Appropriateness of antibiotic prescription for targeted therapy of infections caused by multidrug-resistant bacteria: assessment of the most common improper uses in a tertiary hospital in Southern Italy

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SUMMARY

A huge proportion of antibiotic therapies for infections caused by multidrug-resistant bacteria (MDR) are inappropriate. In this study, we described the most common causes of inappropriateness of definitive antibiotic regimes in a large university hospital in southern Italy we evaluated the impact on microbial eradication, length of stay, 30-day readmission and mortality. We retrospectively assessed 45 patients who received a definitive antibiotic therapy after isolation of multidrug-resistant *Staphylococcus aureus*, *Enterococcus* spp., Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter* spp. strains between 2014 and 2015. From the literature, we set a series of criteria to retrospectively determine the appropriateness of the therapy. In all, 61% of the prescribed antibiotic regimes were found to be inappropriate, especially due to incorrect drug dosage. It emerged that meropenem was the antibiotic most frequently inappropriately used. In 46% of infections caused by MDR but not extended-spectrum β-lactamase-producing Enterobacteriaceae, carbapenems were inappropriately administered. Microbial eradication was achieved in 87% of the appropriate therapy group compared to 31% of the inappropriate therapy group (chi-square=6.750, p<0.027). No statistically significant association was found between inappropriate therapy and the length of stay (chi-square=3.084, p=0.101) and 30-day readmission (p=0.103). Definitive antibiotic therapy in infections caused by multidrug-resistant bacteria in a large university hospital is often inappropriate, especially due to the drug dosing regimen, particularly in the case of meropenem and colistin. This inappropriateness has a significant impact on post-treatment microbial eradication in specimens collected after antibiotic therapy.

Keywords: inappropriate prescriptions, antibiotics, multidrug resistance, colistin, carbapenems.

INTRODUCTION

Between 2010 and 2014, the systemic antibiotic consumption, both in the community and in the healthcare-related setting, has dramatically increased in most European countries, albeit with striking geographical variation in terms of daily doses and classes of antibiotics. In Italy, where the antibiotic consumption has reached the third highest rate in Europe, the economic burden of antibiotic therapy has increased by 94.9% in 2015 compared to 2014, representing the second therapeutic category for public expenditure and

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costing an overall of 2.9 billions of euros to the National Healthcare system [1, 2].
Further to the economic considerations, the overuse of systemic antibiotics in the nosocomial setting, when it is not strictly necessary and/or administered inappropriately, is one of the driving factors leading to antibiotic resistance [3-5]. Naturally, the emergence of antibiotic resistance has a further significant impact on mortality, morbidity and healthcare costs [6]. The literature data indicate that patients with Gram-negative infections treated with an inappropriate antibiotic therapy have a higher rate of mortality (38.4%) compared to patients treated with an appropriate therapy (27.4%) [7]. The risk of receiving inappropriate therapy seems to be higher in patients with infections caused by multi drug-resistant (MDR) bacteria: for instance, it has been reported that 69% of patients with bloodstream infections caused by MDR bacteria receive an inappropriate antibiotic therapy compared to 9% of patients with non-MDR infections [8].
Adherence to guidelines, *per se*, should guarantee a proper use of anti-infective drugs to manage infections, but guidelines often do not apply to each individual patient and in such contexts do not keep up to pace with the rapid spread of MDR bacteria [9, 10].
Therefore, the evaluation of antibiotic prescribing remains an unanswered question in some health institutions, particularly in the absence of an antimicrobial stewardship program (ASP).
This study aims to retrospectively determine and characterize the rate of inappropriate antibiotic definitive prescribing for infections by MDR bacteria in some selected clinical and surgical wards of a large university hospital in Southern Italy, and to identify the most frequent causes of incorrect prescribing.
Furthermore, we evaluate the impact of the prescription of antibiotics on the following endpoints: post-treatment microbial eradication, 30-day mortality, length-of-stay (LOS), and 30-day hospital readmission.

