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WORKSHOP 6
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Brown Room 2

Antibiotic consumption and resistance: results of the SPIN-UTI project of the GISIO-SItI

Consumo di antibiotici e resistenze: i risultati del progetto SPIN-UTI del GISIO-SItI

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Abstract

Objective. To evaluate trends and association between antibiotic consumption and resistance during an eight-year period, from 2006 to 2013.

Design. Prospective multicenter study.

Setting and participants. Intensive Care Units (ICUs) participating in the four editions of the Italian nosocomial infections surveillance in the ICU Network (Sorveglianza Prospettica delle Infezioni Nosocomiali nelle Unità di Terapia Intensiva, SPIN-UTI project).

Main outcome measures. The isolation density of selected species of microorganisms, antibiotic resistance rates (RRs), incidence density of resistant isolates and antimicrobial usage density were calculated.

Results. RRs of carbapenem-resistant *Acinetobacter baumannii*, of carbapenem-resistant *Klebsiella pneumoniae*, of third-generation cephalosporin (3GC)-resistant *K. pneumoniae* and of 3GC-resistant *Escherichia coli* showed significant increasing trends ($p \leq 0.001$). The consumption of each antibiotic class varied with years, although not significantly. Significant strongly positive correlations were detected between RRs and antibiotic consumption.

Conclusions. The present study describes high RRs and increasing trends of resistant microorganisms and highlights the need for continuous comprehensive strategies targeting not only the prudent use of antibiotics, but also infection control measures to limit the epidemic spread of resistant isolates.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 94-98)

Key words: antibiotic resistance, resistance rates, antimicrobial usage density, surveillance

Riassunto

Obiettivo. Valutare l'andamento e l'associazione tra consumo di antibiotici e resistenze durante un periodo di otto anni, dal 2006 al 2013.

Disegno. Studio prospettico multicentrico.

Setting e partecipanti. Unità di terapia intensiva che hanno partecipato alle quattro edizioni del progetto SPIN-UTI (Sorveglianza prospettica delle infezioni nosocomiali nelle unità di terapia intensiva).

Principali misure di outcome. Sono stati calcolati i seguenti indicatori: la densità di isolamento di specie di microrganismi selezionate, i tassi di resistenza agli antibiotici (RR), la densità di incidenza di isolati resistenti e la densità di utilizzo di antibiotici.

Risultati. I RR di *Acinetobacter baumannii* e *Klebsiella pneumoniae* resistenti ai carbapenemici, e di *K. pneumoniae* ed *Escherichia coli* resistenti alle cefalosporine di terza generazione, hanno mostrato significativi andamenti in aumento ($p \leq 0.001$). Il consumo di ciascuna classe di antibiotici varia con gli anni, sebbene non significativamente. Alcune significative correlazioni positive sono state evidenziate tra tassi di resistenza e consumi di specifici antibiotici.

Conclusioni. Il presente studio descrive elevati RR di microrganismi resistenti, in aumento nel tempo, ed evidenzia la necessità di ampie e continue strategie indirizzate all'utilizzo prudente di antibiotici e a misure di controllo delle infezioni per limitare la diffusione epidemica di isolati resistenti.

(*Epidemiol Prev* 2015; 39(4) Suppl 1: 94-98)

Parole chiave: resistenza agli antibiotici, tassi di resistenza, densità di utilizzo di antibiotici, sorveglianza

INTRODUCTION

Italy is one of the European countries with high antibiotic consumption in the hospital setting,[1-3] especially in Intensive Care Units (ICUs) where the highest prevalence of patients on antibiotic treatment is observed.[4] The intensive use and misuse of antibiotics have triggered the global spread of highly resistant pathogenic bacteria,[5-7] a serious public health problem in Europe and worldwide affecting costs, treatment, and mortality rates.[1,8] In particular, Gram-negative bacteria, such as *Escherichia coli*, *Klebsiella spp.*, *Pseudomonas aeruginosa*, and *Acinetobacter spp.*, are becoming resistant to all currently available antibiotics and in the near future no new antibiotic classes active against multi-resistant Gram-negative bacteria can be awaited.[9] Surveillance of multidrug-resistant microorganisms and of the burden and trends of resistance are considered important components of an effective strategy against this problem.[1] High resistance rates (RRs) to antibiotics have been observed among pathogens that cause healthcare-associated infections (HAIs) worldwide and significant gaps in surveillance have been underlined,[8] as well as the need of a prudent and rational use of antimicrobial agents.[2]

The objective of the present study is to evaluate trends and association between antibiotic consumption and resistance in the ICUs participating in the four editions of the Italian Nosocomial Infections Surveillance in the ICU Network (Sorveglianza prospettica delle infezioni nosocomiali nelle unità di terapia intensiva, SPIN-UTI project) during an eight-year period, from 2006 to 2013.

