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Risk factors associated with nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection including previous use of antimicrobials

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major nosocomial pathogen worldwide. To investigate an association between antimicrobial use and MRSA, a case control study of 121 patients infected with MRSA compared with 123 patients infected with methicillin-susceptible *S. aureus* (MSSA) was carried out. Antimicrobial use was analysed by three different logistic regression models: all β-lactam antibiotics, β-lactam antibiotics grouped in classes and antimicrobial use in grammes. Patients infected with MRSA tended to have more co-morbidities, longer lengths of stay (LOS) and greater exposure to antibiotics than MSSA-infected patients. Multivariate analysis identified levofloxacin [odds ratio (OR) 8.01], macrolides (OR 4.06), previous hospitalization (OR 1.95), enteral feedings (OR 2.55), surgery (OR 2.24) and LOS before culture (OR 1.03) as independently associated with MRSA infection. All models were concordant with the exception of macrolides, which were not significant based on the number of grammes administered. There were no significant differences in the types of infection or the attributed mortality in either group. MRSA-infected patients had a significantly longer LOS before infection [18.8 ± 18.2 compared with 8.4 ± 6.9 ($P < 0.001$)] and a significantly longer post-diagnosis LOS [27.8 ± 32.9 compared with 18.6 ± 21 ($P = 0.01$)] than MSSA-infected patients.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major nosocomial pathogen worldwide.[1–3] The Centers for Disease Control (CDC) National Nosocomial Infection Surveillance System (NNIS) reported that methicillin resistance among *S. aureus* in US hospitals increased from 2.4% in 1975 to 29% in 1991, with a higher degree of resistance in intensive care units.[4–5] More recent data from 1990 through 1997 identified that the MRSA incidence rate increased 260% in hospitals that participated in the International Networks for the Study and Prevention of Emerging Antimicrobial Resistance (INSPEAR) Programme.[6] Traditionally, MRSA was identified infrequently from patients in the community, but over the last few years reports have documented increases in community MRSA, which may suggest a changing epidemiology.[7–11]

The reasons for the emergence of MRSA are multifactorial and can be attributed to host factors, infection control practices and antimicrobial pressures.[12–14] The appearance of bacterial resistance phenotypes has been linked to the clinical use of antimicrobial agents to which the bacteria express resistance.[15] One study demonstrated that a patient's normal colonizing flora changes within 24–48 h under selective antibiotic pressures.[16] A recent review of more than 20 studies by Monnet & Frimodt-Moller[17] identified consistent associations and dose–effect relationships that support a causal relationship between MRSA and antimicrobial drug use. One of these studies demonstrated that ciprofloxacin and cephalosporins promoted the colonization and ultimately the spread of MRSA in one hospital.[18] In studies where antimicrobial classes are analysed separately both cephalosporins and fluoroquinolones are often identified as risk factors for MRSA.[19] A multi-centre study of 50 Belgian hospitals associated an increasing incidence of MRSA with increasing use

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Table 1. Patient characteristics (before MRSA/MSSA infection) that were significantly different in the MRSA-infected population