PATIENTS AND METHODS

Study design
A retrospective observational study was carried out across four wards, one in the medical area of Nephrology and the remaining three in the surgical areas of Maxillo-Facial Surgery, Vascular Surgery and General Surgery of Pre- and Post-Transplant. All studies were carried out in our institution: the University of Naples "Federico II", one of the largest university hospitals in Southern Italy. The study investigates a time frame ranging from 1st January 2014 to 31th December 2015, during which our center had not yet implemented an ASP.
Clinical data from medical records of the selected wards were cross-checked with information from the database of clinical microbiology laboratory, in order to gain a complete susceptibility profile (antimicrobial susceptibility testing, AST) of the following causative agents of infection: *Staphylococcus aureus, Enterococcus* spp., Enterobacteriaceae - no *Salmonella* or *Shigella* -, *Pseudomonas aeruginosa* and *Acinetobacter* spp.
Only patients above eighteen years of age with MDR infection (as later defined) were included in the study. The data collected refers strictly to hospitalized patients receiving at least four days of systemic antibiotic therapy within the three days following the AST result.
A patient could be included more than once solely if:
1) he/she had been newly re-admitted in the same ward after an interval of at least sixty days from discharge;
2) during the subsequent admission a MDR bacteria among the ones mentioned above had been isolated.

The Vitek 2 (bioMérieux, Marcy l'Étoile, France) and/or Phoenix (Becton Dickinson Microbiology Systems) systems were used for the bacterial identification and the antimicrobial susceptibility testing (AST). Vitek and/or Phoenix Minimum Inhibitory Concentrations (MICs) were classified according to EUCAST breakpoints [11].

Patient's data collection
The following information was recorded: patient's demographic data (age, sex, weight); date of hospital admission and date of discharge or death (within 30 days from admission), overall LOS (days), any 30-day readmission in the same department, outcome of hospitalization (mortality); iatrogenic risk factors for infections such as presence of a solid organ graft, corticosteroid use, Intensive Care Unit (ICU) admission before the antibiotic therapy, ICU LOS, presence of a central venous catheter (CVC) or a peripherally inserted

central catheter (PICC), enteral nutrition, parenteral nutrition, anti-neoplastic chemotherapy, radiotherapy, dialytic procedures, immune suppressive therapy performed during the hospital stay. Any other diagnosis reported in the clinical record such as comorbidity diseases and relative severity calculated by the Age-Adjusted Charlson Comorbidity Index (ACCI), the glomerular filtration rate calculated by Cockcroft-Gault Formula and the conditions that may prevent patients from receiving oral antibiotic therapy were also collected [12, 13].

The microbiological data of infections caused by MDR bacteria included: site of infection, date of collection of the specimen, isolated pathogens, antibiotic susceptibility and minimum inhibitory concentration (MIC); additional specimens collected after the antibiotic therapy in order to verify the microbiological eradication.

Lastly, all the data referring to any empiric therapy regimen (given in the previous three days before AST result) and the definitive antibiotic therapy regimen prescription after AST results (active drug, dosage, way of administration, duration of antibiotic therapy) were recorded.

We determined *ex post* the appropriateness of the antibiotic that had been prescribed during the hospitalization by the ward's physicians and not by an infectious diseases specialist. Consequently, the collected data were analysed by comparing the data from patients who received an appropriate antimicrobial prescription with those from patients who received an inappropriate antibiotic prescription.

This study has been approved by the Ethics Committee of the University of Naples "Federico II".

End-points

The main outcome measure used was the eradication of the Multidrug-resistant pathogen in the specimens collected after the definitive antibiotic therapy. The secondary outcomes were the 30-day mortality rate, the 30-day readmissions in the same ward and LOS.

Definitions of multidrug resistance and appropriate definitive antibiotic prescribing

The definition of multidrug-resistant isolate was based on the European Centre for Disease Prevention and Control's (ECDC) definition established in 2011 [14].

The bacterial strains were considered MDR if the isolate was non-susceptible to at least 1 agent in ≥3 antimicrobial categories listed by the ECDC, whereas it was considered Extensive Drug-Resistant (XDR) if it was non-susceptible to at least 1 agent in all but 2 or fewer listed antimicrobial categories and Pandrug-resistant (PDR) if it was non-susceptible to all agents in all the listed antimicrobial categories.

