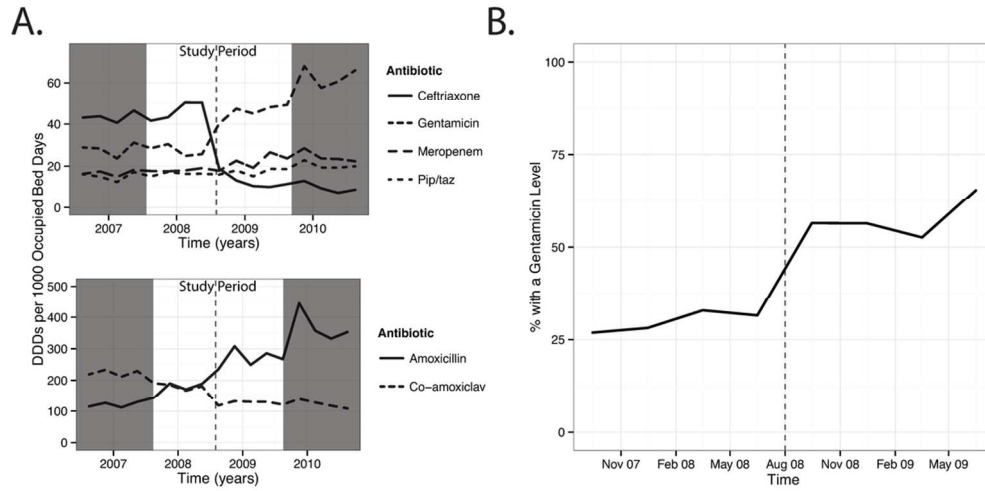


Figure 2. Antibiotic utilization data for period covering the introduction of restrictive antibiotic guidelines. Temporal trends in (A) pharmacy dispensing records and (B) gentamicin therapeutic drug monitoring within one week of detection of gram-negative bacteraemia. DDD: designated daily dose.

figure 2
104x51mm (300 x 300 DPI)

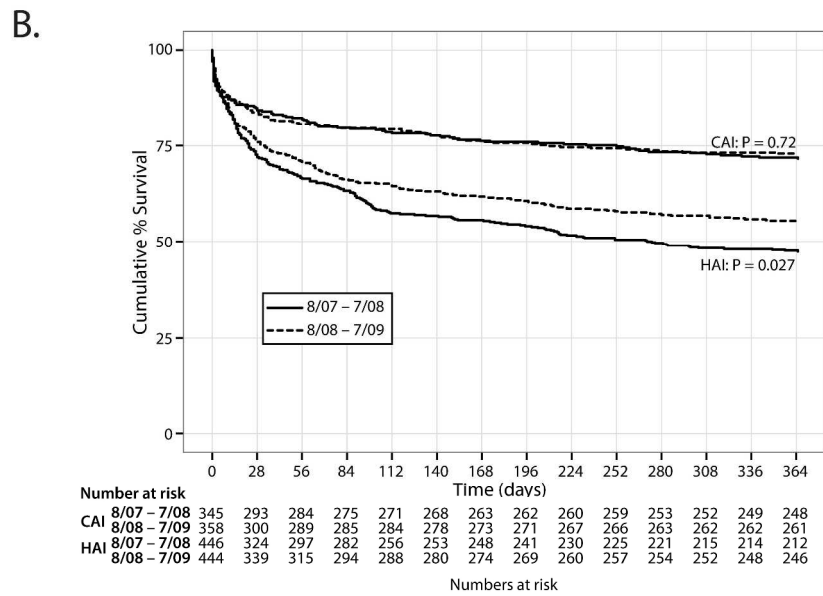
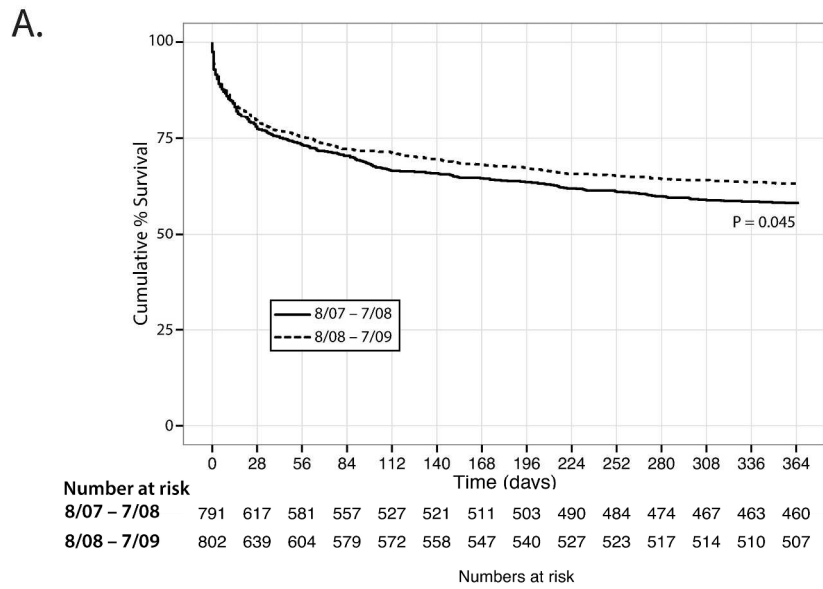


