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Letter to the Editor

Antimicrobial consumption in Albanian reference teaching hospital (2012-2015)

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Dear Editor,

Human antibiotic consumption has been increasing globally with the greatest increase being observed in low and middle income countries (LMICs). Despite an estimated 80% of use being attributed to the community, where both prescribed and over the counter (OTC) use are common, especially in LMICs, the volume of patients with serious medical conditions in hospitals and the resultant high density of antibiotic use in such institutions, makes hospital antibiotic use disproportionately important [1]. A recent publication from Albania showed the combined community and hospital consumption in Albania for 2011-2012 [2]. However, in a recent World Health Organization (WHO) European Region (WHO/Euro) press release no data from Albania was reported [3]. LMICs generally lack resources for surveillance of antimicrobial consumption rendering any antimicrobial stewardship initiatives more difficult.

We assessed the feasibility and reliability of hospital antimicrobial distribution data between the years 2012-2015 at the University Hospital Centre 'Mother Teresa' of Tirana (QSUT), which is the major Hospital Centre in Albania. This is the only tertiary-care referral centre for acute and critical patients in Albania, a hospital with over 1500 beds, of which, more than 100 are classified as intensive-care.

Data is reported using the 2016 WHO Anatomical Therapeutic Chemical (ATC) Classification System and defined daily dose (DDD) methodology, the gold standard for international drug utilization research studies. Data for ATC codes A07AA (Intestinal Antibiotics), J01 (Antibacterials for Systemic Use), J02 (Antimycotics for Systemic Use), J04 (Antimycobacterials), J05 (Antiviral agents) and P01AB (nitroimidazole derivatives) were recorded by ATC code and route of administration.

Consumption data were obtained from the QSUT central distribution pharmacy. In addition, data on occupied beds (OBD) and admissions were also collected from Hospital administration. Total Albanian population could not be used as a denominator because QSUT does not represent 100% of hospital beds in Albania.

For the different drug classes presenting a simple comparison of the slopes of regression lines would have been misleading [4]. In order to compare the change in each class over time, the slopes (trends) were scaled with their intercepts (baselines) to produce the mean annual change using the following formula which was adapted from Ansari and colleagues:

$\% \Delta \text{ Variable} = (\text{slope}/\text{intercept}) \times 100$

Consequently, for each class, the mean annual change was estimated with 95% confidence intervals (CIs). Changes were considered significant if the 95% CIs for the percentage difference did not cross zero.

Results

The overall antimicrobial consumption at QSUT, was lowest in 2013 (48.3 DDD/100OBD) and highest in 2015 (67.0 DDD/100OBD). The data using admissions as denominator showed a very similar pattern [the lowest in 2013 (289.3 DDD/100 Admissions) and the highest in 2015 (390.4 DDD/100 Admissions)]. It was therefore decided to show data only based on DDD/100OBD.

Table 1. Trends in antibiotic use by ATC category in defined-daily-doses (DDD) /100 occupied-bed-days (100OD) / year.

ATC-CLASS	DDD/100 OD/ respective year				Standard Deviation	95%|CI|	R^2	slope	intercept	% Δ Variable = [slope/intercept]×100	% Δ LOWER 95% CI	% Δ HIGHER 95% CI	Significance
	2012	2013	2014	2015									
J01D-Other Beta Lactams	19.34	21.89	26.67	34.01	6.45	6.32	0.95	4.88	13.28	36.76	30.44	43.08	Yes (Increase)
J01C-Penicillins	15.72	11.62	7.85	8.26	3.65	3.58	0.85	-2.61	17.40	-15.02	-18.60	-11.45	Yes (Decrease)
J01M-Quinolones	9.01	5.12	6.16	8.68	1.90	1.87	0.00	0.00	7.23	0.05	-1.81	1.92	No
J01G-Aminoglycosides	6.96	7.12	6.52	6.80	0.25	0.25	0.29	-0.11	7.12	-1.50	-1.74	-1.25	-
J01X-Other Antibacterials	3.26	0.68	5.95	7.36	2.96	2.90	0.59	1.76	-0.09	-2059.83	-2062.74	-2056.93	-
J01E-Sulfonamides and trim	1.38	1.50	0.92	0.15	0.61	0.60	0.81	-0.43	2.05	-20.75	-21.35	-20.15	-
J01B-Amphenicols	0.15	0.08	0.08	0.96	0.04	0.42	0.84	-0.04	-0.29	13.33	12.91	13.76	-
J01A-Tetracyclines	0.23	0.07	0.22	0.48	0.17	0.17	0.47	0.09	0.02	401.47	401.30	401.63	-
J01F-Macrolides, Lincosamides and Streptogramins	0.01	0.20	0.64	0.00	0.30	0.30	0.03	0.04	0.11	39.01	38.72	39.31	-

Table 2. Proportions by route of administration by ATC group (and by year for macrolides and fluoroquinolones).