Characteristic	MRSA (n = 121)	MSSA (n =123)	OR and 95% CIs	P value
LOS before culture[a]	18.8 (2–97)	8.4 (2–45)		<0.001
Unit changes[a]	1.2 (0–6)	0.70 (0–7)		0.003
Total number of grammes of antibiotics[a]	33.1 (0–323)	9.1 (0–127)		<0.001
Central line days[a]	12.0 (0–141)	4.0 (0–77)		<0.001
Urinary catheter days[a]	10.7 (0–84)	3.6 (0–20)		<0.001
Ventilator days[a]	6.1 (0–71)	1.7 (0–20)		<0.001
Respiratory therapy days[a]	6.5 (0–71)	2.3 (0–25)		<0.001
Drug interaction	6.6%	0	n/a	0.003
Previous hospitalization	73.6%	53.7%	1.4 (1.1, 1.7)	0.001
Medical ICU	14.9%	4.1%	3.7 (1.4, 9.5)	0.004
Rehabilitation unit	6.6%	0.8%	8.1 (1.0, 64)	0.02
ET tube/Trach/NG tube[b]	74.4%	55.3%	1.3 (1.1, 1.6)	0.002
Urinary catheters	77.7%	64.2%	1.2 (1.0, 1.4)	0.02
Previous antibiotics	86.0%	53.7%	1.6 (1.3, 1.9)	<0.001
Total parenteral nutrition	19.8%	6.5%	3.1 (1.4, 6.5)	0.002
Enteral feedings	59.5%	30.9%	1.9 (1.4, 2.6)	<0.001
Enteral feedings within 2 h of oral levofloxacin dose	14%	0.8%	17.3 (2.3, 127.8)	<0.001
Physical therapy	44.6%	19.5%	2.3 (1.5, 3.4)	<0.001
Surgery	57.9%	35.8%	1.7 (1.2, 2.1)	0.001
Abdominal surgery	20.7%	8.9%	2.3 (1.2, 4.5)	0.01
Sepsis	19.8%	6.5%	3.1 (1.4, 6.5)	0.002
Hypoalbuminaemia	84.3%	65%	1.3 (1.1, 1.5)	0.001
Multi-organ failure	15.7%	4.9%	3.2 (1.3, 7.8)	0.006
Skin ulcers, eczema, etc.	33.1%	17.9%	1.8 (1.2, 4.5)	0.008
Graft	29.8%	17.1%	1.7 (1.1, 2.8)	0.02

[a]Mean and range.
[b]ET, endotracheal; Trach, tracheostomy; NG, nasogastric.

of ceftazidime and cefsulodin, co-amoxiclav and fluoroquinolones.[19] Dziekan *et al.*[20] also showed that fluoroquinolone use was an independent risk factor for MRSA as well as nasogastric tubes and central venous catheters. In separate studies, both Crossley *et al.*[21] and Hershow *et al*.[22] noted that patients with MRSA infection had a significantly longer length of stay (LOS) before infection and were likely to have received antimicrobial therapy. A recent publication identified levofloxacin therapy, ICU setting and LOS as being independently associated with MRSA.[23]

Over the past 3 years, there has been a significant increase in the incidence of nosocomial MRSA at our institution. During this time, there was no significant difference in the number of admissions or patient days. Concurrent with this increase in MRSA incidence was an increase in the usage of fluoroquinolone and β-lactam/β-lactamase inhibitor antimicrobials. The purpose of this study was to identify characteristics that were associated with nosocomial MRSA infection.

Materials and methods

This study was conducted at Albany Medical Center, a 600 bed tertiary care facility. Cases were patients infected with nosocomial MRSA from 1997 to 1999. Controls were selected randomly from a database of all patients infected with nosocomial MSSA from the same time period. A nosocomial case was defined as a patient without any evidence of infection on admission and who was culture positive >48 h after admission. A retrospective review of the patient's medical record was conducted using a standardized data collection form. All of the data were collected before MRSA or MSSA infection. Antibiotic data were grouped into antimicrobial classes for analysis. Infections were defined using the CDC NNIS definitions.[24] Crude and attributable mortality rates were calculated. Death was considered attributed to infection if the infection either directly caused death or exacerbated a pre-existing condition that otherwise would not have resulted in the patient's death. Antimicrobial susceptibility testing on *S. aureus* was carried out by disc diffusion according to

Table 2. Patient characteristics (before MRSA/MSSA infection) not significantly different in the MRSA-infected population