The definition of antibiotic appropriateness used for this study, though a universal consensus upon it is lacking, relies on the most authoritative guidelines and previous works [15-18].

We solely assessed prescriptions made following the positivity of microbiological cultural examination, for targeted/definitive therapy. Therefore, we considered the antibiotic prescription as appropriate if the antibiotic:

1) had *in vitro* activity against the isolated pathogen;
2) was given at an optimal dosing regimen, duration of the therapy and route of administration, respectful of pharmacokinetic/pharmacodynamic parameters of the drugs (time-dependence and concentration-dependence) and of the clinical indication;
3) the dosage had been adjusted for renal impairment;
4) the antibiotic therapy had been started within 24 hours from the AST result;
5) the antibiotic plan had been fully documented in the clinical record (indication, name, doses, route, interval of administration). Additional criteria included switching from empiric therapy regimen to definitive regimen after antimicrobial tests.

The definitive antibiotic prescription was considered inappropriate if it did not meet at least one of the above listed criteria.

Microbiological eradication was defined as absence of pathogen from culture of sample (obtained at the end of treatment) according to the original site of infection, as elsewhere described for bloodstream district, respiratory tract, urinary tract and skin and soft tissue [19-22].

Statistical analysis

Continuous variables were compared by the Mann-Whitney U test for non-normally distributed variables. Categorical variables were evaluated by using the chi-square or the two-

tailed Fisher exact test. Values were expressed as means ± IQR (continuous variables) or as percentages of the group from which they were derived (categorical variables). Two-tailed tests were used to determine statistical significance; a *P* value of <0.05 was considered significant. All statistical analyses were performed by using the IBM SPSS Statistics® program, version 20 (IBM Corp., Armonk, NY, USA).

RESULTS

During the study period, 57 bacterial strains with a MDR or XDR profile were isolated from 45 patients. Nine patients were included twice in the analysis and one three times, fulfilling the above-mentioned inclusion criteria. No bacteria with a PDR profile was isolated.

The demographic characteristics and most salient clinical features of the study population are reported in the Table 1. The mean (± standard deviation, SD) age was 61.5 years (±10.43 SD) and 43 patients (75.5%) were male. The median score of the ACCI was 4 (IQR 1.75 – 6.00) and 34 patients (59.64%) had had a solid organ transplant. In most cases an immunosuppressive therapy (32 out of 57, 56.14%) or a corticosteroids treatment (36 out of 57, 63.15%) had been given during hospitalization.

Most isolates (34 out of 57, 59.6%) were related to patients admitted in the Nephrology ward; the most common MDR pathogen was *Escherichia coli* (34 out of 57, 59.6%), and the most frequent infection site was the urinary tract (31 out of 57, 54.3%).

In all 57 cases, a definitive antibiotic therapy had been prescribed following the AST and reported in the clinical record. According to the aforementioned selected appropriateness criteria, the therapies resulted appropriate in 22 out of 57 cases (39%) and inappropriate in 35 out of 57 (61%). The baseline characteristics of the patients belonging to the two groups are listed in Table 1. No significant difference has been observed between the two groups except for the presence of solid organ transplants (p=0.032) and for the admission in the Nephrology ward (p=0.028), which resulted to be more frequent in the appropriate therapy group.

The causes of inappropriate definitive antimicrobial prescribing are listed in Figure 1. Most therapies resulted to be not proper on the basis of a not optimal dosing regimen (21 of 35 cases, 60%), followed in order by: delayed antibiotic administration (45.7%); *in vitro* inactivity of the chosen drug (34.2%); lack of antibiotic plan documented in the case note (34.2%); missed empirical-definitive therapy switch (34.2%); missed dose adjustment on renal function (11.4%). Meropenem was the antibiotic characterized by the most inappropriate use (13 out of 35 cases, 37.1%), followed by ceftazidime (5 out of 35 cases, 14.3%), teicoplanin (5 out of 35 cases, 14.3%) and colistin (5 out of 35 cases, 14.3%).