METHODS

Study design

The present study was conducted in the framework of the SPIN-UTI project, established in Italy in 2005 by the Italian Study Group of Hospital Hygiene (GISIO) of the Italian Society of Hygiene, Preventive Medicine and Public Health (SItI).[10-12] The SPIN-UTI project has adopted a protocol based on the HAIICU protocol of the European Centre for Disease Prevention and Control (ECDC).[13]

Each project survey included a six-months patient-based study conducted between the last quarter of one year and the first quarter of the following year. At present, since 2006, five editions have been conducted; in this study, the first four have been included.

Hospital participation was voluntary and results were handled confidentially. For the surveillance of HAIs, a web-based data collection procedure using four electronic data forms (for the collection of data regarding: **i.** characteristics of hospitals and ICUs, **ii.** patients, **iii.** HAIs, and **iv.** microorganisms) was used. Particularly, for each microorganism-associated HAI, antimicrobial resistance data were collected into the "microorganism" data form.

Microorganisms and antibiotic susceptibility tests

Data on microorganisms were obtained from clinical laboratories of the participating hospitals. Identification and routine antibiotic susceptibility testing were performed in each laboratory. Only susceptibility data for pathogens associated with HAIs were collected. Particularly, in the present study, resistance data for *A. baumannii*, *K. pneumoniae*, *E. coli* and *Staphylococcus aureus* were analyzed.

For each species, the isolation density was calculated as the number of isolates per 1,000 patient-days. Antibiotic RRs were calculated as the number of non-susceptible isolates (resistant or intermediate isolates) divided by the total number of isolates of the same species tested against the corresponding antibiotic, multiplied by 100. Furthermore, the incidence density of resistant isolates was calculated as the number of non-susceptible isolates per 1,000 patient-days.

Antibiotic consumption

Data on antibiotic consumption were obtained from the pharmacies of the participating hospitals. Consumption – that is, the Antimicrobial usage Density (AD) – was expressed as Defined Daily Dose (DDD) and was normalized per 1,000 patient-days. The DDD is the standard adult daily dose of an antimicrobial agent for a 1-day treatment defined by the World Health Organization.[14] Particularly, data on consumption of aminoglycosides, carbapenems, fluoroquinolones, glycopeptides, penicillins, and third-generation cephalosporins (3GCs) were collected.

Statistical analyses

Statistical analyses were performed using the SPSS 22.0 statistical package (SPSS Inc., Chicago, IL, USA).

Trends over time of RRs were determined by the chi-square test (linear by linear association). Trends over time of incidence densities of resistant isolates and of ADs were analyzed by linear regression model. Pearson's correlation coefficient (r) was used to determine the relationship between ADs and RRs. A p value <0.05 was considered statistically significant.

RESULTS

Setting, microorganisms and antibiotic resistance

During the four editions of the SPIN-UTI project a total of 52 hospitals and 75 ICUs participated in at least one edition of the project. A total of 10,703 patients and 113,977 patient-days were included (table 1).

Data on 2,255 HAI-associated microorganisms were collected: 27.1% of microorganisms in the first, 20.7% in the second, 25.1% in the third, and 27.1% in the fourth edition. Overall, the most frequently isolated microorganisms were: *P. aeruginosa* (16.7% of isolates), *A. baumannii* (14.2% of isolates), *K. pneumoniae* (10.0% of isolates), *E. coli* (7.6% of isolates), and *S. aureus* (7.3% of isolates). Considering all four editions, isolation densities were: *P. aeruginosa* 3.3 per 1,000 patient-days; *A. baumannii* 2.8 per 1,000 patient-days; *K. pneumoniae* 2.0 per 1,000 patient-days; *E. coli* 1.5 per 1,000 patient-days; and *S. aureus* 1.4 per 1,000 patient-days. Table 1 shows incidence densities of microorganisms isolated and of resistant isolates during the four editions of the project. Incidence density of carbapenem-resistant *K. pneumoniae* increased significantly from the first to the last edition of the project (p=0.027).

Considering all editions, the RR of carbapenem-resistant *A. baumannii* was 86.0%, of carbapenem-resistant *K. pneumoniae* 35.5%, of 3GC-resistant *K. pneumoniae* 68.1%, of carbapenem-resistant *E. coli* 4.9%, of 3GC-resistant *E. coli* 38.0%, and of methicillin-resistant *S. aureus* (MRSA) 45.2%.