Characteristic	MRSA (n = 121)	MSSA (n = 123)	OR and 95% CIs	P value
Age[a]	60.9 (22–95)	57.1 (18–91)	n/a	0.11
Chest tube days[a]	1.4 (0–15)	0.85 (0–13)	n/a	0.11
Sex: female	41.3%	36.6%	1.1 (0.82, 1.5)	0.51
ICU[b]	65.3%	58.5%	1.1 (0.92, 1.4)	0.29
Drains	28.9%	22.0%	1.3 (0.85, 2.0)	0.24
Prosthetic devices	14.0%	12.2%	1.2 (0.60, 2.2)	0.71
Ventilators	54.5%	44.7%	1.2 (0.95, 1.6)	0.16
Central lines	71.9%	61.8%	1.2 (0.97, 1.4)	0.10
Chest tube	24.0%	24.4%	0.98 (0.63, 1.5)	1.0
Diabetes	30.6%	20.3%	1.5 (0.97, 2.3)	0.08
Dialysis	8.3%	7.3%	1.1 (0.48, 2.7)	0.82
Chemotherapy	2.5%	4.1%	0.61 (0.15, 2.5)	0.72
Haemodynamic instability	19.8%	15.4%	1.3 (0.74, 2.2)	0.40
Bronchoscopy	9.9%	6.5%	1.5 (0.65, 3.6)	0.36
H_2 blockers/ion pump	67.8%	58.5%	1.2 (0.96,1.4)	0.15
Sucralfate	25.6%	20.3%	1.3 (0.79, 2.0)	0.36
Steroids	24.0%	16.3%	1.5 (0.88, 2.5)	0.15
HIV[b]	9.9%	4.9%	2.0 (0.79, 5.2)	0.15
ARDS[b]	9.9%	4.1%	2.4 (0.88, 6.7)	0.08
COPD[b]	39.7%	29.3%	1.4 (0.95, 1.9)	0.11
Kidney failure	16.5%	9.8%	1.7 (0.87, 3.3)	0.13
Radiation therapy (previous year)	5.8%	3.3%	1.8 (0.53, 5.9)	0.37
Immunosuppression	17.4%	13.8%	1.3 (0.70, 2.3)	0.48
Respiratory therapy	57.9%	46.3%	1.2 (0.98, 1.6)	0.08
History of aspiration	18.2%	10.6%	1.7 (0.97, 1.4)	0.10

[a]Mean and range.
[b]ICU, intensive care unit; HIV, human immunodeficiency virus; ARDS, adult respiratory distress syndrome; COPD, chronic obstructive pulmonary disease.

National Committee for Clinical Laboratory Standards (NCCLS).[25] This study was approved by the institutional review board

Statistical methods

Statistical analysis was carried out using SPSS Version 8 (SPSS, Chicago, IL, USA). Continuous variables were compared with a *t*-test for independent samples (two-tailed). Dichotomous variables were compared with a two-tailed Fisher's exact test for 2×2 comparisons or a Pearson's χ^2 test for greater than two variables. Odds ratios (ORs) and their 95% confidence intervals (CIs) were computed. A logistic regression model was carried out by a forward selection using the likelihood ratio statistic.

Results

Univariate analysis was conducted on 121 MRSA-infected patients and 123 MSSA-infected patients from the same time period. Tables 1 and 2 list the ORs and significant levels for potential risk factors collected. MRSA-infected patients tended to have longer LOS before infection, and had more ward changes and device days. With regard to hospital location, there was a significant difference in the two units. Both the medical intensive care and rehabilitation units had a significantly higher number of patients infected with MRSA. Patients infected with MRSA tended to have more antibiotics, particularly β-lactam antibiotics, levofloxacin and macrolides (Table 3).

Multiple logistic regression analysis identified six risk factors that were associated independently with MRSA infection. These risk factors were previous hospitalization, longer LOS before infection, surgery, enteral feedings, levofloxacin use and macrolide use. Three logistic regression models were carried out to assess antimicrobial usage. The first model included the significant β-lactam antibiotics grouped in classes, whereas the second model combined all the β-lactam antibiotics together. This was conducted because the selective pressures for all β-lactam antibiotics are approxi-

Table 3. Univariate analysis of antimicrobial therapy before MRSA/MSSA infection

Antimicrobial class	MRSA (%) (n = 121)	MSSA (%) (n = 123)	OR and 95% CIs	P value
β-Lactam/β-lactamase inhibitor combinations	37.2	16.3	2.3 (1.4, 3.6)	<0.001
Levofloxacin	41.3	5.7	7.3 (3.4, 15.4)	<0.001
Penicillins	6.6	4.1	1.6 (0.54, 4.8)	0.41
Aminoglycosides	19.0	2.4	7.8 (2.4, 25.3)	<0.001
Macrolides	16.5	3.3	5.1 (1.8, 14.4)	<0.001
1st generation cephalosporins	40.5	33.3	1.2 (0.87, 1.7)	0.29
2nd generation cephalosporins	8.3	0.8	10.2(1.3, 78.2)	0.005
3rd generation cephalosporins	6.6	3.3	2.0 (0.63, 6.6)	0.25
Vancomycin	24.8	5.7	4.4 (2.0, 9.5)	<0.001
Metronidazole	11.6	2.4	4.7 (1.4, 16.1)	0.005
Trimethoprim/sulfamethoxazole	10.7	2.4	4.4 (1.3, 15.1)	0.01
Carbapenems	5.8	0.8	7.1 (0.89, 5.7)	0.04
All β-lactam antibiotics	67.8	48.8	1.4 (1.1, 1.7)	0.003

