Decrease of methicillin resistant *Staphylococcus aureus* prevalence after introduction of a surgical antibiotic prophylaxis protocol in an Italian hospital

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SUMMARY

The use of antimicrobials is an important factor contributing to the emergence of antibiotic resistance. The goal of our study was to evaluate the impact of the introduction of an antibiotic surgical prophylaxis protocol on the prevalence of methicillin resistant *Staphylococcus aureus* (MRSA) infections in a tertiary care hospital.

The protocol of surgical antibiotic prophylaxis was designed by a multidisciplinary team and was implemented in December 2001. Between January 2002 and December 2002, pharmacy, laboratory and active surveillance-records were prospectively reviewed to calculate prevalence rates of defined daily doses (DDD), microorganism isolation and health-care related infections.

A progressive decrease from 1.58 to 0.56 of MRSA isolations per 1000 patient-days and from 76.4% to 29.4% MRSA prevalence rate was reported ($p<0.001$). Monthly prevalence rates of MRSA showed a significant linear correlation with the reduction of the DDD of the 3rd generation cephalosporins ($r=0.90$; $p<0.001$). MRSA surgical site and blood stream infections decreased from 78% to 38% and from 89% to 38%, respectively ($p=0.017$ and $p=0.026$).

In our experience, the reduction of 3rd generation cephalosporin use was an effective strategy to reduce the MRSA infection rate and was associated with the reduction of the overall expenditure for antibiotics in the hospital.

KEY WORDS: Antibiotic surgical prophylaxis, MRSA incidence, Cephalosporins, Hospital infection control policy, Antibiotic policy

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INTRODUCTION

Methicillin resistant *Staphylococcus aureus* (MRSA) was first described in 1961, and since then it has become a worldwide problem (Jevons, 1961; Diekema *et al.*, 2004). MRSA is currently the most commonly identified antibiotic-resistant pathogen in US hospitals, and contributes significantly to morbidity and mortality in addition to pronounced healthcare costs (Diekema *et al.*, 2004). Recent evidence showed that MRSA surgical site infections (SSIs) are associated with higher mortality, greater length of stay, and greater costs than methicillin sensitive *S. aureus* (MSSA) infections (Engemann *et al.,* 2005). Several studies observed that the indiscriminate use of antimicrobial drugs has been identified as an important factor contributing to the increasing dissemination of MRSA and that antibiotics used for surgical prophy-

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laxis represent a substantial proportion of the overall antibiotics used in the hospital setting (Bantar *et al.*, 2003; Bantar *et al.*, 2004; Fridkin *et al.*, 2001; Fridkin *et al.*, 2002). The aim of our study was to evaluate the effect of the introduction of an antibiotic surgical prophylaxis (ASP) on the prevalence of MRSA infections at our hospital.

METHODS

This prospective observational study was carried out between January 2002 and December 2002 at San Filippo Neri Hospital, a non-teaching 700-bed hospital placed in the northern urban area of Rome, Italy. In 2002, 37% of all hospital admissions involved surgical patients. In 2001 the local Infection Control Committee (ICC) created a multidisciplinary team that included infection control nurses (ICN), infectious disease specialists, medical microbiologists, clinical pharmacists, surgeons and anaesthesiologists, in order to develop a protocol of ASP in clean and clean-contaminated surgical procedures and to control costs and improve appropriate antimicrobial usage. The Centers for Disease Control and Prevention (CDC) recommendations for ASP, including choice of antimicrobial for perioperative prophylaxis, timing, and duration of antimicrobial prophylaxis were used (Mangram *et al.*, 1999). The protocol was implemented in December 2001 after a two-hour training program conducted in each surgical site followed by a one-day meeting session with academic presentation and discussion. Antibiotic drugs costs were measured in Euros and antibiotic usage was evaluated using defined daily doses (DDDs), which is the international measure of a drug for an adult patient. Indeed, in our study, we defined the consumption of drugs as DDD/100 patients-days (WHO Collaborating Centre for Drug Statistics Methodology, 2002). At the beginning of the study, active surveillance of nosocomial blood stream infections (BSI), ventilator acquired pneumonia (VAP), and SSI was implemented in Intensive Care Units (ICUs) according to CDC criteria and was carried out by four ICNs on a daily basis (Garner *et al.*, 1996). No screening policy for detecting colonization was ongoing. In the microbiology laboratory *Staphylococci* are currently identified using Vitek 2™, and Staphytect™ coagulase test. Oxacillin resistance is tested by Vitek 2 (Biomerieux, Cards, France; NCCLS, 1999) and confirmed, if needed, with detection of PBP2a (Denka Seiken, Japan). Within the microbiology Laboratory Information System software (Italab c/s®, DNGroup, Italy) microbial isolates are labelled as 'clinically relevant' or 'clinically not relevant' isolates. The statistical analysis is performed only on clinically relevant records. Duplicates, with the same patient identification data and the same susceptibility biotype, within a 15-day interval, are excluded. The rates of MRSA infections per 1000 patient days were obtained combining the microbiological data with the number of admitted patients and the hospital stay. MRSA and MSSA prevalence rates and the prevalence of the health-care related infections were compared by ANOVA and X^2 tests. Linear regression analysis was used to determine the correlation between MRSA prevalence rate and antibiotic DDD per 100 patients per day. SPSS for Windows (Version 10.1.3, SPSS Inc 1989-2000) was used.

