



Providing background for antimicrobial stewardship strategy using costs data: a mission impossible?

Giorgia Montrucchio^{1,2^}, Gabriele Sales^{1,2}, Silvia Corcione^{3,4}, Antonio Curtoni⁵, Rosario Urbino², Luca Brazzi^{1,2}

¹Department of Surgical Sciences, University of Turin, Turin, Italy; ²Department of Anesthesia, Intensive Care and Emergency, 'Città della Salute e della Scienza', Hospital, Turin, Italy; ³Department of Medical Sciences, Infectious Diseases, University of Turin, Turin, Italy; ⁴Tufts University School of Medicine, Boston, MA, USA; ⁵Microbiology and Virology Unit, 'Città Della Salute e Della Scienza' Hospital, Turin, Italy

Contributions: (I) Conception and design: L. Brazzi, G. Montrucchio, G. Sales; (II) Administrative support: G. Montrucchio, G. Sales; (III) Provision of study materials or patients: G. Montrucchio, G. Sales, A. Curtoni; (IV) Collection and assembly of data: G. Montrucchio, G. Sales, S. Corcione, A. Curtoni; (V) Data analysis and interpretation: G. Montrucchio, G. Sales, L. Brazzi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Giorgia Montrucchio. Department of Surgical Sciences, University of Turin, Turin, Italy; Department of Anesthesia, Intensive Care and Emergency, 'Città della Salute e della Scienza', Hospital, Corso Dogliotti 14, Turin 10126, Italy. Email: giorgiagiuseppina.montrucchio@unito.it.

Background: In the context of intensive care units (ICUs), antimicrobial stewardship (AS) projects are often hampered by the lack of dedicated human resources. Added to this is the limited effectiveness of the measurement parameters available to date. The combination of these two factors heavily impacted either the possibility of containing healthcare costs or limiting the increase of infections induced by microorganisms resistant to antibiotics.

Methods: We tested the possibility of using administrative cost reports produced every six months by the Management Control Structure of the 'Città della Salute e della Scienza' Hospital of Turin (Italy) to obtain a reliable estimate of the consumption of antimicrobial drugs of all ICUs that make up the Department of Anesthesia and Intensive Care.

Results: It was found that antimicrobial drugs account for about 50% of drug cost differences with huge differences between the eight ICUs that make up the Department of Anesthesia and Intensive Care. Antifungal drugs represented altogether a percentage of expenditure of about 30% of the total expenditure on antimicrobial drugs. Multi-drug resistant germs, especially Carbapenem resistant-*Klebsiella pneumonia* subtype KPC, *Acinetobacter baumannii* and extended spectrum beta-lactamase (ESBL) *Escherichia coli*, were higher in 2016 in comparison with 2015.

Conclusions: From a methodological point of view, it emerged that the implementation of this approach, not involving human resources and easily applicable repeatedly and continuously in the context of the various intensive structures that make up the Department of Anesthesia and Intensive Care, seems capable to provide the appropriate basis for an internal comparison followed by the implementation of more complex AS strategies.

Keywords: Antimicrobial stewardship (AS); intensive care units (ICUs); drug resistance (multiple); drug resistance (microbial)

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[^] ORCID: 0000-0001-9341-965X.

Introduction

Existing health systems sustainability depends on the ability to reduce waste and costs. Among the drug-related cost, one of the most relevant is that induced by antibiotics being about one-third of hospitalized patients, and more than two-thirds of critical patients treated with them (1,2). It has also been reported that around 30% to 50% of the prescribed antibiotics are unnecessary prescribed or inappropriate (3-5), leading to an avoidable health expenditure that has been estimated to be \$35.1 billion (6) in 2013 in the United States.

Antibiotic-resistant micro-organism has been reported to cause yearly, in Europe, at least 400,000 cases of antibiotic-resistant infections with 25,000 deaths and hospitalization costs higher than 1.5 billion euros (7). The need of limiting the increase of multi-drug-resistant (MDR) infections might be associated with the possibility of contain spending.

COVID-19 pandemic exacerbated the problem, forcing intensive care units (ICUs) to work in a state of emergency and increasing either the empirical antibiotic use or antimicrobial resistance (8). Other aspects of the clinical course of COVID-19 patients contributed to exacerbate critical issues, such as the difficult distinction between infectious and non-infectious causes of respiratory deterioration and the much-debated relevance of fungal and viral co-infections (9-11).

The challenge that is now involving not only high-income, but also low- and middle-income countries (12), is therefore the implementation of effective antimicrobial stewardship (AS) projects to control spending and contain antibiotic resistance growth.

