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Major Article

Surgical antimicrobial prophylaxis prescribing practices and impact on infection risk: Results from a multicenter surveillance study in Italy (2012-2017)

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Key Words:
Surgical site infections
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Background: Italy is one of the largest consumers of broad-spectrum agents (BSAs) in Europe. This study evaluated surgical antimicrobial prophylaxis (SAP) compliance with the Italian national guidelines and its impact on surgical site infection (SSI) risk.

Methods: A prospective study was conducted in 42 hospitals participating in the national surveillance system for SSIs. SAP compliance was evaluated considering antibiotic choice, duration of administration, and timing of first dose. Trends in the consumption of 5 BSAs were also evaluated.

Results: Between 2012 and 2017, 24,861 surgical procedures were monitored. The risk ratios (RRs) for appropriate SAP increased by 22% each year, and significant increasing trends over time were found for overall compliance, timing, and duration. Adequate antibiotic choice and duration of administration were associated with a significantly reduced SSI risk (RR = 0.57; 95% confidence interval [CI], 0.5-0.65 vs RR = 0.51; 95% CI, 0.45-0.57, respectively), and overall compliance was associated with a RR of 0.65 (95% CI, 0.59-0.72).

Conclusions: These findings suggest that appropriate narrow-spectrum agents could be more effective than BSAs in preventing SSIs. Interventions to improve SAP compliance with guidelines could significantly contribute to reducing antimicrobial resistance by reducing SSIs and promoting more prudent use of antimicrobials.

BACKGROUND

Surgical site infections (SSIs) significantly increase morbidity, mortality, and health care costs and are considered to be among the most preventable health care–associated infections (HCAIs).[1] Appropriate preventive strategies, such as surgical antimicrobial prophylaxis (SAP), have proven to substantially reduce their risk,[2] as up to 50% of SSIs may be preventable by administering SAP according to evidence-based guidelines.[3] In Italy, national SAP guidelines have been available since 2003 and were updated in 2011.[4]

However, the inappropriate over-administration of SAP and the indiscriminate use of broad-spectrum agents (BSAs) increases the risk of adverse reactions and promotes the emergence of resistant bacteria.[2] Italy is one of the European countries with the highest rates of antimicrobial-resistant pathogens such as methicillin-resistant *Staphylococcus aureus*, carbapenem-resistant *Klebsiella pneumoniae*, Enterobacteriaceae, and *Acinetobacter baumannii*, the last 2 having reached hyperendemic levels.[5] A recent review[6] estimated that, in 2015, about a third of deaths attributable to antimicrobial-resistant infections in Europe occurred in Italy. To address this major public health threat, the Italian Ministry of Health issued the 2017-2020 National Action Plan to fight antimicrobial resistance[7] and defined targets for the reduction of HCAIs and antimicrobial consumption.

SAP contributes significantly to antibiotic consumption. According to the most recent European Centre for Disease Prevention and Control (ECDC) point prevalence survey performed in Italy,[8] SAP accounts for 17.4% of all antibiotics prescribed in acute care hospitals. The optimization of prophylactic prescribing practices has long been considered crucial in the global attempt to prevent antimicrobial

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resistance.[9] Previous studies have estimated that compliance with SAP guidelines in Italy ranges from 20% to 84.5%.[10,11] It has been suggested that Italian surgeons do not routinely follow recommendations and excessively and inappropriately administer antibiotics for the prevention of SSIs,[10] often choosing antibiotics for prophylaxis that the national guidelines reserve for the treatment of multiresistant infections, such as third- and fourth-generation cephalosporins, carbapenems, and combinations of penicillin and β-lactamase inhibitors.[11] Italy is one of the largest consumers of BSAs in Europe, ranking second with regard to the proportion of BSAs among all antibiotics for systemic use in acute care hospitals[12] and first for the overall consumption of penicillin–β-lactamase inhibitor combinations.[5]

For the current study, SAP data collected through the Italian surveillance system for SSIs (Sistema Nazionale Sorveglianza Infezioni del Sito Chirurgico [SNICh]) between 2012 and 2017 were evaluated to assess (1) prescribing practices and SAP compliance with the Italian national guidelines, and (2) the association between SAP compliance and SSI risk.