In Table 2 the main causes of improper antibiotics dosing are described and compared to the recommended dosing regimen [23, 24]. The most noteworthy administration strategy mistakes resulted to be: the too much long interval between time-dependent antibiotics doses (such as carbapenems, amoxicillin-clavulanate and ceftazidime); the lack of loading doses for teicoplanin and tigecycline, which are time-dependent antibiotic drugs with moderate to long post-antibiotic effect and the under-dosing of ciprofloxacin, piperacillin-tazobactam and gentamicin. In most of the cases treated with colistin (71%), the antibiotic had been inappropriately prescribed as monotherapy regimen, or under-dosed or without a loading dose. Moreover, in 6 out of 13 (46%) cases of infections due to MDR but non-Extended Spectrum Beta-lactamase (ESBL) producers Enterobacteriaceae, carbapenems had been inappropriately administrated instead of other active drugs.

In 24 out of 57 cases (42.1%), we found data about the post-therapy microbial specimens from the infected sites in the clinical records. Overall, the microbiological eradication efficacy was achieved in 12 cases (50%); the difference between the group receiving an appropriate antibiotic prescription (87%) as opposed to the group receiving inappropriate antibiotic prescribing (31%) is statistically significant (chi-square =6.750, p=0.027). There were no statistically significant differences in microbial eradication between appropriate and inappropriate therapy groups according to involved pathogens.

The average LOS in the group receiving an inappropriate therapy (29 days ±20.6 SD) was greater than the one in the group that received an appropriate therapy (22 days ±18 SD), but the difference was not statistically significant (p=0.101).

The proportion of 30-day re-admissions in the group receiving an inappropriate therapy (10 out of 35, 28%) was higher than the other group (2 out of 22. 9%) but the difference was not statistically significant (chi-square=3.084, p=0.101).

Of note, 25 infective episodes on 57 (43.8%), has been no treated with any empirical antibiotic therapy. Among the 32 empirical regimens, the most common were: a quinolone as monotherapy (5/32, 15.6%), third-generation cephalosporin

Table 1 - Baseline characteristics of the patients receiving appropriate antibiotic prescribing and patients receiving inappropriate antibiotic prescribing. *BAL: Brochoalveolar lavage; CVC: Central Venous Catheter; ESBL: Extendend Spectrum Beta-lactamase; MRSA: Methicillin Resistant Staphylococcus aureus; VRE: Vancomycin Resistant Enterococci.*

	Study population	*Appropriate therapy group (n=22)*	*Inappropriate therapy group (n=35)*	
Age (years, median, IQR)	61.53 (± 10.43 SD)	62.50 (51.75 – 70.00)	60 (53.00 – 68.00)	p=0,863
Sex (M/F)	43/14	16/6	27/8	p=0,706
Charlson Comorbidity Index (median, IQR)	4.00 (1.75 – 6.00)	3.00 (1.75 – 6.00)	4.00 (3.00 – 6.00)	p=0,294
Solid organ transplant (n, %)	34 (59.64)	17 (77,3)	17 (48.6)	p=0,032
Glucocorticoid therapy (n, %)	36 (63.15)	16 (72.7)	20 (57.1)	p=0,235
Immunosuppressive therapy (n, %)	32 (56.14)	15 (68.2)	17 (48.6)	p=0,146
Chemio- or radiotherapy (n, %)	0 (0)	0 (0)	0 (0)	p=1
CVC (n, %)	3 (5.2)	2 (9.1)	1 (2.9)	p=0,553
Artificial nutrition (n, %)	5 (8.7)	1 (4.5)	5 (14.3)	p=0,389
Dialytic therapy (n, %)	3 (13.6)	3 (13.6)	2 (5.7)	p=0,364
ICU admission before antibiotic therapy (n, %)	6 (10.5)	2 (9.1)	4 (11.4)	p=1
Ward of admission: (n, %)				
General Surgery	3 (5.2)	0 (0)	3 (8.5)	p=0.224
Maxillo-Facial Surgery	3 (5.2)	1 (4.5)	2 (5.7)	p=0.671
Vascular Surgery	17 (29.8)	4 (18.1)	13 (37.14)	p=0.109
Nephrology	34 (59.6)	17 (77.2)	17 (48.5)	p=0.028
Involved pathogens: (n, %)				
S. aureus (MRSA)	10 (17.5)	2 (9.1)	8 (22.8)	p=0.287
P. aeruginosa	7 (12.2)	1 (4.5)	6 (17.1)	p=0.230
Enteroccoccus spp. (VRE)	1 (1.7)	0 (0)	1 (2.9)	p=1
E. coli (ESBL producers)	34 (59.6)	13	21 (60)	p=0.582
K. pneumoniae	4 (7)	2 (9.1)	2 (5.7)	p=0.265
Other Enterobacteriacee	5 (8.7)	3 (13.6)	2 (5.7)	p=0.364
Acinetobacter spp.	4 (7)	0 (0)	4 (11.4)	p=0.151
Sites of infection: (n, %)				
Intraabdominal	1 (1.7)	0 (0)	1 (2.9)	p=1
Skin and soft tissue	9 (15.7)	1 (4.5)	8 (22.8)	p=0.065
Bloodstream	6 (10.5)	3 (13.6)	3 (8.5)	p=0.425
Urinary tract	31 (54.3)	9 (40.9)	22 (62.8)	p=0.172
Surgical site	9 (15.7)	3 (13.6)	6 (17.1)	p=0.516
Lungs	5 (8.7)	2 (9.1)	3 (8.5)	p=0.647
Liver and biliary tree	1 (1.7)	0 (0)	1 (2.9)	p=1
Specimen: (n, %)				
Blood	8 (14)	3 (13.6)	5 (14.2)	p=0.945
Urine	31 (54.3)	9 (40.9)	22 (62.8)	p=0.172
Tissue biopsy	18 (31.5)	3 (13.6)	11 (31.4)	p=0.128
BAL	1 (1.7)	0 (0)	1 (2.9)	p=1