Even if the literature is consistent that adherence to local guidelines, use of targeted therapies, early suspension of unnecessary therapies, shift from intravenous to oral therapy, should all to be included in AS programs (13), the general characteristics of these programs (14-16) and the measures to evaluate their effectiveness are still unclear. This is particularly true if we refer to the ICU contest, where the lack of dedicated human resources and the poor effectiveness of available measurement parameters are limiting further their implementation (17-19).

We therefore tested the possibility of providing the basis for an effective AS project to be developed in the context of the Department of Anesthesia and Intensive Care starting from the situation described by the administrative reports produced every six months by the Hospital Management Control Structure.

Methods

The Department of Anesthesia and Intensive Care of 'Città della Salute e della Scienza' hospital of Turin (Italy) include eight ICUs: two general, one neuro-surgical, one cardio-surgical, one obstetric-gynecological, one mainly dedicated to trauma, one pediatric and one directly located in the Emergency Department with an ICU/general beds relationship equal to 71/1,910.

Cost data referring to anti-microbial drugs used in the Department, proposed as surrogate consumption indices, were evaluated referring to the first 6 months of year 2015 and 2016, using the reports produced by the Management Control Structure. Data were analyzed in collaboration with an infectious disease specialist and all ICU prescribers were actively involved in the analysis. The ethics approval and informed consent were not required as this study focused on cost data.

Due to the fact that a subset of antimicrobial drugs is known to be particularly prescribed to treat infections induced by MDR pathogens, MDR infections trends and characteristics in five out of the eight ICUs of the Department (two general, one neuro-surgical, one cardio-surgical and one directly located in the Emergency Department) using the same Microbiological Laboratory were specifically studied.

The actual use of indirect fungal infection markers, such as 1,3-b-D-glucan, in supporting the antifungal drugs prescriptions was even evaluated.

Results

Both in 2015 or in 2016, the twelve most expensive antimicrobials induced, by their own, an expenditure equal to 783,681/1,763,084 euros (44.5%) and 697,058/1,659,702 (42%) of the total expenditure of the Department (*Table 1*). More detail, although the more expensive and used drugs remained in the 2-year period considered, Linezolid, Tigecycline, Daptomycin, Meropenem, Teicoplanin and Colistin (*Table 1*) a comparison between 2015 and 2016 shows a reduction in Tigecycline and Linezolid expenditure and a slight increase in Daptomycin and Meropenem expenditure (*Figure 1*).

Among antifungal drugs, representing altogether a percentage of expenditure equal to 33% and 29.2% (respectively in 2015 and 2016) of the total expenditure on antimicrobial drugs, a major role seems to be due to Amphotericin (15% *vs.* 13.4%, respectively in 2015 and 2016) and Echinocandins (16.8% *vs.* 12.9%, respectively in

Table 1 Costs induced by the 12 most expensive and used antimicrobial drugs in the first semester of 2015 and 2016

Drugs	First semester 2015		First semester 2016	
	Cost (€)	%	Cost (€)	%
Antibiotics	269,568	17.3	242,340	14.6
Linezolid	88,625	5.7	73,849	4.5
Tigecycline	106,128	6.8	69,130	4.2
Daptomycin	22,555	1.4	34,576	2.1
Meropenem	18,710	1.2	29,011	1.7
Teicoplanine	12,605	0.8	8,965	0.5
Colistin	10,609	0.7	8,000	0.5
Piperacillin/Tazobactam	10,332	0.7	14,073	0.8
Antifungals	514,113	33.0	454,718	29.2
Amphotericin B	231,281	15.0	221,655	13.4
Voriconazole	21,185	1.4	18,158	1.1
Echinocandins	261,647	16.8	214,904	12.9
Caspofungin	223,009	14.3	137,801	8.3
Anidulafungin	33,813	2.2	75,093	4.5
Micafungin	4,824	0.3	2,010	0.1

Percentages are computed referring to the total expenditure for drugs referring to the same period.