Figure 1 reports RRs of the selected species during the four editions of the project. RRs of carbapenem-resistant *A. baumannii*, of carbapenem-resistant *K. pneumoniae*, and of 3GC-resistant *K. pneumoniae* showed significant increasing trends from the first to the last edition of the project (p≤0.001). Furthermore RRs of 3GC-resistant *E. coli* showed a significant increasing trend from the first to the third edition of the project and a decreasing trend in the last edition (p=0.048).

Antibiotic consumption

Antibiotic consumption over the eight-year period was 8,750 DDD per 1,000 patient-days (AD). Overall penicillins were the main antibiotic class consumed (32.1% of the total AD), followed by fluoroquinolones (19.7% of the total AD), glycopeptides (16.8% of the total AD), carbapenems (11.9% of the total AD), aminoglycosides (17.3% of the total AD), and 3GCs (6.0% of the total AD). The consumption of each antibiotic class (i.e., ADs) varied with editions, although not significantly (table 1).

Correlation between antibiotics consumption and resistance rates

Significant strongly positive correlations were detected between RRs of carbapenem-resistant *E. coli* and 3GC consumption (r=0.953; p=0.047) and penicillin consumption (r=0.983; p=0.017), and between RRs of MRSA and aminoglycosides consumption (r=0.965; p=0.035).

No correlations between the usage of other antimicrobial agents and resistance data were found.

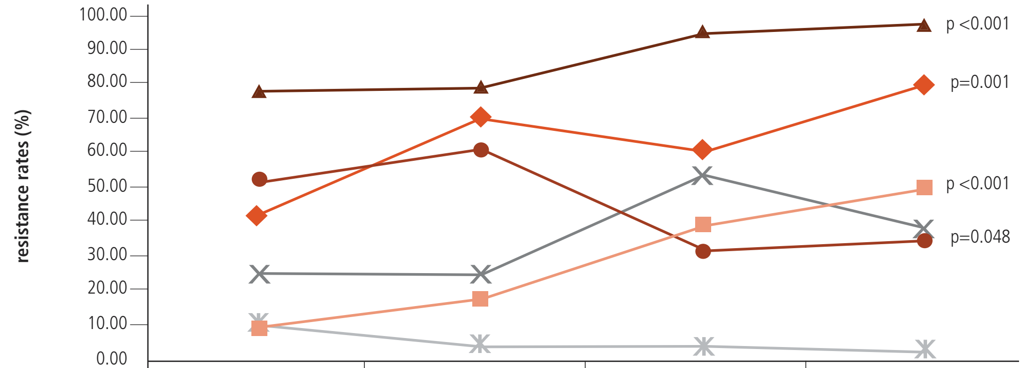
DISCUSSION AND CONCLUSIONS

Antibiotic consumption contributes to the prevalence of resistant pathogens in the hospital setting, together with their clonal spread,[15,16] especially in Italian ICUs where the highest prevalence of patients on antibiotic treatment[4] has been

	SPIN-UTI PROJECT				
	2006-2007	2008-2009	2010-2011	2012-2013	p-value*
number of hospitals	32	22	22	22	-
number of ICUs	49	28	27	26	-
number of patients	3,053	2,163	2,478	3,009	-
patient-days	35,498	22,683	24,724	31,072	
incidence density (*per* 1,000 patient-days)					
Klebsiella pneumoniae	0.9	2.1	2.0	3.1	0.067
Acinetobacter baumannii	1.4	3.0	4.1	3.2	0.253
Escherichia coli	1.1	1.3	2.3	1.5	0.460
Staphylococcus aureus	1.5	1.2	1.2	1.7	0.684
incidence density of resistant isolates (*per* 1,000 patient-days)					
3GC-resistant *K. pneumoniae*	0.4	1.3	1.1	2.3	0.095
carbapenem-resistant *K. pneumoniae*	0.1	0.3	0.8	1.5	**0.027**
carbapenem-resistant *A. baumannii*	1.1	2.3	3.8	3.0	0.188
carbapenem-resistant *E. coli*	0.1	0.04	0.1	0.03	0.487
3GC-resistant *E. coli*	0.3	0.3	1.1	0.5	0.523
methicillin-resistant *S. aureus*	0.7	0.5	0.3	0.3	0.056
antimicrobial densities (ADs: DDD *per* 1,000 patient-days)					
aminoglycosides	384	441	124	237	0.318
carbapenems	345	189	222	283	0.713
3GCs	227	137	83	80	0.070
fluoroquinolones	469	338	531	387	0.920
glycopeptides	418	363	280	406	0.754
penicillins	1,101	541	646	516	0.218

*linear regression
ICU: Intensive Care Unit; 3GC: third-generation cephalosporin; DDD: defined daily dose
Significant values are indicated in colour

Table 1. Incidence density of microorganisms and of resistant isolates and Antimicrobial usage Densities (ADs) during the four editions of the SPIN-UTI project.
Tabella 1. Densità di incidenza dei microrganismi e degli isolatI resistenti e densità di utilizzo di antibiotici durante le quattro edizioni del progetto SPIN-UTI.