Figure 3. Survival for 1 year following episode of bacteraemia before and after the introduction of restrictive antimicrobial guidelines. A. All patients. B. Stratified according to status of infection. CAI: community associated infection; HAI: hospital associated infection. P values shown are for log rank test.

figure 3
256x366mm (300 x 300 DPI)

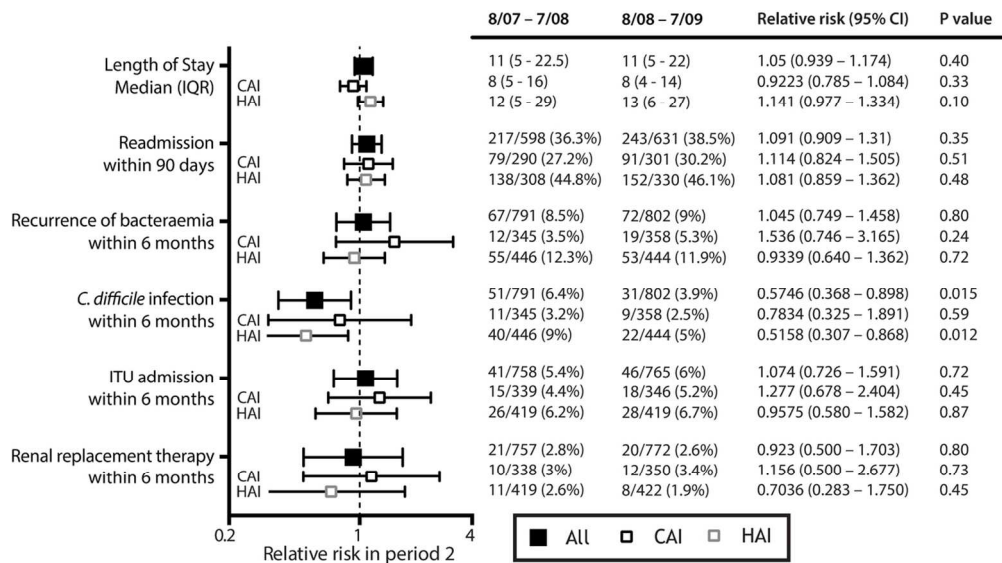


Figure 4. Analysis of pre-specified secondary end-points. Outcomes were assessed by univariate Cox proportional hazard model and represent relative risk of outcome except for length of stay which represents relative change in median time to discharge. IQR: inter-quartile range; ITU: intensive care unit; CAI: community associated infection; HAI: hospital associated infection.

figure 4
116x64mm (300 x 300 DPI)