METHODS

A prospective study was conducted in 42 hospitals in the northwest of Italy participating in SNICh. Participation in the network is voluntary, surveillance is conducted for a minimum of 3 months each year, and continuous surveillance is encouraged. The national protocol[13] is based on the ECDC HAISSI network protocol[14] and applies the same definitions for SSIs. Patients undergoing included procedures are identified at admission. Infection control staff collect demographic and clinical data, including the following information regarding SAP: SAP administration, chosen antibiotic agent(s), beginning and end dates, and timing of first dose within 120 minutes prior to the surgical incision. Patients are monitored for 30 days after the operation or for 1 year for surgeries involving the implant of prosthetic material. Post-discharge surveillance is performed through postoperative visits in the same hospital or through a standardized telephone interview.

Compliance with ethical standards

As stated in the SNICh protocol,[13] considering that the aims of the program are surveillance of diseases and improvement of health care quality and that the program is coordinated by public entities (National Centre for Disease Prevention and Control, Ministry of Health, Regions of Emilia-Romagna and Piedmont), the written consent of patients involved in surveillance or any other authorization from the Ethics Committee and/or the Protection Commissioner is not required. All involved patients are provided with an information sheet to notify them of their participation in the surveillance program, and all collected data are anonymized.

Included procedures

For the current study, SAP and SSI data from elective procedures performed between January 1, 2012, and December 31, 2017, were analyzed. According to the national guidelines, SAP is recommended for clean and clean-contaminated procedures. Contaminated or dirty/infected procedures were excluded from the analysis, as it was possible that antibiotics were administrated as therapy rather than prophylaxis. Although procedures monitored through SNICh are classified into National Healthcare Safety Network (NHSN) operative procedure categories according to ICD-9-CM codes,[15] for the current study procedures involving a common anatomic site or surgical discipline were combined when the national guideline indications for SAP were aligned. The included procedures were hip and knee arthroplasty, colorectal surgery, cranial and spinal surgery (excluding procedures with endonasal, paranasal, or oropharyngeal access), cardiovascular and thoracic surgery (excluding pacemaker and defibrillator insertion), laparoscopic cholecystectomy, and prostate surgery.

Compliance assessment

SAP compliance with the national guidelines was evaluated considering the following key components of SAP: antibiotic choice, duration of administration, and timing of first dose.[16] For each procedure, all 3 parameters were evaluated separately, and SAP was considered entirely adherent to the guidelines if all 3 were concordant and no information was missing. If data on one or more of the parameters were missing, then the procedure could not be evaluated for overall SAP compliance.

The choice of antibiotic was considered adequate if it was concordant with the national guidelines[4] or narrow spectrum and active against the most likely pathogens. BSAs were considered inadequate if they were not specifically recommended by the guidelines. An infectious disease specialist was consulted to determine whether agents should be considered adequate or inadequate for each procedure category. The criteria for evaluation of agent adherence are summarized in Supplementary Table S1. Timing was considered compliant if the first dose was administered within 120 minutes prior to incision. If SAP was discontinued within 24 hours (or 48 hours for cardiovascular and thoracic surgery), duration was considered compliant. Also evaluated for each surgical category was the use of 5 BSAs included in the “watch” and “reserve” groups of antimicrobial agents on the World Health Organization Model List of Essential Medicines[17] (third- and fourth-generation cephalosporins, glycopeptides, carbapenems, quinolones, and piperacillin/tazobactam).