	2006-07	2008-09	2010-11	2012-13
3GC-resistant *K. pneumoniae*	41.90	70.70	60.50	79.30
carbapenem-resistant *K. pneumoniae*	9.40	17.50	38.80	50.00
darbapenem-resistant *A. baumannii*	78.40	79.70	95.90	97.90
3GC-resistant *E. coli*	24.30	25.00	52.80	38.60
carbapenem-resistant *E. coli*	10.50	3.80	3.60	2.30
methicillin-resistant *S. aureus*	52.20	61.10	31.80	34.50

p-values from chi-square test, linear by linear association
Only significant p-values are indicated

p-value dal test del chi quadrato, associazione lineare-lineare
Sono indicati solo i valori statisticamente significativi

Figure 1. Resistance rates of selected species during the four editions of the SPIN-UTI project.
Figura 1. Tassi di resistenza delle specie selezionate durante le quattro edizioni del progetto SPIN-UTI.

observed and outbreaks due to multidrug-resistant pathogens are frequently reported.[17-19]
The European Antimicrobial Surveillance Network (EARS-Net) published resistance data from European countries based only on invasive isolates from hospitals (not only from ICUs), not representative of isolates from other sites, and thus, comparison should be undertaken with caution.[1] In any case, the present study confirms higher RRs of carbapenem-resistant *A. baumannii* than those in the other European countries[1] and an increasing trend, indicating seriously limited options for the treatment of patients infected with this microorganism. In 2013, the Italian Ministry of Health established a national surveillance of carbapenemase-producing *Enterobacteriaceae* (particularly, *K. pneumoniae* and *E. coli*) in order to monitor the frequency and geographical distribution of these microorganisms.[20] In the SPIN-UTI project a significant increasing trend was observed for carbapenem-resistant *K. pneumoniae*, confirming high RRs among the European countries.[1] Conversely, carbapenem-resistant *E. coli* remain generally rare as in the other European countries.[1]
The spread of clonally related multidrug-resistant *A. baumannii* and *K. pneumoniae* isolates have been described in Italy[17-19] contributing to the increasing trend of carbapenem resistance of such microorganisms. Thus, specific control measures should be implemented in order to limit the dissemination of extensively drug- or pandrug-resistant isolates.[21-23]
In the SPIN-UTI project the percentage of 3GC-resistant *K. pneumoniae* isolates was higher than that reported for Italy in the European report[1] and an increasing trend was observed. RRs of 3GC-resistant *E. coli* showed an increasing trend from 2006 to 2011 time frame of the project and a decreasing trend in 2012-2013.
MRSA is one of the most frequent resistant microorganisms associated to HAIs worldwide and even though a decreasing trend was observed in the last years, in Europe MRSA remains a significant public health problem.[1] In the SPIN-UTI project a decreasing trend of RRs was observed in the last years, although not significant. Notably, RRs of MRSA were higher than European data and prevention measures to control the spread should be improved.[24]
Significant strongly positive correlations were detected between RRs of carbapenem-resistant *E. coli* and 3GC and penicillin consumption and between RRs of MRSA and aminoglycoside consumption. No correlations between the use of other antimicrobial agents and resistance data were found. The complex nature of the spread and emergence of antibiotic resistance can, at least partly, explain this result. Furthermore, as previously reported, DDD measurements are useful for benchmarking but may not fully correlate with antibiotic resistance due to the intrinsic biases.[25]
One of the strengths of this study is that it was conducted in the framework of a prospective multicentre patient-based project. One limitation is the ecological study design that cannot fully prove a causative relationship between antibiotic consumption and resistance. In fact, other factors, including the volume of antibiotics prescribed in the outpatient setting, antimicrobial stewardship interventions implemented in participating ICUs, and the occurrence of outbreaks due to multidrug-resistant organism, already reported in a sample of

ICUs participating in the SPIN-UTI network,[17-19] should be taken into account to explain this complex issue.
In conclusion, the present study describes high RRs and increasing trends of resistant microorganisms and highlights the need for continuous comprehensive strategies targeting not only the prudent use of antibiotics, but also infection control measures to limit the epidemic spread of resistant isolates.

Conflicts of interest: none declared

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