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Original article

ANTIMICROBIAL STEWARDSHIP - A STRATEGIC TASK IN INSTITUTIONAL AND NATIONAL HEALTHCARE

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SUMMARY

Purpose: Antimicrobial stewardship (AS) is a consensus multidisciplinary activity aimed at better care for patients and containment of Antimicrobial resistance (AR). The purpose of this article is to characterize AS process in Bulgaria at hospital and national level.

Material/Methods: Analysis of national AS activities was performed. AS program of the Medical Institute – Ministry of the Interior (MI) – is presented as a model of hospital implementation.

Results: In Bulgaria, the first National program for a rational antibiotic policy was developed in 2001, and National AR Surveillance system BulSTAR works since more than 15 years. Ministry of healthcare is the main regulator: hospital AS is mandatory and required for the process of hospital accreditations. At MI antibiotic policy program includes Guidelines for: - Empiric antibiotic therapy, - therapy by specialities, - Antibiotic prophylaxis in Surgery. According to the results of point prevalence survey Global PPS-2015, antibiotic use in MI was 24 %, quality indicators showed 100 % written reason for the use of antibiotics and tailoring to the microbiology result. Approaches in antimicrobials prescribing were similar to those of the other EU countries. However, the spectrum of the prescribed antibiotics was more limited and with higher usage of generic ceftriaxone. To improve the usage of antibiotics in Ambulatory care Guidelines were issued in 2016. It remains: to introduce National action plan for AS, with appropriate funding, staffing and control.

Conclusions: AS activities in Bulgaria should be broaden, better controlled and supported as official Governmental policy.

Keywords: hospital antibiotic policy, national antibiotic policy, Bulgaria

INTRODUCTION.

Antibiotic resistance – a global healthcare problem

Antibiotics (ABs), „the miracle drugs" that changed morbidity and mortality from infections and allowed the success of surgical operations, chemotherapy and transplantations, could not be more effective [1, 2, 3].

Increase in Antibiotic resistance (AB R) and the emergence of extended-drug resistant (XDR) and pan-drug-resistant strains as well as "the epidemy" of their mobile genetic determinants (plasmids, transposons, integrons) pose difficult problems to the healthcare. According to the European Center for Diseases Prevention and Control (ECDC), about 25000 people in Europe die annually because of multiple drug resistance (MDR). The menace of AB R is serious: experts from WHO forecast: in 2050 in the world from MDR infections could die about 10 millions of patients (more than from malignancy).

The combination with the exhausted AB therapeutic arsenal (a lack of opportunity new AB to be introduced in a near future) draws unfavourable perspective for the majority of cases, if Antimicrobial resistance would not be contained and the activity of available ABs not conserved for the current and future generations [3, 4].

Today not only scientific healthcare organizations, but International organizations and governments undertake measures to improve the use of ABs and contain AB R: at local, national and global level [4, 5, 6, 7, 8, 9]. WHO published official guidelines how the countries to combat AB R and establish a national plan for the prudent use of ABs [3]. The European Commission issued Guidelines for AB stewardship demanding appropriate AB usage to become a priority in all EU countries [1].

The primary goal of Antimicrobial stewardship (AS) is to improve the use of ABs in patients, based on the choice of most appropriate AB and AB regimen: to impove infection cure rates and reduce mortality and morbidity; to reduce the rates of surgical site infections (SSI) [1, 4, 10,11]. Improving patients'safety implies also to reduce the adverse AB effects: toxicity, the incidence of *C. difficile* associated diarrhoea and the other disturbancies of normal flora. The second important goal is to contain the AB R through reduction of the total AB consumption (ABs to be prescribed only for a proven or highly suspected bacterial infection), the usage of ABs promoting AB R to be restricted [4, 5, 6, 7, 10]. Collaboration is neaded with the Infection control (IC) activities [3, 4, 10].

MATERIALS AND METHODS

Analysis of national AS activities was performed. AS program of the Medical Institute – Ministry of the Interior (MI) – is presented as a model of hospital implementation.