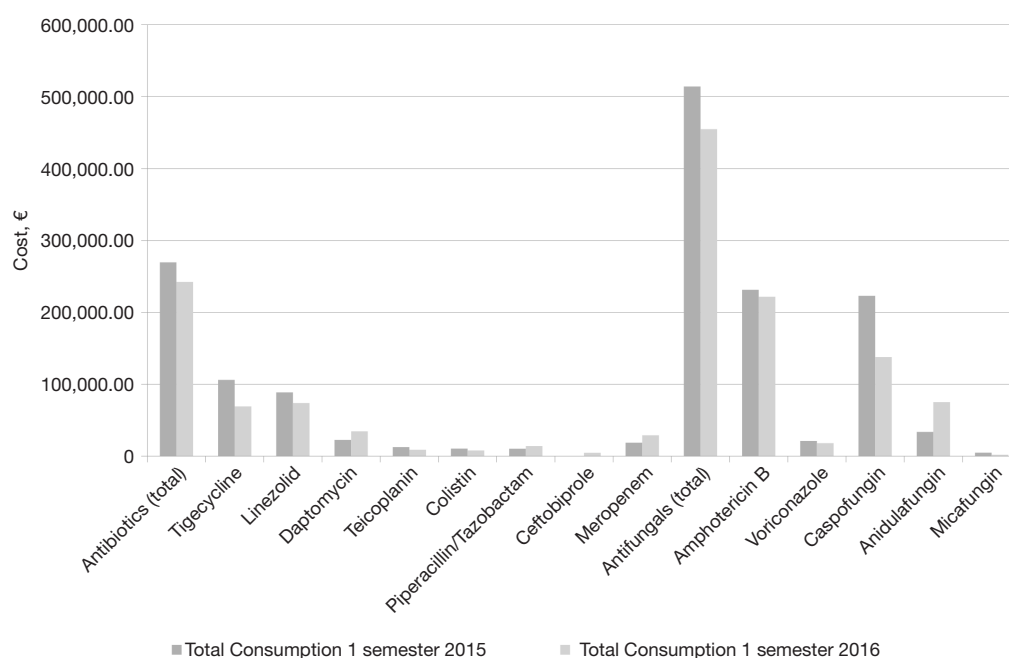
**Figure 1** Antimicrobial drugs use in the first semester of 2015 and 2016 in all the considered ICUs. ICUs, intensive care units.

Table 2 Comparison among costs induced by the 12 most expensive and used antimicrobial drugs in the different ICUs

Type of ICU	1° semester of 2015	% on total expenditure	1° semester of 2016	% on total expenditure
General ICU 1	236,278	30	232,308	33
Cardio-surgical ICU	59,374	8	89,400	13
General ICU 2	251,089	32	222,340	32
ED-ICU	34,544	4	20,062	3
Neurosurgical ICU	4,480	1	11,593	2
Trauma ICU	80,932	10	55,340	8
Gynecological and obstetric ICU	20,269	3	4,235	1
Pediatric ICU	56,447	7	31,225	4
Cardio-surgical pediatric ICU	40,268	5	30,032	4

Percentages are computed referring to the total expenditure for drugs in each ICU in the same period. ICU, intensive care unit; ED, emergency department.

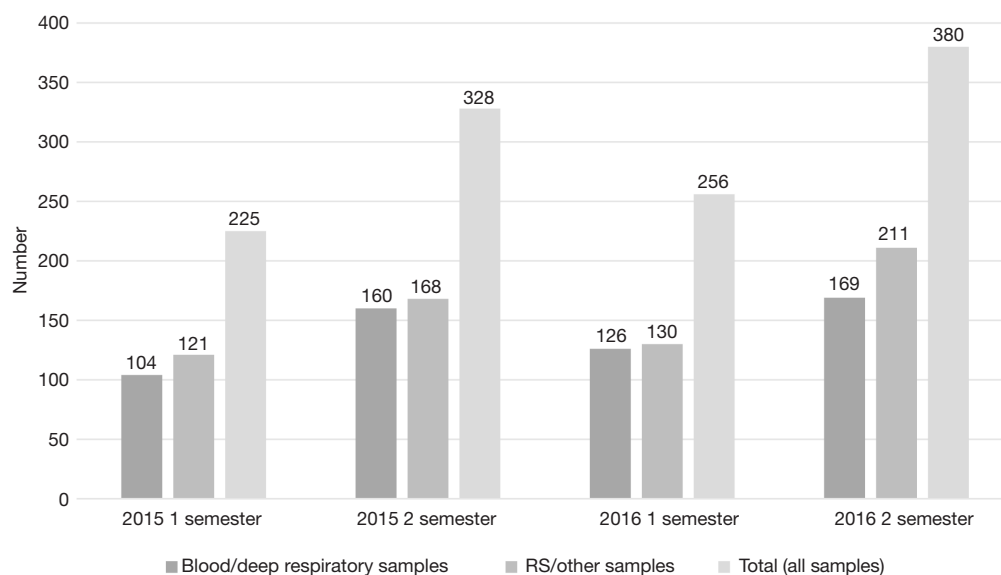


Figure 2 Number of multi-drug resistant bacteria (20) isolated in 2015 and 2016 in the five ICUs of the Department of Anesthesia and Intensive Care using the same microbiological laboratory. Data from deep sterile sites (blood and deep respiratory samples) are presented separated from data from potentially contaminated samples (urinary samples, rectal swabs, abdominal drainage fluids, surgical site swabs and other). RS, rectal swab; ICU, intensive care unit.

