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Appropriate Utilization of Restricted Antibiotics in a General Hospital of a Perfecture Area in Greece

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Abstract: *Introduction*: Over-consumption of antibiotics has led to increased bacterial resistance and higher prevalence of hospital -acquired infections, resulting in rising treatment costs and prolonged length of hospital stay. The purpose of the study was to correlate the use of restricted antibiotics with recommended diagnosis and cost.

Material and Methods: All restricted antibiotics that were administered in a 240-bed general hospital in a semi-urban area within a year were recorded. The reason for administering each such antibiotic during the first three months of the study was also recorded. PASW 18 (SPSS Inc.) was used for the statistical analysis; a variable was considered statistically significant when statistical significance was p= 0.05.

Results: 1118 patients were registered, of which 35,05% were employees, insured with IKA, 33,05% were farmers and covered by OGA and 31,9% were insured in other Social Insurance Funds or uninsured. The most commonly administered antibiotic combination was that of piperacillin/tazobactam, which was mainly used in the Internal Medicine Dept. of the Hospital. The most commonly used restricted antibiotic, administered after an antibiogram, was the combination of piperacillin/tazobactam (n= 13), mainly prescribed for respiratory infection. One third of the recorded restricted antibiotics were administered before an antibiogram had been taken for fever of unknown origin (n= 128).

Conclusions: Rational use of restricted antibiotics is an important component of public health policies aiming at reducing hospital-acquired infections. Hospitalization costs rise when restricted antibiotics are used, and the possibility for the development of resistant bacteria increases.

Keywords: Antibiotic consumption, antibiotics, antimicrobial resistance, chemoprophylaxis, cost, under restriction antibiotics.

INTRODUCTION

Irrational over-consumption of antibiotics has led to the development of antibiotic-resistant bacteria that can replace the normal microbial fauna [1, 2]. Microbial resistance is an important public health issue, since it can restrict the menu of antibiotics available to the physician, it can increase patient length of stay, and can accordingly increase treatment costs and mortality rates [3]. The plethora of antibiotic drugs since the 1980s has also led to the irrational use and misuse of those valuable drugs [4, 5].

Since 2003, Greece is continuously first among the other European countries in antibiotic consumption in community and hospital level.

According to the European Surveillance of Antimicrobial Consumption (ESAC), Greece is first in Europe especially in community antibiotic use with a graduated increase from 25.06 DID in 1997 to 34.73 DID in 2005 (DID: Daily Defined Dose per 1000 Inhabitants per Day) [6].

Antimicrobials are very often prescribed for viral conditions or diseases for which antibiotics are not indicated, or are administered in incorrect dosages deviated from the international prescribing guidelines. It is also common the incorrect choice of an antibiotic used empirically, which is not in agreement with the results of cultures and antibio-gramme.

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The irrational use of antimicrobial agents especially those of broad spectrum, contributes significantly to the continuous increase of antimicrobial resistance with many consequences, as raise of hospital infection caused by multi resistant micro organisms, increase of morbidity and mortality, length of hospital stay, and financial burden for the Health Care Systems [7].

Greek epidemiological data showed that the prevalence of multi-drug resistant bacteria is 30-60%, which calls for immediate action. It has also been noted that treatment costs are five times higher on average than the respective costs for ordinary infections, and that 10% of all patients suffer from hospital-acquired infections. It has been estimated that treatment of patients with nosocomial infections can be twice as long compared to treatment of patients with ordinary infections [8-10].

According to the Committee of Antimicrobial Surveillance, in depts. of surgery, internal medicine depts. and ICUs of Greek hospitals, gram negative bacteria have been isolated (Klebsiella spp., Acinetobacter spp. και Pseudomonas spp.), which are highly resistant to carbapenems and β- lactamases, whereas pneumonia due to Klebsiella is resistant to carbapenems and aminoglycosides (excluding gentamycin). P. Aeruginosa and A. Baumannii have been shown to have a combined resistance to carbapenems, aminoglycosides and quinolones. But increased bacterial resistance is by no means a Greek phenomenon [11, 12]. It has been documented in other European countries, the United States, in Sub-Saharan Africa and Southeast Asia. Thus, the Center for Disease Control and Prevention (CDC) had to launch surveillance mechanisms in order to curb this alarming situation [13-15]. In other words it is crucial that a framework of rules and guidelines regarding rational use of antibiotics be created. Although the antibiotics used within a hospital are by and large just a fraction of those consumed in the community, nevertheless hospital-administered antibiotics are more advanced and modern, and they have been shown to play a major role in creating resistant bacteria, which in turn constitute a very serious public health problem.