1	Inappropriate dosing regimen	21/35	60%
2	Therapy started >24h from microbiological test results	16/35	45.7%
3	*in vitro* inactivity of the therapy	12/35	34.2%
4	Lack of antibiotic plan documented in the case notes	12/35	34.2%
5	No empirical-definitive therapy switch	7/35	20%
6	No renal dosing adjustment	4/35	11.4%

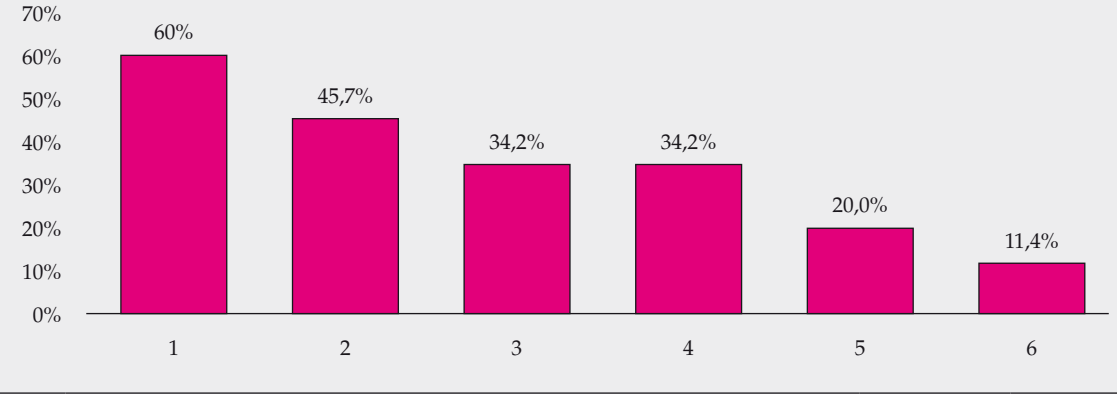

Figure 1 - Causes of improper user of antibiotics.

Table 2 - Main characteristics of the improper dosing regimen of antibiotics compared to the recommended dosing regimen.