Statistical analysis

Data analysis was performed by a custom computational pipeline designed on top of the R framework.[18] The association between SAP compliance and SSI risk was expressed as a risk ratio (RR) with a 95% confidence interval (CI) and *P* value. To evaluate the impact of confounding factors on SSI risk, a multigroup analysis was performed. The following independent risk factors for SSI[19] were included: age, sex, infection risk index (IRI), and preoperative hospital stay. The IRI was calculated following NHSN methodology and according to procedure duration, American Society of Anesthesiologists physical status score, and wound contamination class.[15] SSI risk was evaluated by stratifying patients in different risk groups for each factor: age (<65 years, 65-80 years, or >80 years), sex (female or male), IRI (0-1 or 2-3), and preoperative stay (<2 days, 2-4 days, or >4 days). The same independent variables were included in a multivariable logistic regression model, and results were expressed as odds ratios (ORs).

The risk analysis was performed with epiR[20] and meta[21] packages to compute ORs and RRs, incidental risks, and 95% CIs. The pipeline also computed values for Fisher exact tests for count data for each confusion matrix and returned *P* values to better assess the overall robustness of further computations. Fisher test enforcement guarantees stricter constraints and more reliable results.

For the trend analysis, the pipeline automatically computed 2 timelines that contained the absolute and relative (yearly averaged) counts of observed occurrences for each observed variable or stratification of interest. A linear regression model was then fitted against both timelines, and the resulting linear models were compared against the Mann-Kendall test to eventually detect monotonic trends.

Table 1
Characteristics of monitored procedures and adherence to surgical antibiotic prophylaxis national guidelines[4] (2012-2017)

Characteristic	Value (N = 24,861)
Monitored procedures, n (%)	
Hip and knee arthroplasty	14,530 (58.44)
Colorectal surgery	6,029 (24.25)
Cranial and spinal surgery	733 (2.95)
Cardiovascular and thoracic surgery	1,890 (7.60)
Laparoscopic cholecystectomy	587 (2.36)
Prostate surgery	1,091 (4.39)
Patient age (y)	
Median	72
25th percentile	64
75th percentile	79
Male sex, n (%)	11,661 (46.9)
Infection risk index, n (%)	
0	11,790 (47.42)
1	10,050 (40.42)
2	1,909 (7.68)
3	116 (0.47)
Not applicable	996 (4.01)
Endoscopic or laparoscopic procedure, n (%)	2,909 (11.70)
Mean preoperative hospital stay (d)	2.42
Mean hospital stay (d)	
Infection	21.67
No infection	11.60
Antimicrobial prophylaxis, n (%)	23,925 (96.24)
Compliance with SAP guidelines, n (%)	
Antibiotic choice	19,427 (78.14)
Duration	15,189 (61.10)
Timing	18,070 (72.68)
Overall compliance	11,536 (46.4)

SAP, surgical antibiotic prophylaxis.

RESULTS

Between 2012 and 2017, 24,861 surgical procedures were monitored. A total of 827 SSIs occurred, of which 87 (10.52%) were reported through patient interview. The characteristics of the study population and adherence to SAP guidelines are summarized in Table 1. Over 95% of patients (23,925) received a prophylactic antibiotic regimen, and in 72.43% of procedures (18,008) data on all 3 considered parameters were available, allowing overall compliance to be assessed. Overall compliance with national guidelines was achieved in 35.41% of procedures in 2012 and increased to 60.79% of procedures in 2017. Considering the 6-year study period, complete compliance was achieved in 46.4% of all procedures (11,536), ranging from 30.43% for colon surgery to 86.71% for cholecystectomy.

The annual RRs associated with receiving SAP in compliance with national guidelines are shown in Table 2. For all categories except prostate surgery, an improvement in overall compliance over time was observed, most notably for cardiovascular and thoracic surgery (RR = 1.69). When analyzing the parameters separately, a significant decrease in compliance over time was found for SAP duration for hip and knee (2% each year) and prostate surgery (13% each year), as well as timing for cranial and spinal surgery (9% each year). Considering all procedures, a significant annual improvement in compliance was observed for all 3 parameters (15% for antibiotic choice, 3% for duration, 6% for timing, and 22% overall), and significant increasing trends over time were found for overall compliance (absolute Mann-Kendall test for trends, $P = .024$) and for all parameters except antibiotic choice ($P = .26$).