mately the same, and segregating or combining them may have diluted their effect. The third model substituted the number of grammes of drug administered for significant antimicrobial agents to assess for dose–effect relationships. The results of the three models were concordant, with the exception of macrolides, which were not significant based on the number of grammes (Tables 4 and 5).

With regard to outcome, the only significant difference between MRSA-infected and MSSA-infected patients was LOS. The mean LOS for MRSA-infected patients was significantly longer (46.1 ± 38.1 compared with 26.2 ± 20.7, $P < 0.001$) than MSSA-infected patients. MRSA-infected patients had longer LOS before infection (18.8 ± 18.2 versus 8.4 ± 6.9, $P < 0.001$), and longer post-diagnosis LOS (27.8 ± 32.9 versus 18.6 ± 21, $P = 0.01$). There was no difference in the types of infection identified. The most common types of infection were bloodstream infections, 23.1% and 29.3% ($P = 0.31$); lower respiratory tract infections, 21.5% and 20.3% ($P = 0.88$); and pneumonia, 21.5% and 15.4% ($P = 0.25$), for MRSA- and MSSA-infected patients, respectively. Surgical site infections were higher in the MRSA-infected population, 12.4% versus 5.7% ($P = 0.08$), and soft tissue infections were higher in the MSSA-infected population, 14.6% versus 9.1% ($P = 0.24$). Less common infections included urinary tract infections, 5.0% and 4.1% ($P = 0.77$); cardiovascular system infections, 4.1% and 4.9% ($P = 1.0$); infections of the ears, eyes and oral cavity, 1.7% and 2.4% ($P = 1.0$); and infections of the reproductive system, 0.8% and 0.8% ($P = 1.0$), for MRSA- and MSSA-infected patients, respectively. The remaining three infections were gastrointestinal (one), and bone and joint system (two).

Although patients infected with MRSA tended to have a higher crude mortality rate, 28.9% compared with 19.5% ($P = 0.10$), most of these deaths were not related to infection. In a separate analysis, independent risk factors for attributed mortality were bacteraemia with an OR of 4.2 (95% CIs 1.3, 13.5), diabetes OR 3.9 (95% CIs 1.2, 12.0), kidney failure OR 4.9 (95% CIs 1.4, 16.5), steroids OR 3.5 (95% CIs 1.0, 12.1) and haemodynamic instability OR 5.7 (95% CIs 1.8, 18.7). The attributed mortality rate for MRSA-infected patients, 8.3%, was not significantly different from that of the MSSA-infected patients, 5.7% ($P = 0.46$).

Table 4. Multiple logistic regression analysis of factors associated with MRSA infection (models I and II)

Risk factor	OR	95% CIs	P value
Levofloxacin	8.01	3.15, 20.3	<0.001
Macrolides	4.06	1.15, 14.4	0.03
Enteral feeding	2.55	1.37, 4.72	0.003
Surgery	2.24	1.19, 4.22	0.01
Previous hospitalization	1.95	1.02, 3.76	0.04
LOS before culture	1.03	1.0, 1.07	0.05

Table 5. Multiple logistic regression analysis of factors associated with MRSA infection (model III)

Risk factor	OR	95% CIs	P value
Number of grammes of levofloxacin	1.76	1.21, 2.56	0.003
Enteral feeding	2.94	1.62, 5.33	0.004
Surgery	2.01	1.10, 3.68	0.02
Previous hospitalization	2.16	1.15, 4.06	0.03
LOS before culture	1.04	1.01, 1.08	0.02