RESULTS

During the 12-month observational period, 2799 clinically relevant microorganisms were isolated from in-patients. Of them, 294 (10.5%) *Staphylococcus aureus* were considered infectious agents with a 62% overall MRSA prevalence rate. The distribution of clinically relevant MRSA-associated infections during the 12 months follow-up period is shown in Figure 1. The MRSA prevalence was higher in the blood cultures (73%), followed by the respiratory tract specimens (68%) and the surgical sites (59%). Table 1 shows the pattern of prescription of different classes of antibiotic drugs: during all four 2002 quarters, the DDD reduction of the 3rd generation cephalosporins was associated with a 63.9% decrease in antibiotic expenditure resulting in a saving of more than 40,000 euros. Similarly, a sustained reduction in both vancomycin DDD and vancomycin-related direct expenditure by about 30% was recorded throughout the study period. No major changes in quinolone and carbapenem DDD were reported. Figure 2 shows the relationship between 3rd generation cephalosporin use and MRSA isolation during the 12-month study period. A sustained reduction in

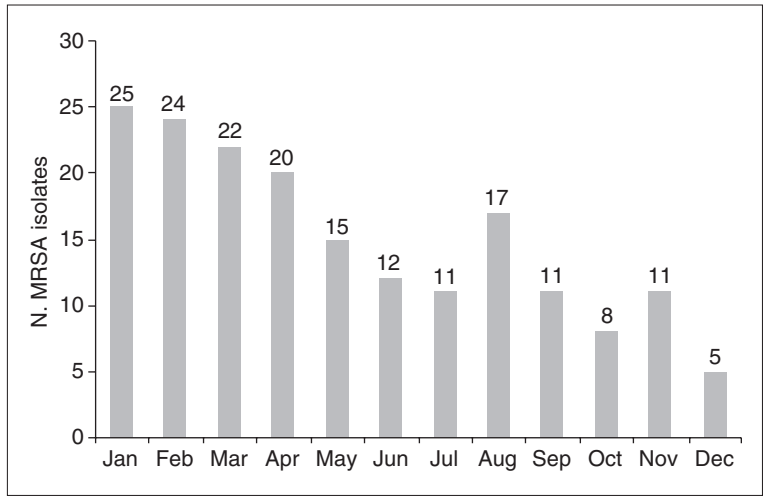

FIGURE 1 - *Distribution of clinically relevant MRSA isolates during the 12 month follow-up period.*

TABLE 1 - *Change in the defined daily doses and in the relative costs in euro (€) of the main antibiotic drugs during the 12 months follow-up period.*

	3rd generation cephalosporins		*Ciprofloxacin*		*Imipenem*		*Vancomycin*	
	DDD	*€*	*DDD*	*€*	*DDD*	*€*	*DDD*	*€*
1st quarter[1]	2183	69776	531	3186	324	14645	803	12848
2nd quarter[2]	1467	45024	463	2778	209	9447	757	12112
3rd quarter[3]	1390	45227	492	2952	278	12566	621	9936
4th quarter[4]	871	26735	494	2964	248	11210	560	8960

[1]January-February-March; [2]April-May-June; [3]July-August-September; [4]October-Novenber-December.