Regarding the use of BSAs, no apparent trend over time was observed for the use of the considered agents during the study period. There were non-significant decreases in the 6-year trends for third- and fourth-generation cephalosporins and piperacillin/tazobactam considering all procedures, for third- and fourth-generation cephalosporins in hip and knee arthroplasty (absolute Mann-Kendall test for trends, $P = .06$), and for quinolones in colorectal surgery ($P = .06$). Non-significant increasing trends were found for piperacillin/tazobactam in colorectal and prostate surgery ($P = .26$ and $P = .051$, respectively) and for glycopeptides in cranial and spinal surgery ($P = .18$).

Table 3 shows the association between SAP compliance and SSI risk. Complete compliance was associated with a reduced risk in all procedure groups except colon surgery (where no significant trend was found); the strongest and most significant association was observed for cranial and spinal surgery (RR = 0.37) and cardiovascular and thoracic surgery (RR = 0.46). Analysis by parameter showed that adequate antibiotic choice and duration of administration were associated with a significantly reduced SSI risk by approximately 40% and 50%, respectively, and overall compliance was associated with a RR of 0.65. Conversely, appropriate timing was associated with a slightly increased risk (RR = 1.05), although this result was not significant. The results of the multigroup risk analysis are shown in Table 4. Of the considered confounding factors, the strongest predictor of SSI risk was preoperative hospital stay ($P = .02$).

Logistic regression analysis also found adequate antibiotic choice and duration to be associated with a significantly decreased SSI risk, compared to receiving inadequate SAP according to these parameters. An OR of 0.65 (95% CI, 0.52-0.81; $P < .01$) was found for adequate antibiotic choice, and an OR of 0.60 (95% CI, 0.48-0.75; $P < .01$) was found for adequate duration of administration, considering all procedure categories. Furthermore, the logistic model identified IRI and preoperative hospital stay as the other most significant factors associated with SSI risk. Having an IRI score of 2-3 compared to 0-1 was associated with an OR of 2.67 (95% CI, 2.12-3.36; $P < .01$), and a preoperative hospital stay longer than 4 days compared to fewer than 4 days was associated with an OR of 1.67 (95% CI, 1.34-2.09; $P < .01$).

Table 2
Annual risk ratios and 95% confidence intervals associated with receiving surgical antibiotic prophylaxis in compliance with national guidelines[4] by procedure category (2012-2017)

	Antibiotic choice		Duration		Timing		Overall compliance	
Procedure category	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Hip and knee arthroplasty	1.09 (1.08-1.10)	.17	0.98 (0.98-0.99)	<.01	1.07 (1.06-1.08)	<.01	1.20 (1.18-1.23)	<.01
Colorectal surgery	1.29 (1.24-1.34)	.28	1.09 (1.05-1.13)	<.01	1.04 (1.03-1.05)	.02	1.21 (1.15-1.28)	.02
Cranial and spinal surgery	1.02 (0.99-1.06)	.23	1.31 (1.22-1.41)	.22	0.91 (0.88-0.94)	<.01	1.1 (1.02-1.19)	<.01
Cardiovascular and thoracic surgery	1.08 (1.05-1.11)	.09	1.73 (1.63-1.83)	.02	1.13 (1.11-1.15)	.61	1.69 (1.59-1.81)	.03
Laparoscopic cholecystectomy*	1.03 (1-1.07)	.97	—	—	—	—	1.03 (1-1.07)	.97
Prostate surgery*	1.21 (0.85-1.73)	.95	0.87 (0.83-0.92)	<.01	—	—	—	—
All	1.15 (1.14-1.16)	<.01	1.03 (1.02-1.04)	<.01	1.06 (1.05-1.06)	<.01	1.22 (1.20-1.25)	<.01

CI, confidence interval; *RR*, risk ratio; *SAP*, surgical antibiotic prophylaxis.
*Due to surveillance not having been performed continuously every year for these categories or to the small number of procedures in some subgroups, compliance could not be assessed for all parameters.