Discussion

Factors that were independently associated with MRSA infection were previous hospitalization (within the last 12 months), longer LOS before infection, previous surgery, enteral feedings, macrolide use and levofloxacin use. Based on the results of the three models the role of macrolides is debatable. All of the other risk factors were concordant across the three analyses with the most significant risk factors being enteral feedings and levofloxacin use. Previous hospitalization and longer LOS before infection are well known risk factors for antimicrobial resistance.[26–28] These factors may represent chronic illness and previous exposure to antibiotics as well as opportunities to be colonized with resistant organisms. Patients with MRSA infections tended to have more comorbidities but these factors failed to achieve statistical significance in multivariate analysis. Surgery has previously been identified as a risk factor for MRSA infection and may represent a breakdown of the normal host defences, surgical technique or post-operative care.[29] Surgical site infections were 50% more prominent in the MRSA-infected population. Enteral feedings may represent greater severity of illness in the MRSA-infected population or may have served as a portal of entry for MRSA. Contamination of enteral nutrition solutions can occur during the assembly or administration via a contaminated feeding tube. Factors that contribute to the contamination of enteral feedings include the duration of administration, the composition of the enteral solution and the number of manipulations in the feeding process. MRSA-infected patients tended to have received more concurrent dosing of oral levofloxacin and enteral feeds. Previous studies have demonstrated that a significant reduction in fluoroquinolone bioavailability (26–72%) occurs when these drugs are co-administered with enteral feedings.[30–34] Clinically, this may contribute to therapeutic failure but there have been limited studies conducted that directly assess outcome or development of antibiotic resistance as a result of decreased bioavailability. Further studies designed directly to assess this relationship need to be conducted.

Patients who received levofloxacin had the highest risk for MRSA infection with an OR of 8.01. More MRSA-infected patients received macrolides but macrolides did not retain statistical significance based on the total amount of drug administered. In our adult population from 1997 to 1999, 33.9% of the *S. aureus* isolates were resistant to levofloxacin and 44.8% were resistant to macrolides. Antimicrobial use has historically been associated with MRSA and a number of different classes of antibiotics.[12–23,27,28,35–41] Mechanisms of fluoroquinolone resistance in *S. aureus*, DNA gyrase, IV topoisomerase and *NorA*-mediated efflux and macrolide resistance *ermA* and *ermC* genes are well documented.[40,42,43] In addition to the molecular studies, several clinical studies have shown an association with fluoroquinolone use and *S. aureus* resistance.[44,45] Isaacs *et al*.[44] postulated that the factors which predispose *S. aureus* to develop methicillin resistance may also predispose them to ciprofloxacin resistance. In their study, they identified an increase in ciprofloxacin resistance in isolates after using ciprofloxacin to treat MRSA infections. Although there are no known biological mechanisms for fluoroquinolones to select resistance to β-lactam antibiotics in staphylococci, evidence is mounting that fluoroquinolones exhibit some type of influence on MRSA. Ciprofloxacin resistance in MRSA developed rapidly whereas the rate of ciprofloxacin resistance in MSSA nationwide is *c.* 2.4%. These data indicate that there are intrinsic factors which lead to greater acquisition of fluoroquinolone resistance in MRSA.[46] Hetero-resistant *S. aureus* populations include sub-populations that contain the *mecA* gene and these resistant sub-populations can be selected for by exposure to increasing concentrations of antibiotics below MIC levels.[16] It was demonstrated that *mecA*-positive *S. aureus* strains which exhibit this hetero-resistance showed an increase in the proportion of oxacillin-resistant cells following exposure to fluoroquinolones.[47]

In summary, patients infected with MRSA were more likely to have had surgery, a previous hospitalization and a longer LOS before infections. All of these factors are known to increase the probability of a patient developing an MRSA infection. The two risk factors that contributed the greatest risk for developing an MRSA infection were enteral feedings and levofloxacin as shown by their ORs and highly significant *P* values. Whether these two risk factors have an associated effect is unknown and beyond the scope of this analysis. Further investigation is warranted because this could lead to a modifiable practice change. The relationships between antimicrobial use and MRSA are complex and more studies that address these issues are needed. However, most studies agree that, in addition to good infection control practices, the prudent use of antimicrobial agents is one of the major steps to reducing the growing problem of antibiotic resistance.