2015 and 2016). It should be noticed, comparing 2015 and 2016 a small reduction of global antifungal consumption associated with an increase in the use of Anidulafungin (from 2.2% in 2015 to 4.5% in 2016).

As expected, and probably due to the different characteristics of patients admitted in the different ICUs, a huge variability in the use of antimicrobial drugs has been observed among the eight ICUs considered in the present

analysis (Table 2). However, supporting the reproducibility of the data collection method used, these differences remained stable over the two considered semesters.

MDR germs, especially Carbapenem resistant-*Klebsiella pneumoniae* subtype KPC, *Acinetobacter baumannii* and extended spectrum beta-lactamase (ESBL) *Escherichia coli*, were higher in 2016 in comparison with 2015 (Figures 2,3), mainly in the ICUs admitting more severe patients such

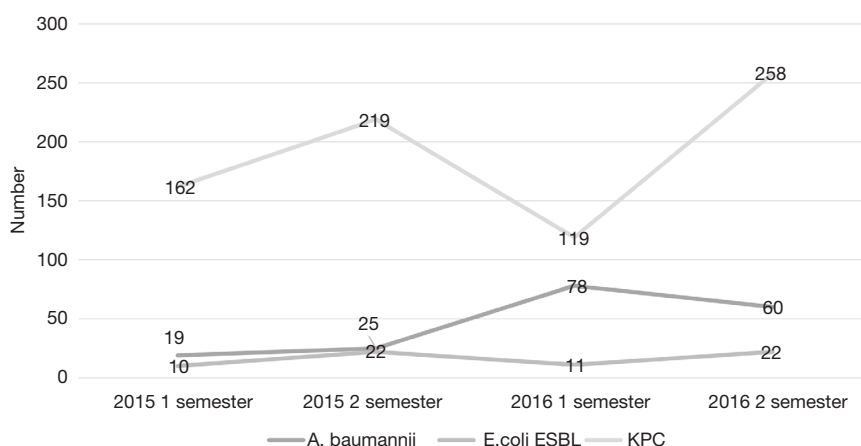


Figure 3 Trend of the most represented multi-drug resistant bacteria in 2015 and 2016 in the five ICUs of the Department of Anesthesia and Intensive Care using the same microbiological laboratory. KPC, Carbapenem-producing *Klebsiella pneumoniae*; ESBL, extended-spectrum beta-lactamase; ICU, intensive care unit.

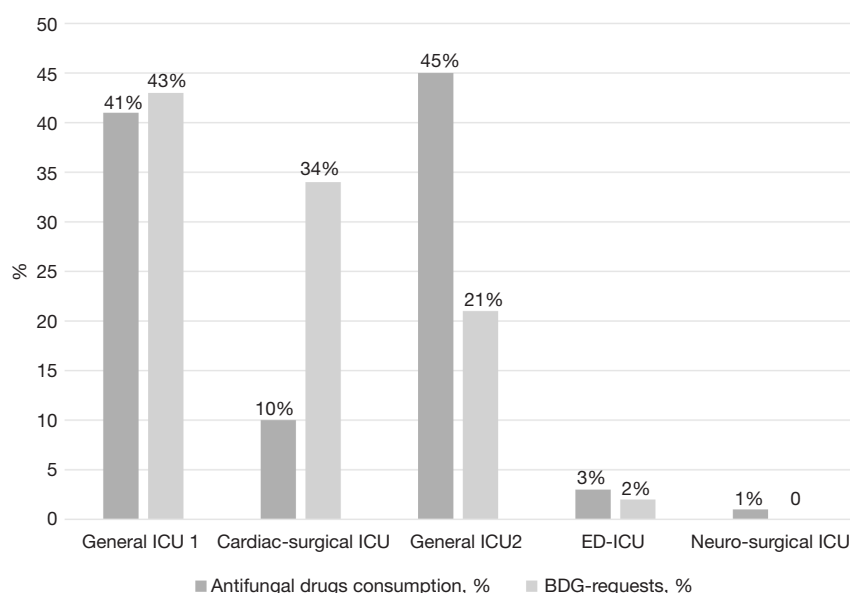


Figure 4 Antifungal drugs consumption and 1,3-b-D-glucan request in the first semester of 2016 in the five ICUs of the Department of Anesthesia and Intensive Care using the same microbiological laboratory. ED, emergency department; ICU, intensive care unit; BDG, 1,3-b-D-glucan.

as general and cardio-surgical ones. For the treatment of these infections, that, according to literature, are commonly approached with Meropenem, Colistin and Tigecycline, around 6.4% of total drug-expenditure of the Department has been used.