Table 3
Association between surgical antibiotic prophylaxis compliance with national guidelines[4] and surgical site infection risk by procedure category (2012-2017)

	Antibiotic choice		Duration		Timing		Overall compliance	
Procedure category	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Hip and knee arthroplasty	0.6 (0.42-0.86)	<.01	0.63 (0.37-1.06)	.09	1.1 (0.6-2)	.76	0.75 (0.56-1)	.06
Colorectal surgery	1.28 (1.09-1.5)	<.01	0.88 (0.79-1)	.052	0.95 (0.62-1.45)	.81	1.07 (0.95-1.2)	.27
Cranial and spinal surgery	0.48 (0.07-3.21)	.45	0.79 (0.23-2.77)	.72	0.37 (0.1-1.31)	.14	0.37 (0.18-0.76)	.02
Cardiovascular and thoracic surgery	0.19 (0.14-0.25)	<.01	0.54 (0.37-0.78)	<.01	1.16 (0.38-3.56)	.799	0.46 (0.37-0.58)	<.01
Laparoscopic cholecystectomy	0.43 (0.03-7.08)	.66	0.46 (0.03-7.31)	.65	0.15 (0.01-2.78)	.8	0.43 (0.03-7.08)	.66
Prostate surgery	0.64 (0.35-1.16)	.18	0.8 (0.44-1.46)	.48	0.1 (0.01-0.88)	.01	0.69 (0.43-1.11)	.17
All	0.57 (0.5-0.65)	<.01	0.51 (0.45-0.57)	<.01	1.05 (0.77-1.44)	.75	0.65 (0.59-0.72)	<.01

CI, confidence interval; *RR*, risk ratio; *SAP*, surgical antibiotic prophylaxis; *SSI*, surgical site infection.

Table 4
SSI risk ratios and 95% confidence intervals associated with inadequate surgical antibiotic prophylaxis (according to national guidelines)[4] in multiple risk groups

Risk group	RR (95% CI)	*P*
Patient age (y)		
<65	2.22 (1.55-3.17)	
65-80	1.75 (1.38-2.23)	
>80	2.01 (1.39-2.91)	
Fixed-effect model	1.91 (1.60-2.27)	.54
Sex		
Female	2.01 (1.54-2.61)	
Male	1.82 (1.44-2.29)	
Fixed-effect model	1.90 (1.59-2.26)	.58
Infection risk index		
0-1	1.71 (1.38-2.10)	
2-3	1.91 (1.32-2.76)	
Fixed-effect model	1.75 (1.46-2.10)	.61
Preoperative hospital stay (d)		
<2	1.47 (1.16-1.87)	
2-4	2.46 (1.57-3.85)	
>4	2.44 (1.72-3.46)	
Fixed-effect model	1.83 (1.53-2.19)	.02

CI, confidence interval; *RR*, risk ratio; *SSI*, surgical site infection.

DISCUSSION

The main findings of this study were (1) a sustained increase in compliance with SAP national guidelines over the 6 years studied, and (2) a statistically significant association between SAP compliance and reduced infection risk. In the current study, SAP was found to be completely compliant with national guidelines in 46.4% of cases, varying by procedure category. An improvement in overall compliance of 22% each year was observed, and significant increasing trends over the 6 years were found for overall compliance, timing, and duration. These results are in line with those found by a previous Australian study, which identified an improvement over 13 years in overall compliance with guidelines for the same characteristics and an increase in the odds of receiving an adequate agent of 13% each year.[22] The reasons that led to the amelioration in prescribing practices and increased adherence with national guidelines were not the focus of this study, although it is possible that participating in a surveillance network contributed to these improvements due to the "surveillance effect" (ie, an improvement in clinical practices due to the simple fact of being aware of being observed).[23] A recent Brazilian study identified a series of factors associated with improved compliance with SAP guidelines and found audit and feedback to be the most important.[24]