References

1. Wenzel, R. P., Nettleman, M. D., Jones, R. N. & Pfaller, M. A. (1991). Methicillin-resistant *Staphylococcus aureus*: implications for the 1990s and effective control measures. *American Journal of Medicine* **91**, 221S–7S.

2. Witte, W. (1999). Antibiotic resistance in Gram positive bacteria: epidemiological aspects. *Journal of Antimicrobial Chemotherapy* **44**, 1–9.

3. Cunha, B. A. (1998). Antibiotic resistance. Control strategies. *Critical Care Clinics* **14**, 309–27.

4. Panlilio, A. L., Culver, D. H., Gaynes, R. P., Banerjee, S., Henderson, T., Tolson, J. *et al.* (1992). Methicillin-resistant *Staphylococcus aureus* in U. S. hospitals, 1975–1991. *Infection Control and Hospital Epidemiology* **13**, 582–6.

5. Archibald, L., Phillips, L., Monnet, D., McGowan, J. E., Tenover, F. & Gaynes, R. (1997). Antimicrobial resistance in isolates from inpatients and outpatients in the United States: increasing importance of the intensive care unit. *Clinical Infectious Diseases* **24**, 211–5.

6. Bartlett, M., McIntyre, L., Moseley, R., O'Connor, J., Shaw, J. & Whitehead, C. (2000). Methicillin-resistant *S. aureus* rates increase 260% in hospitals participating in HIP's international monitoring systems. *Centers for Disease Control and National Center for Infectious Diseases Focus* **9**, 4.

7. Akram, J. & Glatt, A. E. (1998). True community-acquired methicillin-resistant *Staphylococcus aureus* bacteremia. *Infection Control and Hospital Epidemiology* **19**, 106–7.

8. Centers For Disease Control. (1999). Four pediatric deaths from community-acquired methicillin-resistant *Staphylococcus aureus*—Minnesota and North Dakota, 1997–1999. *Morbidity and Mortality Weekly Report* **48**, 707–10.

9. Goetz, A., Posey, K., Fleming, J., Jacobs, S., Boody, L., Wagener, M. *et al*. (1999). Methicillin-resistant *Staphylococcus aureus* in the community: a hospital-based study. *Infection Control and Hospital Epidemiology* **20**, 689–91.

10. Kallen, A., Driscoll, T., Thorton, S., Olson, P. & Wallace, M. (2000). Increase in community-acquired methicillin-resistant staphylococcus at a naval medical center. *Infection Control and Hospital Epidemiology* **21**, 223–6.

11. Kak, V. & Levine, D. P. (1999). Editorial response: community-acquired methicillin *Staphylococcus aureus* infections—where do we go from here? *Clinical Infectious Diseases* **29**, 801–2.

12. Ayliffe, G. A. J. (1996). *Recommendations for the Control of Methicillin-Resistant Staphylococcus aureus (MRSA)*. Division of Emerging and other Communicable Diseases Surveillance and Control, World Health Organisation, Geneva, Switzerland.

13. Herwaldt, L. A. (1999). Control of methicillin-resistant *Staphylococcus aureus* in the hospital setting. *American Journal of Medicine* **106**, 11s–8s.

14. Monnet, D. (1998). Methicillin-resistant *Staphylococcus aureus* and its relationship to antimicrobial use: possible implications for control. *Infection Control and Hospital Epidemiology* **19**, 552–9.

15. Rice, L. (1999). Editorial response: a silver bullet for colonization and infection with methicillin-resistant *Staphylococcus aureus* still eludes us. *Clinical Infectious Diseases* **28**, 1067–70.

16. Schentag, J. J., Hyatt, J. M., Carr, J. R., Paladino, J. A., Birmingham, M. C., Zimmer, G. S. *et al.* (1998). Genesis of methicillin-resistant *Staphylococcus aureus* (MRSA). How treatment of MRSA infections has selected for vancomycin resistant *Enterococcus faecium* and the importance of antibiotic management and infection control. *Clinical Infectious Diseases* **26**, 1204–14.