In Greece, policies aiming at monitoring antibiotics use and resistance have been implemented, mainly by incorporating continuous data collection, information provision, issuing guidelines concerning rational use of antibiotics and also assessing compliance to them. In 2000 the National Committee of Nosocomial Infections published a manual about antimicrobial protection of hospitalized patients. Those guidelines were updated in 2007 by the Scientific Committee of Nosocomial Infections and the manual was distributed to clinical physicians all over the country. A normative guideline put 3rd generation cephalosporins and quinolones under restriction, but the exceptions accompanying quinolones have given room for increased use even in the community, something that apparently has contributed to the high resistance rates [16-18]. Another interpretation of the increased prescription of advanced antibiotics might be a common trend in Greek hospitals, i.e. some physicians prescribe very soon and too easy those advanced antibiotics in order to shorten the duration of the treatment, which has also led to the development of resistant bacteria [10, 19, 20].

According to the Ministry of Health guidelines, the prescription process of restricted antibiotics and their correct use have been clearly defined since 2002. Prescribing a restricted antibiotic presupposes an antibiogram in order to justify the selection of a specific antibiotic. If no antibiogram is carried out, then the reasons for this should be reported in detail on a special form. The form (in four copies) also includes detailed data about the patient and his/her condition. An important part of this form is about the reasoning for the prescription of the specific antibiotic, daily dosage and treatment duration expectancy. The prescription has to be signed by the attendant doctors, and then it has to be checked and approved by the hospital's Nosocomial Infections Committee and the hospital's chief pharmacist. A copy of every prescription of restricted antibiotics is sent every three months to the (Greek) National Organization for Medicines (EOF).

The aim of the present study was to record the use of advanced antibiotics in a medium-sized Greek hospital and to correlate their administration with cost and reasons for prescription.

MATERIALS AND METHODS

Population Study

This study was part of a coordinated attempt, launched by the hospital's Hospital Infections Committee, to curb the prescription of restricted antibiotics. We retrospectively collected, on the basis of hospital data, consumption rates of all advanced antibiotics prescribed in a 220-bed hospital during 2009. The hospital has an electronic prescription system of restricted antibiotics, and also makes use of special prescription forms. Based on the medical records of the patients and the special forms, we recorded data of all patients who had been administered those antibiotics during the first three months of 2009. Quantities (number of packs) of each patent antibiotic and current cost were also recorded. Demographic data, such as gender, treating Hospital Unit, hospitalization days and Social Insurance Fund were also recorded. Patent antibiotics were classified according to active ingredient (or ingredients, if more than one). Overall quantities (packs) and costs for each active ingredient and hospital sector were calculated. Finally, the five more expensive advanced antibiotics were further examined.

Research Ethics

Anonymity of patients and prescribing physicians was thoroughly observed. The research protocol had been approved by the scientific committee of the hospital and the whole research was carried out under the supervision of a Hospital Infections Committee member.

Statistical Analysis

The PASW 18 (SPSS Inc.) software was used for the statistical analysis; statistical significance level was set to p=0.05. Overall annual antibiotics consumption for each department was calculated. Average number of medicines for each patient and for each hospital admission was also calculated, as was average cost per patient and per admission during the three-month period. For comparison among males and females, the x^2 test was used; statistically significant differences were the cell count values when adjusted standardized means were higher than 2 (in absolute value).

RESULTS

Demographic Data

All patients who were prescribed restricted antibiotics over 2009 were recorded (n=1118). Of them, 57,96% (n=648) were men and 41,94% (n=469) women. Average hospitalization days were higher for Intensive Care Unit, the Pathology Sector and the Orthopedic Sector. Main Social Insurance Fund was IKA, which insures employees of the private sector, (35,05%, n=392), followed by OGA, which insures farmers and provides basic coverage to uninsureds, (33,05%, n=369), OPAD, which insures public servants (10,9%, n=122), and other funds ((17,25%, n=193), whereas a 3,75% (n=42) were without any coverage.