Regarding the use of 1,3-b-D-glucan to support the prescription of antifungal drugs we evidenced a diffused under-use of this diagnostic methods, with an inverse

relationship with antifungal drugs prescription and 1,3-b-D-glucan use (Figure 4).

Discussion

Several projects have been proposed in the context of the 'Città della Salute e della Scienza' hospital with the aim of describing and optimizing the practice of antimicrobial

therapy. Due to the number of antimicrobial drugs used and the lack of human resources available to collect timely data regarding on the use of these drugs, ICUs always remained outside these programs. Using the economic data routinely collected by the Management Control Structure, we were able to obtain a reliable estimate of the consumption of antimicrobial drugs in all the ICUs constituting the Department of Anesthesia and Intensive Care.

The results so far obtained confirmed that antimicrobial drugs are heavily impacting the Department's budget, representing about 50% of the drug costs, but also that huge differences are present within the 'intensive care' domains.

Although some of these observed differences can be justified taking into account the different case-mix of the different ICUs of the Department, as in the case of the particularly complex transplanted patients, the results of the analysis correlating the incidence of MDR and the use of MDR-specific drugs seems to highlight a too 'liberal' use of high-cost drugs (Meropenem, Colistin and Tigecycline) whose use should be instead limited to 'rescue' therapies to apply only in the presence of MDR germs. And this evidence strongly supports the need to boost the 'carbapenem sparing culture', strongly recommended in the literature (21), which seems to be absent in our department. This objective, combined with the need to better analyze the differences, till now hypothesized and now demonstrated, confirmed that it worth implementing an AS program in the Department of Anesthesia and Intensive Care.

Another interesting result is that about 30% of the expenses for antimicrobial drugs are due to the purchase of antifungal drugs (mainly echinocandins and amphotericin). These drugs, in the great majority of cases, are prescribed empirically in absence of adequate diagnostic test, either direct culture, that are known to be difficult to obtain and rarely positive, or indirect testing such as 1,3-b-D-glucan whose negative predictive value has been reported (22), and recently confirmed (23).

The work has several limitations. First, cost data, chosen as readily available and part of a routine surveillance, were taken as surrogate consumption indices. However, it must be considered that an increase in expenditure is not necessarily due to increased consumption since the total expenditure depends on both the unit cost and the frequency of use.

Second, cost data were computed using the so called 'weighted average price' and not the 'definite daily

dose' (DDD) used by standard literature to estimate the consumption (24).

Third, changes in drug availability due to the introduction of new molecules or expiration of patents risk invalidating the cost analysis and must be critically evaluated by the multidisciplinary AS team.

Finally, the data presented here refer to a pre-pandemic context and therefore antecedent to the development of new important antimicrobials gradually added in recent years to the therapeutic armamentarium particularly against MDR pathogens. However, it should be noted that their prescription, at least in Italy is regulated by the infectious diseases' specialist, and therefore already part of the AS programs.

Furthermore, even if the data collected show a reduction in the costs incurred for antimicrobials between 2015 and 2016 and an apparent increase in cases of infection with multidrug-resistant pathogens, the design of the study and the methodology used do not allow a statistical analysis that allows an interpretation of the observed phenomena.

Similarly, the relapses of a more widespread use of indirect diagnostic methods, such as the use of BDG, cannot be read as the result of the clinical implementation of an intervention. However, it should be noted that the correlation between the use of this biomarker and the reduction in the cost of antifungals is to be considered of interest for future studies designed for this purpose.

Despite the limitations illustrated above, the results so far obtained clearly support the need for a thorough review of the antimicrobial prescribing approach used up to now in the ICUs of the Department of Anesthesia and Intensive Care of the Città della Salute e della Scienza' university hospital of Turin (Italy).

Beyond this, we do consider the ability of this approach to provide a picture of the antimicrobial practice used in the Intensive Care facilities using administrative data that are routinely collected by the Control Management Structure of each Italian hospital to monitor the achievement of the objectives annually assigned to the operating structures extremely interesting and new. Furthermore, it must be considered as an approach capable of considering costs may be useful to engage administrators for support for stewardship strategies and make them attractive and cost-effective also in terms of investments.

Even with their intrinsic limitations, these data are, in fact, always available, regardless of dedicated human resources, and therefore always potentially usable to provide the basis for an AS project aimed at continuous

improvement of clinical practice and data containment.

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