17. Monnet, D. & Frimodt-Moller, N. (2001). Antimicrobial-drug use and methicillin-resistant *Staphylococcus aureus*. *Emerging Infectious Diseases* **7**, 1–3.

18. Hill, D. A., Herford, T. & Parratt, D. (1998). Antibiotic usage and methicillin-resistant *Staphylococcus aureus* and analysis of causality. *Journal of Antimicrobial Chemotherapy* **42**, 676–7.

19. Crowcroft, N. S., Ronveaux, O, Monnet, D. L. & Mertens, R. (1999). Methicillin-resistant *Staphylococcus aureus* and antimicrobial use in Belgian hospitals. *Infection Control and Hospital Epidemiology* **20**, 31–6.

20. Dziekan, G., Hahn, A., Thune, K., Schwarzer, G., Schafer, K., Daschner, F. D. *et al*. (2000). Methicillin-resistant *Staphylococcus aureus* in a teaching hospital: investigation of nosocomial transmission using a matched case-control study. *Journal of Hospital Infection* **46**, 263–70.

21. Crossley, K., Loesch, D., Landesman, B., Mead, K., Chern, M. & Strate, R. (1979). An outbreak of infections caused by strains of *Staphylococcus aureus* resistant to methicillin and aminoglycosides I: clinical studies. *Journal of Infectious Diseases* **139**, 273–9.

22. Hershow, R. C., Khayr, W. F. & Smith, N. L. (1992). A comparison of clinical virulence of nosocomially acquired methicillin resistant and methicillin-sensitive *Staphylococcus aureus* infections in a university hospital. *Infection Control and Hospital Epidemiology* **13**, 587–93.

23. Fu-Yu, C., Muddoloro, M. & Alcid, D. (2000). Levofloxacin associated increase in methicillin-resistant *Staphylococcus aureus* infections. In *Program and Abstracts of the Thirty-eighth Annual Meeting of the Infectious Diseases Society of America, New Orleans, LA, 2000.* Abstract 163, p. 241. Infectious Diseases Society of America, New Orleans, LA.

24. Garner, J. S., Jarvis, W. R., Emori, T. G., Horan, T. C. & Hughes, J. M. (1988). CDC definitions for nosocomial infections. *American Journal of Infection Control* **16**, 128–40.

25. National Committee for Clinical Laboratory Standards. (1988). *Performance Standards for Antimicrobial Susceptibility Testing; Ninth Informational Supplement: Document M100-S9*. NCCLS, Wayne, PA.

26. Asensio, A., Guerrero, A., Quereda, C., Lizan, M. & Martinez-Ferrer, M. (1996). Colonization and infection with methicillin-resistant *Staphylococcus aureus*: associated factors and eradication. *Infection Control and Hospital Epidemiology* **17**, 20–8.

27. Boyce, J. M., Landry, M., Deetz, T. R. & Dupont, H. L. (1981). Epidemiologic studies of an outbreak of nosocomial methicillin-resistant *Staphylococcus aureus* infections. *Infection Control* **2**, 110–6.

28. Ayliffe, G. A. J. (1997). The progressive intercontinental spread of methicillin-resistant *Staphylococcus aureus*. *Clinical Infectious Diseases* **24**, S74–9.

29. Barie, P. S. (1998). Antibiotic resistant gram positive cocci: implications for surgical practice. *World Journal of Surgery* **22**, 118–26.

30. Mueller, B. A., Brierton, D. G., Abel, S. R. & Bowman, L. (1994). Effect of enteral feeding with ensure on oral bioavailabilities of ofloxacin and ciprofloxacin. *Antimicrobial Agents and Chemotherapy* **38**, 2101–5.

31. Wright, D. H., Pietz, S. L., Konstantinides, F. N. & Rotschafer, J. C. (2000). Decreased *in vitro* fluoroquinolone concentrations after admixture with an enteral feeding formulation. *Journal of Parenteral and Enteral Nutrition* **24**, 42–8.

32. Healy, D. P., Brodbeck, M. C. & Clendening, C. E. (1996). Ciprofloxacin absorption is impaired in patients given enteral feedings orally and via gastrostomy and jejunostomy tubes. *Antimicrobial Agents and Chemotherapy* **40**, 6–10.