Antibiotics Consumption in Relation with Cost

According to our results, the higher rates of antibiotic consumption in the hospital come from the Internal Medicine Dept., the Intensive Care Unit, and the Urology Dept. On the other hand, local Health Centres, the Thalassaemia Unit, the Otorhinolaryngology Dept., and the Dialysis Unit feature the lowest consumption rates. Overall antibiotics cost follows consumption rates The Orthopedics Dept., features higher antibiotics costs compared to the rest of the Surgical Depts. (Table **1**), despite it having a lower consumption rate. Annual expenditure was 99,599 €, at the Internal Medicine Dept. €, 89, 444 € at the Intensive Care Unit and 38,019€ at the Urology Dept. The average price for each medicine in relation to the overall consumption was 15 €.

Antibiotics in Relation to Cost

The most commonly prescribed antibiotic was the piperacillin/tazobactam combination, followed by ciprofloxacin and ceftriaxone. The piperacillin/tazobactam combination, ciprofloxacin, and teicoplanin displayed the higher costs. The highest quantity of the piperacillin/tazobactam combination was prescribed in the Internal Medicine Dept. (2,560 packs), followed by the Urology Dept. (1,129 packs), and the Intensive Care Unit (594 packs). The highest quantity of ciprofloxacin was also prescribed in the Internal Medicine Dept. (1,665 packs), followed by the Urology Dept. (921 packs), and the Orthopedics Dept. (359 packs) (Table **2**).

Cost in Relation to Hospital Stay

Costs were correlated with hospital stay and average quantity of drugs per hospitalization during the first 3 months of 2009. The Intensive Care Unit features by far the highest average number of drugs per hospitalization, (120.90), followed by the Orthopedics Dept. (20.05) and the General Surgery Dept. (18.96). The Dialysis Unit and the Otolaryngology Dept. show the lowest average number of medicines administered per hospitalization. Costs run a different course, thus the ICU and the Orthopedics Dept. have a higher average cost per hospitalization day (1,902.65 € and 706.14 € respectively), followed by the Ob/Gyn Dept. follows at317.25 €, the Internal Medicine Dept. at 260.16 €

Table 1. Total costs of formulations per department and quantity in 2009.

Department	Quantity (PACKS)	Cost (€)	Cost Per Pack (€)
Internal Medicine Dept.	6,809	99,599.32	14.63
ICU	4,069	89,444.49	21.98
Urology Dept.	2,868	38,019.05	13.26
Orthopaedics Dept.	939	24,631.86	26.23
Dept. of Surgery	1,911	24,022.91	12.57
Gynaecology-Obstetrics Dept.	601	13,331.85	22.18
Dialysis Unit	149	4,389.23	29.46
Cardiology Dept.	153	3,497.76	22.86
Pediatrics Dept.	415	2,673.31	6.44
Otorhinolaryngology Dept.	104	1,668.10	16.04
Ophthalmology Dept.	213	1,419.24	6.66
Thalassaemia Unit	2	665.34	332.67
Out-patient Clinics	50	219.24	4.38
Out-patients	134	139.18	1.04
Loutraki Health Centre	4	26.29	6.57
Xylokastro Health Centre	2	13.15	6.58
Goura Health Centre	2	13.15	6.58
Total	18,425	303,773.46	16.49

Table 2. Classification of advanced antibiotics according to overall costs (2009).

Antibiotic	Quantity (Packs)	Cost (€)	Cost Per Pack (€)
Piperacillin/tazobactam	4,741	62,075.97	13.09
Ciprofloxacin	3,732	55,164.23	14.78
Teicoplanin	684	30,002.57	43.86
Amphotericin	155	23,127.55	149.21
Cefepime	1,825	21,721.97	11.90
Meropenem	810	20,968.96	25.89
Imipenem/Cilastatin	1,417	18,549.87	13.09
Ceftriaxone	1,874	13,624.60	7.27
Levofloxacin	287	10,007.47	34.87
Immunoglobulin	29	9,647.38	332.67
Daptomycin	110	8,689.80	79.00
Moxifloxacin	234	7,736.03	33.06
Vancomycin	885	7,413.62	8.38
Ceftadidime	1,089	6,231.79	5.72
Linezolide	96	4,998.63	52.07
Acyclovir	274	1,772.86	6.47
Tigecyclin	20	938.76	46.94
Ertapenem	15	635.11	42.34
Monobactam	45	416.43	9.25
Norfloxacin	103	49.86	0.48
Total	18,425	303,773.46	16.49

and the Dialysis Unit at 237.36 €. The lowest costs per hospitalization day were recorded at the Out-patients department (22.07 €), followed by the Otolaryngology Dept. (60.80 €) and the Ophthalmology Dept. (63.18 €) (Table **3**).