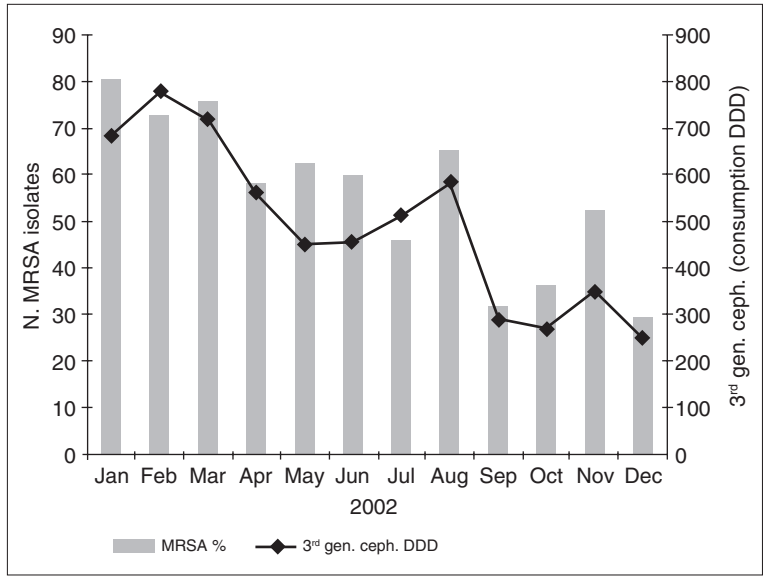

FIGURE 2 - *Prevalence of clinically relevant MRSA isolates and 3rd cephalosporin defined daily doses during the 12 month follow-up period.*

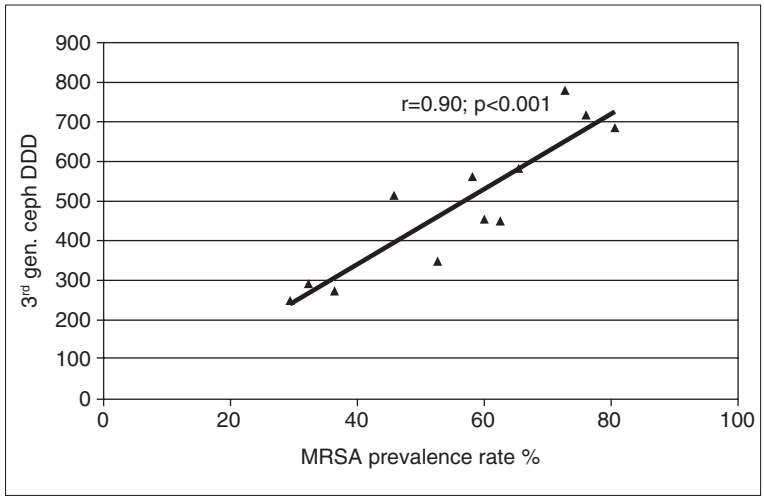

FIGURE 3 - *Linear correlation between the monthly MRSA prevalence rate and the 3rd cephalosporin defined daily doses during the 12 month follow-up period.*

the use of the 3rd generation cephalosporins, from 4.85 DDD per 100 patients per day in the 2002 first quarter to 2.03 DDD per 100 patients per day in the 2002 last quarter was observed (p<0.001). A progressive decrease from 1.58 to 0.56 of MRSA isolations per 1000 patient-days and from 76.4% to 29.4% MRSA prevalence rate was reported (Figure 3) (p<0.001 for both analyses). The MRSA monthly prevalence rates showed a significant linear correlation with a reduction of crude DDD use of the 3rd generation cephalosporins (r = 0.90; p<0.001) (Figure 3). A similar result was obtained using patient data aggregated on a quarterly basis: 3rd generation cephalosporin consumption in DDD per 100 patient-days versus clinically relevant MRSA isolates per 1000 patient-days. (Figures 4 and 5) (r =0.98; p=0.011). Moreover, a significant reduction of the isolation of MRSA from SSI and BSI was reported. In particular, a significant decrease in MRSA prevalence among *Staphylococcus aureus*-associated SSI was observed (78% versus 38%, p=0.017). Similar significant reduction of MRSA prevalence was reported both in *Staphylococcus aureus*-associated BSI (89% versus 38%, p=0.026) and in the respiratory specimens of patients affected by VAP in ICUs (from 67 to 33%, p=0.024). No difference in the prevalence of carbapenem-resistant *Pseudomonas* spp., Extended Spectrum β-Lactamase producing *Enterobacteriaceae*, and vancomycin resistant *Enterococcus* was reported