33. Mimoz, O., Binter, V., Jacolot, A., Edouard, A., Tod, M., Petitjean, O. *et al*. (1998). Pharmacokinetics and absolute bioavailability of ciprofloxacin administered through a nasogastric tube with

continuous enteral feeding to critically ill patients. *Intensive Care Medicine* **24**, 1047–51.

34. Vincent, J., Teng, R., Pelletier, S. M., Willavize, S. A. & Friedman, H. L. (1998). The bioavailability of nasogastric versus tablet form oral trovofloxacin in healthy subjects. *American Journal of Surgery* **176**, 23S–6S.

35. Fagon, J. Y., Maillet, J. M. & Novara, A. (1998). Hospital acquired pneumonia: methicillin resistance and intensive care unit admission. *American Journal of Medicine* **104**, 17S–23S.

36. Pujol, M., Pena, C., Pallares, R., Ayats, J., Ariza, J. & Gudio, F. (1994). Risk factors for nosocomial bacteremia due to methicillin resistant *Staphylococcus aureus*. *European Journal of Clinical Microbiology and Infectious Diseases* **13**, 96–102.

37. Witte, W., Braulke, C., Heuck, D. & Cuny, C. (1994). Analysis of nosocomial outbreaks with multiply and methicillin-resistant *Staphylococcus aureus* (MRSA) in Germany: implications for hospital hygiene. *Infection* **22**, S128–34.

38. Rosdahl, V. T. & Knudsen, A. M. (1991). The decline of methicillin resistance among Danish *Staphylococcus aureus* strains. *Infection Control and Hospital Epidemiology* **12**, 83–8.

39. Law, M. R. & Gill, O. N. (1988). Hospital-acquired infection with methicillin-resistant and methicillin-sensitive staphylococci. *Epidemiology and Infection* **101**, 623–9.

40. Acar, J. F. & Goldstein, F. W. (1997). Trends in bacterial resistance to fluoroquinolones. *Clinical Infectious Diseases* **24**, S67–73.

41. Landman, D., Chockalingam, M. & Quale, J. (1999). Reduction in the incidence of methicillin-resistant *Staphylococcus aureus* and ceftazidime-resistant *Klebsiella pneumoniae* following changes in a hospital antibiotic formulary. *Clinical Infectious Diseases* **28**, 1062–6.

42. Kaatz, G. W. & Seo, S. M. (1997). Mechanisms of fluoroquinolone resistance in genetically related strains of *Staphylococcus aureus. Antimicrobial Agents and Chemotherapy* **41**, 2733–7.

43. Ng, E. Y., Trucksis, M. & Hooper, D. C. (1994). Quinolone resistance mediated by nor A: physiologic characterization and relationship to flqB, a quinolone resistance locus on the *Staphylococcus aureus* chromosome. *Antimicrobial Agents and Chemotherapy* **38**, 1345–55.

44. Isaacs, R. D., Kunke, P. J., Cohen, R. L. & Smith, J. W. (1988). Ciprofloxacin resistance in epidemic methicillin-resistant *Staphylococcus aureus*. *Lancet* **ii**, 843.

45. Manhold, C., von Rolbicki, U., Brase, R., Timm, J., von Pritzbuer, E., Heimesaat, M. *et al*. (1998). Outbreaks of *Staphylococcus aureus* infections during treatment of late onset pneumonia with ciprofloxacin in a prospective, randomized study. *Intensive Care Medicine* **24**, 1327–30.

46. Gottlieb, T. & Mitchell, D. (1998). The independent evolution of resistance to ciprofloxacin, rifampin, and fusidic acid in methicillin-resistant *Staphylococcus aureus* in Australian teaching hospitals (1990–1995). *Journal of Antimicrobial Chemotherapy* **42**, 67–73.

47. Venezia, R. A., Damaracki, B. E., Evans, A. M., Preston, K. E. & Graffunder, E. M. (2001). Selection of high-level oxacillin resistance in heteroresistant *Staphylococcus aureus* by fluoroquinolone exposure. *Journal of Antimicrobial Chemotherapy* **48**, 375–81.