ATC-Group	Oral	Parenteral	Total DDD
J01A-Tetracyclines	**69.3%**	**30.7%**	**6558.5**
J01B-Amphenicols	**0.0%**	**100.0%**	**1332.3**
J01C-Penicllins	**0.0%**	**100.0%**	**187374.6**
J01D-Other beta-lactams	**4.5%**	**95.5%**	**445515.8**
J01E-Sulphonamides & trimethoprim	**99.0%**	**1.0%**	**17354.5**
J01F-Macrolides and lincosamides	**52.8%**	**47.2%**	**5930.5**
2012	*100.0%*	*0.0%*	*25.0*
2013	*0.0%*	*100.0%*	*848.0*
2014	*55.0%*	*45.0%*	*2892.3*
2015	*71.6%*	*28.4%*	*2165.2*
J01G-Aminoglycosides	**0.0%**	**100.0%**	**118928.8**
J01M-Fluoroquinolones	**34.1%**	**65.9%**	**126159.9**
2012	*75.9%*	*24.1%*	*38312.1*
2013	*22.6%*	*77.4%*	*21212.0*
2014	*28.9%*	*71.1%*	*27665.0*
2015	*0.9%*	*99.1%*	*38970.8*
J01X-Other Antibacterials	**0.0%**	**100.0%**	**76436.2**
Overall	**8.9%**	**91.1%**	

Table 1 represents all the groups of antibacterials for systemic use (J01) at the third level of aggregation. Amongst the 4 most prescribed classes there is a significant increase in "other beta lactams" (J01D) [+36.8% (95% CI: 30.4%-43.1%)] and a significant decrease in "penicillins" (J01C) {-15.02% (95%CI: -18.0-11.4%)}.

With respect to route of administration an overwhelming proportion of parenteral therapy (> 90%) was observed for all antibacterials for systemic use (J01) except for sulphonamides and trimethoprim (J01E) almost entirely oral and tetracyclines with more than two-thirds of use were also oral. For macrolides (J01F) this varied drastically by year whilst fluoroquinolones changed from predominantly oral to almost entirely parenteral. Interestingly, no oral penicillin use was documented as shown in detail in Table 2.

Cefazolin was the second most frequently utilized drug in 2012 but became the most frequently prescribed during the next 3 years of the study period. Ampicillin was the highest utilized drug in 2012, the second highest utilized drug in 2013 and 2014 and the third highest utilized drug in 2015. From a formulary of 38 drugs, the top 5 drugs accounted for a minimum of 64% to 77% of all antimicrobials.

Discussion

A recent publication stated that in Albania there is no active surveillance system for antimicrobial consumption, but postulated that in Albania antibiotic consumption is too high, broad-spectrum antibiotics are overused, particular brands of antibiotics are overused and misused as a result of marketing by the pharmaceutical industry and there is insufficient knowledge of prescribers [5].

Indeed the overall antimicrobial consumption at QSUT was the lowest in 2013 (48.3 DDD/100OBD) and the highest in 2015 (67.0 DDD/100OBD), slightly higher when compared to a study of European hospitals carried out in 2001 [6]. Our data from 2013 might, however, be somewhat misleading as during 2013 there were gap periods of antibiotic supply and availability at the hospital pharmacy, something one would not consider to be a very likely situation in high-income countries. Thus in such a setting prescribers could give a prescription to patient's relatives who would, in turn, buy antibiotics from private community pharmacies for use within the hospital. This period coincided with a change in the government. Another limitation lies in the fact that the procurement procedures in the Albanian public hospital system is quite restricted. The hospital administration can buy only drugs from a list approved by the Ministry of Health. The hospital centre's budget for drugs and medical materials is also somewhat restricted (Annual State Budget 2015: €42.000,000 from Compulsory Health Insurance Fund). Furthermore, procurement is based on previous consumption and there is limited possibility to forecast a change in proportions of drugs procured.

In a Point-Prevalence Survey (PPS) carried out in 2015, 56.1% of patients surveyed at QSUT were receiving at least one antimicrobial agent [7]. This compares well with the present study. In the PPS 'Other Beta-lactam antibiotics' (J01D) accounted for 49.5% of all antibiotics at QSUT. Once again this corroborates well with our study. The reliance on "other-beta lactams" should be investigated further as it is likely that this might be reduced. This could be done in two ways, either by switching to alternative classes when these drugs are used as treatment or, in the case of cefazolin, shortening the duration of surgical prophylaxis. Excessively prolonged surgical prophylaxis was estimated at around 94% in the PPS carried out at QSUT [7].

Our data also highlighted another important potential target for quality improvement. This is the proportion of parenteral drugs utilized, especially for those drugs with an excellent oral bioavailability (*e.g.,* fluoroquinolones). On average two-thirds of fluoroquinolones used at QSUT were administered parenterally. This should be studied further and stewardship initiatives promoting an intravenous-to-oral switched should be set-up.

Carbapenems are seldom used at QSUT. In view of the high cost these are reserved for selected cases of life-threatening infections. The novel carbapenems (*e.g.* doripenem, ertapenem, panipenem) are not licensed for use in Albanian Public hospitals. Interestingly, despite the extremely low usage, a high carriage of carbapenem resistant non-fermenting Gram-Negative bacteria (*Pseudomonas aeruginosa* and *Acinetobacter baumanii*) were identified but this resistance was not detected in Enterobacteriaceae [8].

Conclusion

This study highlighted three important targets for improvement, namely: an over-reliance on cephalosporins; an excessively prolonged surgical antibiotic prophylaxis; a high proportion of parenteral drugs even for those classes with favourable oral pharmacokinetics. A continual surveillance would possibly identify more issues and also help to assess the

effect that any antibiotic stewardship interventions have on clinical practice.

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