Antibiotics Consumption According to Demographics and Disease Etiology

A statistically significant difference regarding antibiotics consumption among males and females was found [χ^2 (16) = 38.49, p< 0.001]. In general, males were administered

Table 3. Hospital Days in patients with restricted antibiotics use and cost.

Clinic	Number of Hospital Days *	Average Number of Per Pack/Hospital Day*	Average Cost/Hospital Day * (€)
ICU	10	120,90	1902,65
Orthopaedics Dept.	19	20,05	706,14
Gynaecology-Obstetrics Dept.	8	12,50	317,25
Internal Medicine Dept.	99	17,44	260,16
Dialysis Unit	7	6,57	237,36
Urology Dept.	40	15,10	186,22
Dept. of Surgery	23	18,96	167,45
Cardiology Dept.	2	11,00	94,11
Pediatrics Dept.	6	14,17	93,12
Ophthalmology Dept.	6	9,17	63,18
Otorhinolaryngology Dept.	2	8,50	60,80
Out-patients	3	20,00	22,07
Total	225	21,08	333,40

*24 Hospital Day Care.

Table 4. Quantity and percentage of advanced antibiotics according to gender.

Antibiotic	Males		Females		Total
	Number	Percentage (%)	Number	Percentage (%)	Number
Cefepime	16	69.6%	7	30.4%	23
Ceftadidime	6	46.2%	7	53.8%	13
Ceftriaxone	20	76.9%	6	23.1%	26
Ciprofloxacin	26	52.0%	24	48.0%	50
Daptomycin	***9***	***100.0%***	***0***	***0.0%***	***9***
Ertapenem	2	100.0%	0	0.0%	2
Imipenem/Cilastatin	***20***	***95.2%***	***1***	***4.8%***	***21***
Levofloxacin	4	44.4%	5	55.6%	9
Linezolide	3	100.0%	0	0.0%	3
Meropenem	6	46.2%	7	53.8%	13
Moxifloxacin	4	57.1%	3	42.9%	7
Norfloxacin	1	100.0%	0	0.0%	1
Piperacillin/tazobactam	***46***	***68.7%***	***21***	***31.3%***	***67***
Teicoplanin	14	51.9%	13	48.1%	27
Ticarcillin/Clavulanic Acic	***17***	***48.6%***	***18***	***51.4%***	***35***
Vancomycin	6	100.0%	0	0.0%	6
Cefotaxime	4	44.4%	5	55.6%	9
Total	**204**	**63.6%**	**117**	**36.4%**	**321**

Statistically significant differences calculated by adjusted standardized residuals are in italics and highlighted.

advanced antibiotics almost twice as often as females; daptomycin was prescribed exclusively for males, and imipeneme/cilastatin was administered to males 95% of the time (Table **4**). On the other hand, the combination ticarcillin/clavulanic acid was more commonly administered to females (51.4%) than males (48.6%), a very significant difference since males are prescribed advanced antibiotics twice as often as females. Regarding quantity of advanced antibiotics according to reasons for prescription during the first three months of 2009, it was found that one third of antibiotics (128 formulations) were administered for fever before the antibiogram was taken, with ticarcillin/clavulanic acid (n= 29) being the most common, followed by piperacillin/tazobactam (n= 27) and ciprofloxacin (n= 13).