Although a causal association cannot be proven based on the results of this study, compliance with guidelines for agent choice was associated with a significant SSI risk reduction, consistent with previous findings.[22] Conversely, the independent effect of timing on SSI risk was found to be non-significant, although a significant association between appropriate timing and reduced SSI risk was identified in previous studies in which a more stringent indicator (30 to 60 minutes) was used.[22,25] In accordance with the SNICh protocol, in this study timing was considered adequate if SAP administration began within 120 minutes prior to the surgical incision, which may have led to an overestimation of timing appropriateness and may have hindered the results of the risk analysis.

Some target areas for the improvement of BSA prescribing practices were identified by this study. First of all, albeit in a small number of procedures, carbapenems were used for SAP when this class of antibiotics should be reserved for the treatment of multidrug-resistant infections.[26] Second, increasing trends were found for piperacillin/tazobactam consumption in colorectal and prostate surgery and glycopeptides in cranial and spinal surgery. These trends probably reflect an increase in the incidence of extended-spectrum β-lactamase-producing Gram-negative bacteria and methicillin-resistant *Staphylococcus aureus* and should be addressed through targeted stewardship programs.

On the other hand, a decrease was observed in the 6-year trends for the use of third- and fourth-generation cephalosporins and piperacillin/tazobactam in all procedures, third- and fourth-generation cephalosporins in hip and knee arthroplasty, and quinolones in colorectal surgery. These results are encouraging and should be further investigated to determine whether underlying epidemiological changes occurred or if specific strategies were implemented to promote improvements in prescribing practices.

The criteria used for the assessment of agent appropriateness in this study, following recommendations of the national guidelines, led BSAs to be classified as inadequate, except in a few specific cases. In this study, antibiotic agent compliance was found to be independently associated with an SSI risk reduction of more than 40%. Previous studies comparing agents with a narrower versus broader spectrum of activity have provided little evidence suggesting that BSAs are more effective in preventing SSIs, although small sample sizes limited the ability to detect a statistically significant difference.[27] The findings of the current study suggest that appropriate narrow-spectrum agents could, in fact, be more effective than BSAs in reducing infection rates; therefore, the use of BSAs for SAP is not only potentially harmful but also not justified.

This study had limitations that should be considered when interpreting the results. First of all, surveillance in Italy is voluntary, and it is possible that the hospitals willing to participate in the program are those with better infection prevention and control practices and guideline adherence. Second, post-discharge surveillance can be performed through a standardized patient interview, which may not be reliable in reporting infections. Furthermore, the use of data routinely collected through a standardized surveillance system had some disadvantages. An assessment of specific patients' characteristics that could have explained some prescribing choices (such as the presence

of antibiotic allergies) was not possible. Moreover, to increase the generalizability of the results of this study, local guidelines were not considered; although local protocols should generally be aligned with national recommendations, they may differ due to the specific epidemiological context. Finally, even though several known risk factors for SSI[19] were included in the logistic regression model, other confounding factors not taken into account, such as body mass index, the presence of comorbidities, or immunodeficiency, could have influenced the results.

The most recent ECDC Annual Epidemiological Report for antimicrobial consumption[26] highlighted the importance of national consumption data to understand the epidemiology of antimicrobial resistance (AMR). Because antibiotic consumption and AMR trends are country specific, reliable national data are required for tailored stewardship interventions. Considering that HCAIs are responsible for a large proportion of the burden of AMR,[6] enhanced prevention and control measures for SSIs are needed. Interventions to improve SAP compliance with national guidelines could significantly contribute to reducing antimicrobial resistance, both by reducing the burden of HCAIs and by promoting more prudent use of antimicrobials. This study has identified target areas for future interventions and could be useful to guide quality improvement programs and to promote patient safety through enhanced systematic surveillance of surgical interventions and monitoring of SAP prescribing practices.

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SUPPLEMENTARY DATA

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