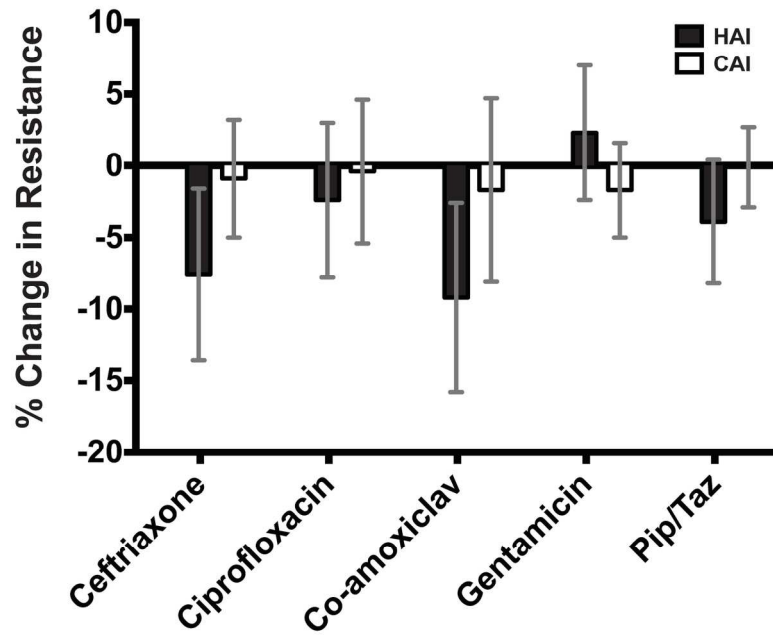


Figure 5. Change in rate of bacterial resistance to commonly used antibiotics between period 1 and period 2 and stratified according to hospital or community associated infection. Bars represent change in resistance with error bars showing 95% confidence intervals. CAI: community associated infection; HAI: hospital associated infection.

figure 5
163x111mm (300 x 300 DPI)

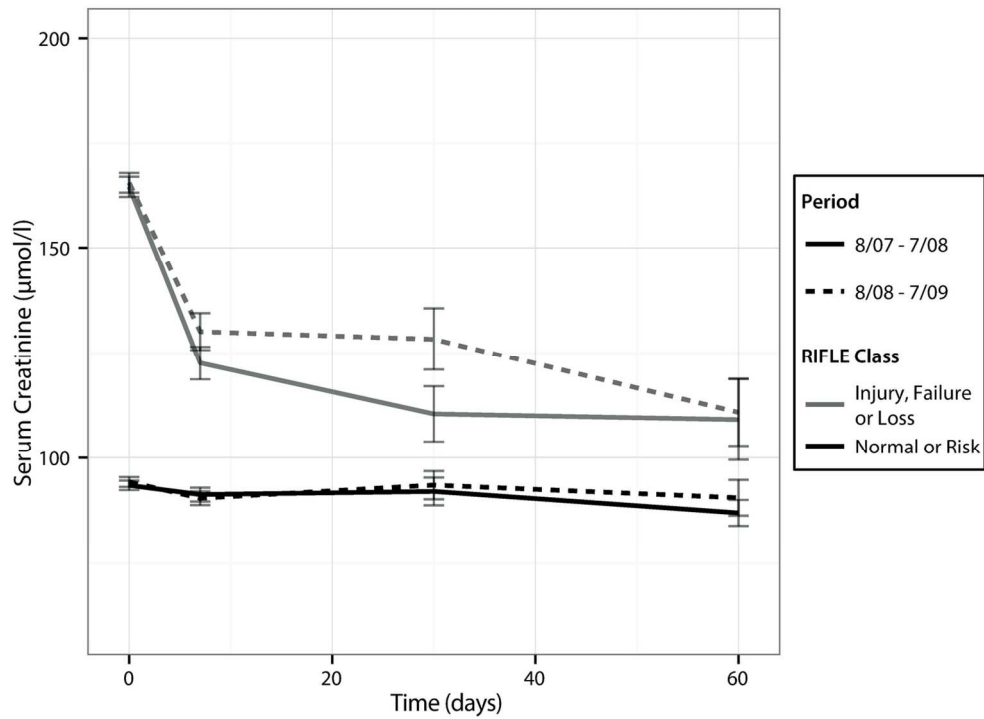


Figure 6. Change in serum creatinine after detection of gram-negative bacteraemia in patients treated in period 1 and period 2 stratified according to RIFLE classification at baseline. Line represents mean serum creatinine at each time point with 95% confidence interval denoted by error bar.

figure 6
128x96mm (300 x 300 DPI)