Respiratory tract infections were prescribed advanced antibiotics after an antibiogram was taken (34 formulations). The most common antibiotic of this category was piperacillin/tazobactam (n=13). Piperacillin/tazobactam (n=10), was also administered for postoperative uraemia (32 formulations), ciprofloxacin (n=10) was administered for fever due to foot ulcers (25 formulations), meropeneme (n=10) was administered for fever due to central-line associated infection (23 formulations), teicoplanin (n= 6) was administered for central line sepsis (6 formulations), and imipeneme/cilastatin (n= 4) was administered for pneumonia (12 formulations); imipeneme/cilastatin (n= 6) was also administered for continuing treatment of septicemia (12 formulations).

Daptomycin was administered to all cases (n= 5) of unsuccessful treatment of central line infection after an antibiogram had been taken. The same antibiotic was administered to 45% of the cases of respiratory tract infections due to chronic renal failure and 100% of the cases (n= 5) of soft tissue inflammation following external osteosynthesis. Finally, piperacillin/tazobactam (n=3) and teicoplanin (n=2) were administered for severe sepsis unsuccessfully treated and after an antibiogram had been taken.

DISCUSSION

Because of a worldwide effort to control microbial resistance, the development of programmes concerning the rational use of antibiotics is necessary. Another reason for such programmes was the need to limit the increasing costs [21, 22]. Published data worldwide more often than not come from individual hospitals, not from a large-scale multicentre study that makes use of an original control programme. Studies from other countries have shown equally alarming situations because of restricted antibiotics, that is more severe microbial resistance rates [23-25].

Amongst recorded patients, a large concentration of patients was insured with OGA and with IKA. This confirms that the hospital under study covers a largely farming population. This study does not correlate antibiotics consumption with social insurance fund, as this was not included as an endpoint in the study protocol.

The highest rates of restricted antibiotics were administered in the Internal Medicine Dept. and the ICU. The high number of hospitalized patients was the main reason at the Internal Medicine Dept.; in the ICU, special treatments, the complexity of the patients' conditions, and the resistant bacteria are reported as the main reasons for high rates of restricted antibiotics administration. At the Orthopaedics Dept., fewer formulations of restricted antibiotics were used, but their cost was almost twice as high as the antibiotics used in the Dept of Surgery.

The piperacillin/tazobactam combination is the most commonly used antibiotic and the most expensive one, as well. It was prescribed most often in the Internal Medicine Dept., followed by the ICU. Ciprofloxacin was the next most expensive antibiotic, mainly used in the Urology Dept. Similar international studies are in agreement with the administration frequencies of our study, but those frequencies do not always follow a (documented or not) diagnosis [14, 22, 25].

The overall cost of restricted antibiotics for this specific hospital amounts to 304,000 € annually. The average cost of restricted antibiotics per hospitalization day is calculated at 333.40 €. Given that, according to the Greek Ministry of Health, the standard per diem hospitalization cost is 240 € [26], the prescription of restricted antibiotics appears to be seriously increasing this cost. The combined efforts of health professionals during the last two decades have a twofold purpose: to reduce costs and to curb microbial resistance rates by prescribing as few restricted antibiotics as possible [27, 28]. The ICU topped all other departments at the correlation of costs to total number of hospitalizations per patient.

The tikarcillin/clavulanic acid combination, which belongs to the antipseudomonal penicillins, was administered to infections caused by Pseudomonas aeruginosa, and infections caused by Proteus and serratia. This treatment has an advantage, especially when combined with an aminoglycoside, in that it can prevent the fast development of resistance in pseudomonas. But since antipseudomonal penicillins are the treatment of choice for fever in leukopenic patients, their wide-scale administration to fever of unknown etiology cannot be justified. According to the guidelines, the initial empirical treatment of febrile neutropenia may include antipseudomonal beta-lactam or carbapenem for low-risk patients (MASCC score- Multinational Association for Supportive Care in Cancer) and also antipseudomonal beta-lactam with amicasin. On the other hand, the combination of piperacillin/tazobactam is mainly administered for hospital-acquired infections (urinary tract infections, pneumonia, and empirical treatment of fever in neutropenic patients).