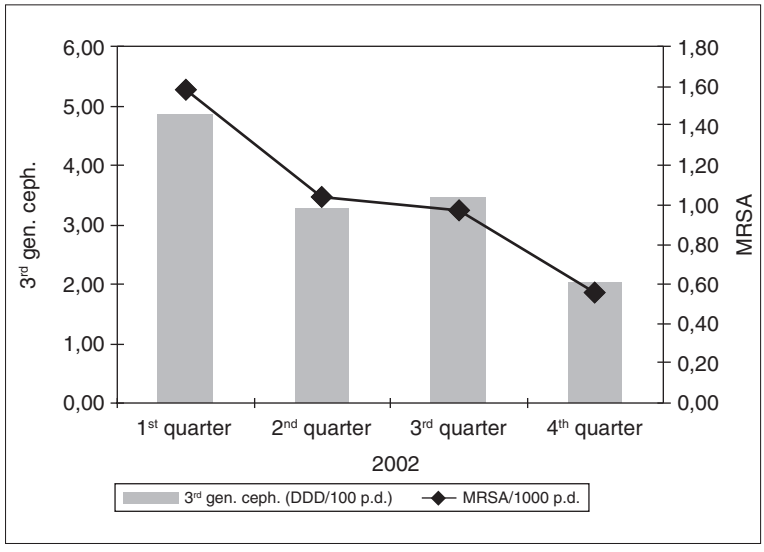

FIGURE 4 - *Clinically relevant MRSA prevalence rate over 1000 patient days and 3rd generation cephalosporin consumption aggregated over quarterly periods.*

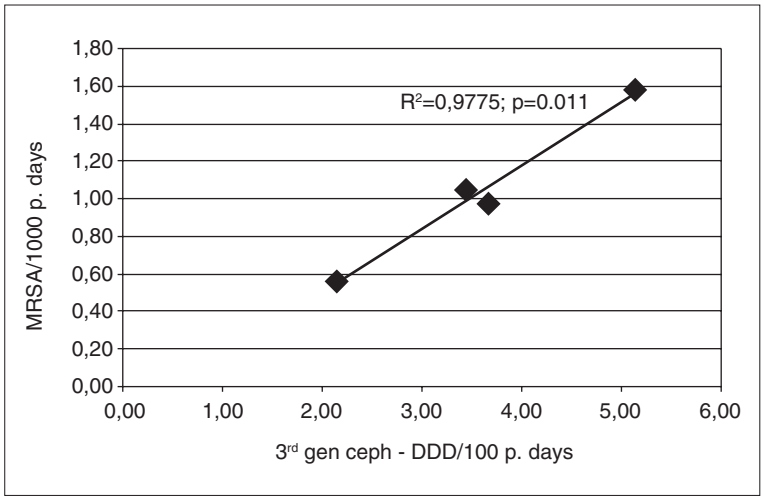

FIGURE 5 - *Linear correlation between MRSA prevalence rate and 3rd generation cephalosporin consumption aggregated over quarterly periods.*

over the study period. A clinical audit was performed 12 months after the introduction of the ASP protocol, and showed a ≥90% adherence of the physicians to the use of ASP, the choice of the antimicrobial, the correct timing and the length of prophylaxis. Furthermore, no substantial difference in the case-mix of our population was reported over the study period either in critical or non-critical areas.