Antibiotic drug	*Recommended dosing regimen* [23-24]	*Inappropriately administered dosing regimen*
Amoxicillin-clavulanate	1 g q8h	1g q12h
Ceftazidime	1 g q8h 2 g q8h (*serious infections*)	1-2g q12h
Ciprofloxacin	250-500 mg q12h 1 g extended release q24h (*UTI and pyelonephritis*) 400 mg ev q8h (*P. aeruginosa infections*)	250 mg q24h
Colistin	Never monotherapy use Dosing calculation as recommended by FDA and EMA Loading dose, maintenance doses after 12h	Monotherapy use Under-dosed No loading dose
Gentamicin	5.1 mg/kg q24h 7 mg/kg (*serious infections*)	Under-dosed for weight
Imipenem-cilastatin	0,5 mg q6h 1g q6-8h (*P. aeruginosa infections*)	0,5 mg q12h (*P. aeruginosa infections*)
Levofloxacin	750 mg q24h (*complicated UTI*)	250 mg q24h for complicated UTI
Meropenem	1 g q6h 2g q8h	1 g q12h
Piperacillin-tazobactam	3.375-4.5g q6-8h	2.25g q8h
Teicoplanin	6 mg/kg loading dose q12h X 3; 6 mg/kg q24h maintenance dose	No loading dose
Tigecycline	100 mg loading dose; 50 mg q12h maintenance dose	No loading dose

plus quinolone (3/32, 9.3%), third-generation cephalosporin plus other drugs (3/32, 9.3%), piperacillin-tazobactam (3/32, 9.3%), teicoplanin (3/32, 9.3%), cotrimoxazole (3/32, 9.3%).
A survival analysis was not performed because of the small sample size. Only one *exitus* was reported, in the group of patients receiving an inappropriate therapy.

DISCUSSION

In the hospital setting, the phenomenon of antibiotic resistance is set to become more relevant due to the high levels of antibiotic pressure; unfortunately, a high rate of patients receives an inappropriate or incorrect antimicrobial treatment [25]. This phenomenon is more marked in our country, where the levels of both antibiotic consumption and antimicrobial resistance are higher compared to other European countries and where the MDR pathogens are undergoing rapid diffusion [26]. Significant amounts of data support the link between antibiotic consumption and development of antibiotic resistance, as demonstrated by a recent meta-analysis, which also highlighted how a stronger link between these two variables is observed in southern Europe, prompting efforts aimed at reducing antibiotic consumption in this area [27]. Several studies also highlighted that the delayed appropriate antibiotic therapy is an important factor toward worse clinical outcomes of infections by MDR bacteria [28].
However, rates of inappropriateness are relevant across the entire world, although a comparison among different studies is not simple since criteria and settings significantly vary [29-32]. A universally accepted definition of appropriate definitive antibiotic therapy against MDR pathogens is still lacking in the literature. All the published studies aimed at identifying appropriateness criteria in antibiotic prescription have several limits: they were targeted on outpatient settings, they were developed to evaluate empiric and not definitive therapies or they were created as generic recommendation, making it impossible to precisely establish how many criteria an antibiotic therapy should satisfy in order to be considered "appropriate".
Based on the main criteria found in the literature, we have selected some criteria including *in vitro* and *in vivo* activity, adequate dosing regimen respectful of pharmacokinetics/pharmacodynamics parameters and renal function, adequate documentation of administration, switching from empiric to definitive regimen after antimicrobial tests [15-18]. On this basis, after retrospectively evaluating the quality of definitive antibiotic prescriptions across some selected non-ICU wards of a university hospital of southern Italy, we found that a high rate (61%) of therapies do not meet the criteria of appropriateness.
The main cause of inappropriateness was the lack of adherence to the recommended dosing regimen as for the time-dependence and concentration-dependence aspects and as for the clinical indications. The third cause of inappropriateness resulted to be the choice of a therapy which was not *in vitro* active against the involved pathogens; this means that, despite a regular written susceptibility test report found by the investigator in the patient's clinical file, it has been administrated an antibiotic therapy for which the bacteria was resistant on the basis of the AST report. This could be explained by a not correct interpretation of the AST result, highlighting the necessity of systematic infectious disease consultation. This can also explain why the microbiological cure rate in the patients that received inappropriate therapy was lower when compared to appropriate therapy group, even if in the appropriate group more broad-spectrum antibiotics were administrated. It must be underlined that all the definitive antibiotic therapies had been prescribed during the hospitalization by the ward's physicians and not by an infectious diseases specialist.
In our study, meropenem was found to be linked with the highest rate of improper use, being often under-dosed or given at improper time intervals. The reason why meropenem was the most common improperly prescribed antibiotic is still unclear, but it might be related to the high efficacy of this broad-spectrum carbapenem in surgical patients with intrabdominal sepsis, that leads surgeons to consider it "the best drug" in the treatment of every kind of post-surgical infection, even when its use is not necessary. Moreover, the frequent under-dosing of meropenem we observed (*i.e.*, 1 g every 12 hours instead of 1 g every 8 hours or 2 g every 8