Ciprofloxacin (quinolone) may also be prescribed for Pseudomonas, and constitutes the empirical treatment of higher and lower urinal tract infections. It is not among the first choice antibiotics against febrile neutropenia, but it can be prescribed for prophylaxis. Even if the hospital is considered to be colonized by Pseudomonas or other bacteria, an antibiogram has to be taken before the administration of the above mentioned antibiotics for fever of unknown etiology, otherwise the treatment cannot be justified in accordance to the guidelines [3, 9, 12, 15, 29]. It was also found that 140 out-patients were prescribed ciprofloxacin (per os) which is in sharp contrast with the guidelines; on the other hand, as far as hospitalized patients were concerned, the higher administration rates came from the Internal Medicine Dept., the Urology Dept., and the Orthopedics Dept. International studies have shown that the prescription of antibiotics to out-patients is limited, and is avoided as much as possible. It is all too clear that restricted antibiotics cannot be the treatment of choice. This tendency is stronger in countries such as France and Germany, but in Turkey high rates of quinolone consumption in the community have been recorded [13, 22, 29]. According to an older study that took place in Greek primary care settings, there was a high rate of antibiotics prescription, mainly the amoxicillin/clavulanic acid combination, 2nd generation cephalosporins and clarithromycin[27]. But more recent research shows that there has been a decline in antibiotics prescription in the community, and the most common are macrolides (mainly clarithromycin) for respiratory infections, quinolones for urinary tract infections and the amoxicillin/ clavulanic acid combination [30-32].

The wide administration of piperacillin/tazobactam after an antibiogram is also justified by its indications, (recommended for nosocomial infections (urinary tract infections, surgical infections, pneumonias, and empirical treatment of febrile infections), and especially for infections caused by piperacillin-resistant bacteria (Klebsiella sp., Enterobacter cloacae, Proteus sp., Providencia sp.).

Meropenem, which belongs to the carbapenems, is mainly used against gram negative bacteria. In our study, it was found that it was administered to patients with fever due to central line infection. According to the guidelines for central line infections, in Greece, where there is a high incidence of MRSA, vancomycin is the suitable antibiotic. But if the patient should be empirically treated for gram-negative or vancomycin-resistant bacteria, as is usually the case in the Dialysis Unit, third or fourth generation cephalosporin or carbapenem can be administere [10,12, 33, 34]. Teicoplanin, and vancomycin, belong to the glycopeptides, which are bactericidal antibiotics, effective against Staphylococcus aureus and Coagulase-negative staphylococci, including bacteria resistant to antistaphylococcal penicillins and cephalosporins. In contrast with vancomycin, teicoplanin is not by definition nephrotoxic. An important indication for teicoplanin is bacteremia with accompanying sepsis. Finally, imipeneme/silastatin also belongs to carbapenems and is mainly administered for severe bacteremia - septicemia caused by multiresistant nosocomial bacteria.

Daptomycin is a relatively new antibiotic which belongs to lipopeptides, effective against gram-positive bacteria and especially against resistant staphylococci, streptococci and enterococci [34, 35]. It is parenterally administered for severe skin and soft tissue infections and infective endocarditis, but it is not effective against pneumonias; nevertheless, it was administered to 45% of the cases of respiratory tract infections with accompanying chronic renal failure. Since this antibiotic can be prescribed for infections caused by MRSA/VRSA, VRE and resistant pneumococci, one could see the reason for the above-mentioned percentage, but its nephrotoxicity dismisses that thought immediately.

CONCLUSION

The antibiotic resistance remained a complicated problem in hospitals with serious consequences for the public health, included the increased morbidity and mortality and the financial burden for the health care systems.

The treatment costs of hospital-acquired infections are at least five times higher than the usual costs, excluding the cost of pharmaceutical treatment and collateral consequences. Consumption of advanced antibiotics can sharply increase that cost and can also contribute to the development of multiresistant bacteria. The effective control of microbial resistance presupposes the implementation of specific public health policies, such as monitoring of epidemiological data, e activation of empirical treatment strategies, and implementation of infection control measures.

Any effort by the Greek Centre for Disease Control and Prevention (KEELPNO), the Antimicrobial Resistance Department (Central Public Health Laboratory, CPHL) and the National School of Public Health (ESDY), with the collaboration of the European Antimicrobial Resistance Surveillance System (EARSS), should be reinforced in terms of legislative and political support.

Keeping the medical/nursing staff constantly updated and applying strict rules on the prescription process can contribute to the containment of irrational restricted antibiotics consumption. The ulterior purpose should be not only to lower the hospitalization costs, but to reduce substantially the microbial resistance rates in the hospitals.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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