DISCUSSION

The widespread use of perioperative antimicrobial prophylaxis makes surgical procedures an important component of overall antibiotic use. Attempts to reduce costs and to limit the emergence of resistance among pathogenic bacteria by altering antibiotic use must therefore encompass ASP (Smith, 2000). During a recent survey conducted on 2,165 patients admitted tp 15 Italian hospitals, 58.7% of 985 inpatients given a antimicrobial agent did not have either community or health care-related infections. Of these, 22.0% received antibiotics as surgical prophylaxis, while the remaining 19.3% received antibiotics for other prophylactic or pre-emptive prescriptions (Nicastri *et al.*, 2003). Many different strategies have proposed to optimise antimicrobial agent use as national and international guidelines (Bratzler *et al.,* 2006). The present study disclosed that a multidisciplinary program to optimize the antibiotic policy in ASP in an Italian 700-bed hospital was associated with a reduction of 3rd generation cephalosporin and vancomyicin use and of the global expenditures for antibiotics in the hospital. Several reports observed the effect of formulary restriction in the use of antibiotics in hospital settings (Bassetti *et al.,* 2001). In our study, we observed that a reduction of 3rd generation cephalosporin use was associated with a reduction of MRSA isolation and of other nosocomial infections such as SSI, VAP, and BSI caused by MRSA. Several studies suggest a direct relationship between increased antimicrobial use and antimicrobial resistance, thus prompting the introduction of programs to prevent and control the spread of antimicrobial resistance in hospitals (Barie *et al.* 2005; Gomez *et al.,* 2006; Weinstein, 2001). When antimicrobial classes are taken into account separately, cephalosporins and fluoroquinolones are often identified as risk factors for MRSA (Monnet *et al.,* 2001). The steady increase in MRSA in Europe, including Italy, and in the USA has also been attributed to the use of cephalosporins (Ayliffe, 1997). The consequence of cephalosporin prophylaxis is illustrated by two clinical studies of surgical patients, the first of which showed that methicillin resistance was detected in high numbers on the skin of surgical patients within 5 days of exposure to per-operatively administered cephalosporins (Kernodle *et al.*, 1988). The second showed that just three doses of cefuroxime encouraged the appearance of MRSE from aortic graft recipients within 1 week (Mannion *et al.*, 1989). Subsequently, Fukatsu *et al.* observed that in the period in which 3rd generation cephalosporins were frequently adminis-

tered for prophylaxis, the MRSA isolation rates from infected sites increased. Otherwise, along with a marked decrease in 3rd generation cephalosporins, the MRSA rates sharply declined (Fukatsu *et al.,* 1997). Our study has some limitations. First, factors other than the introduction of ASP could have contributed to reducing MRSA infection rates, such as active surveillance in critical areas, modification of human behaviour and improvement of performance standards. We are aware that a modification of improper practices, including changes in hand hygiene, barrier measures, and aseptic procedures as effect of a surveillance campaign (Hawthorne effect) could have had a role in reducing also infection rates. However, this is a limitation of all studies that take into consideration the impact of surveillance systems in healthcare facilities. Second, we determined MRSA-isolation rate, and this could substantially differ from the true MRSA-infection rate. However, our laboratory surveillance system reported an overall reduction of the MRSA-isolation rate in all surgical, medical and critical areas. Particularly, in critical areas, the current active surveillance system confirmed the reduction of the microbiologically-confirmed MRSA infections. So, we are confident that MRSA-isolation rates from critical areas are similar to the true infection rates. Consequently, also in non-critical areas, we adopted the MRSA isolation rate obtained by our Laboratory Information System. Finally, we are aware that our experience derives from a study conducted in a single Italian centre and our conclusions cannot be generalized to all Italian hospitals. Nevertheless, most Italian hospitals lack clinically oriented protocols in surgical prophylaxis and the reliable results obtained after the introduction of a multidisciplinary team could be useful to other clinical settings for performing a correct in-hospital antibiotic policy (Nicastri *et al.*, 2003). In conclusion, in our hospital, the reduced prescription of 3rd generation cephalosporins was associated with a reduction in the prevalence rate of MRSA health-care related infections. It was a reliable result in term of cost-efficacy and represented a substantial improvement in the hospital quality of care.

Conflict of interest

The authors declare that they have no competing interests.

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