hours or 1 g every 6 hours for severe infections, as recommended) could be explained with a not satisfactory knowledge of pharmacokinetics/pharmacodynamics of the antibiotics [23, 24]. In addition, our study highlighted the unjustified use of the whole carbapenem class for treating the infections caused by non-ESBL producing Enterobacteriaceae, instead of other classes of efficacious antibiotics such as beta-lactams; this practice could be at very high risk of selecting carbapenemase-producing Gram-negative strains [33]. Another improperly used antibiotic has been colistin; this appears to be particularly alarming, since colistin is one of the last few useful drugs for XDR Gram-negative infections and its use as monotherapy (until new clarifications emerge from the results of ongoing international trials), as well as the improper dose regimen without loading dose, are still strongly discouraged by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), in order to avoid the risk of selecting colistin-resistant nosocomial bacteria [24]. In fact, the superiority of the use of colistin in combination regimen versus stand-alone therapy against MDR bacteria is still controversial and it is currently under investigation in a multicentre controlled trial for the first time [34]. Nonetheless, the current evidence strongly suggests caution with monotherapy, underlining the benefits of different combination regimen [35].

Concerning the route of administration, we noticed that the intravenous route was the most common way adopted by the colleagues to treat urinary tract infection (16 times on 25 urinary tract infections, 64%). Since in all of these cases a carbapenem was administered, although the intravenous route was obviously correct, the main issue remains the choice of the drug since, in many cases, the involved bacteria were susceptible to first-line oral drugs, such as oral quinolones. The use of a first-line oral drug would have avoided both the overuse of carbapenems and the excessive use of the intravenous route of administration.

Moreover, we observed that in 5 cases on 57 (8.7%), the intramuscular administration route was adopted to administrate parenteral antibiotic drugs, especially colistin (2 cases on 5) and teicoplanin (2 cases on 5). The intramuscular administration route should be considered, in most of cases, inappropriate by itself for treating systemic infection or for administering drugs such as colistin [36].

The impact of antibiotic prescription inappropriateness on microbiological outcome of MDR infection is statistically significant; it is disturbing to note that today in less than half of cases the microbiological documentation of cultural samples after definitive therapy is completely missing in the clinical records.

In addition, the exposure to an inappropriate definitive antibiotic therapy seems to be associated with an increase of the average LOS and of the 30-day readmission, although these associations did not reach a statistically significant difference, perhaps due to the small sample size, which also hindered an adequate survival analysis. Further studies – even prospective and extended on larger populations – are required to better investigate the impact of an inappropriate definitive antibiotic therapy on the length of stay, on the 30-day readmission and on the mortality, as well as on the consequences of antibiotic inappropriateness on healthcare costs. Notably, the selected empirical regimens often included narrow-spectrum drugs, not adhering to the principles of "start smart and then focus", calling for a more aggressive and broader therapy followed by a de-escalation whenever possible on the basis of the AST results [37]. Moreover, the role of the infectious disease (ID) specialist as consultant in our hospital is not still standardized. This is a major issue in our facility, since it has been largely discussed that an infectious disease specialist's intervention significantly ameliorates the appropriateness both in the diagnosis and in the treatment of infections [38-41].

In summary, despite its limitations, namely its retrospective nature and the small sample size, our study provides a clear picture of most sub-optimal definitive antibiotic treatment of infections by MDR bacteria in a hospital setting in Southern Italy, where the spread of MDR bacteria is alarming and the ASP is lacking [42]. The results highlight the importance of implementing antibiotic appropriateness educational programmes at our facility, as well as hospital guidelines on antibiotic administration and antimicrobial stewardship programmes [43].

Conflict of interest
None

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