Annual data of Antimicrobial resistance surveillance and of Antibiotic consumption (by ABC calc, D. Monnet; in defined daily doses per 100 bed-day (DDD/100 bed-day) are included. The process of development of Antibiotic policy is described.

RESULTS

The core activities of Antimicrobial stewardship in Bulgaria

Bulgarian scientists – microbiologists and the majority of the physicians have traditionally been aware of the mechanisms of spread of AR and educated in the princilpes of Antimicrobial Chemotherapy [12]. The first Government steps in Antimicrobial stewardship date since1999 when Expert multidisciplinary committee with the Ministry of Health (MH) was created; the first National Program on Rational Antibiotic Policies was issued in two years. A Reference laboratory for Antimicrobial resistance surveillance with the National Center for Infectious and Parasitic Diseases (NCIPD) was created and National AB R surveillance program BulSTAR was implemented [13]. MH, the main regulatory institution, is the author of the Health law: only physicians can prescribe ABs and Pharmacies should sale ABs upon prescriptions only. Important documents issued from the MH were the standards "Microbiology" and "Prevention and control of nosocomial infections".

More recently, in 2015, MH started issuing of Pharmaco-therapeutic guidelines. In 2016 the Parliamentary commission on healthcare together with patient organisations and experts conducted a Round-table discussion: "Rational AB use – a common mission of physicians, patients, and institutions". Practical guidelines for rational antibiotic use in ambulatory care were issued by NCIPD [14]. Many experts have spoken about ABs and AB R on mass-media.

Present medical laws and practices related to the Antimicrobial stewardship in Bulgaria could be summarized as follows [2,15]:

• ABs in human medicine are prescribed only by medical and dental medicine doctors.

• Pharmacies are obliged to sale ABs only upon a physician recipe.

• Every student in medicine, dental medicine and pharmacy obtains knowledge on Antimicrobial chemotherapy and ABs.

• Every medical specialist improves his knowledge and experience about ABs and Antimicrobial Chemotherapy, as well as for the Infection control and Patient' safety through post-graduated specializations, courses, seminars, round-tables, congresses, books etc.

• Every hospital has Antibiotic policy program and Antibiotic team, together with Infection control program and IC team; hospital AS is mandatory and required for the process of hospital accreditations.

Until now no special incencitives for specialists working on Antimicrobial stewardship in Bulgaria were foreseen [15,16].

Antimicrobial stewardship at Medical Institute – Ministry of the Interior

Medical Institute – Ministry of the Interior (MI) is a 310-bed national multiprofile teaching tertiary care hospital. AB policy subcommittee with the Therapeutic drug committee was created in 2002. AB policy program was accepted in 2003 after a wide discussion with the hospital personnel.

The established AB policy is a restrictive, with three levels of prescriptions. Prescription of the ABs of the 3rd level – reserve - requires the signs of clinical microbiologist and Director.

Hospital Guidelines are available for the Empiric therapy of serious infections (prepared by the AB policy team), for Antimicrobial Prophylaxis in surgery (issued by the Clinic of Surgery), for Antibiotic therapy of infections by anatomic sites (prepared by the clinical departments). Compliance with the Guidelines is an important Indicator of Quality in Antimicrobial stewardship [7, 8, 10, 17].

The role of Clinical microbiologist in performing AS activities is very important, as he:

- Provides guidelines for microbiologic specimen collection and transport

- Participates at discussions on patients in clinical meetings at Surgery Clinic, ICUs and other departments, interprete microbiological results and advice for the choice of AB

- Is particularly responsible for patients with sepsis: provides Gram-stain result from positive blood-culture bottle by phone; immidiately performs rapid antibiogram, suggests on the choice of AB therapy, participates in re-evaluation of AB regimen

- Prepares annual AB R report for the hospital, ICUs and other wards

- Prepares annual AB consumption report for the hospital, ICUs, Surgery Clinic

- Organizes periodical audits of AB policy with feedback to the prescribers

- Organizes educational seminars on AB R, new MDR mechanisms and rational use of ABs.

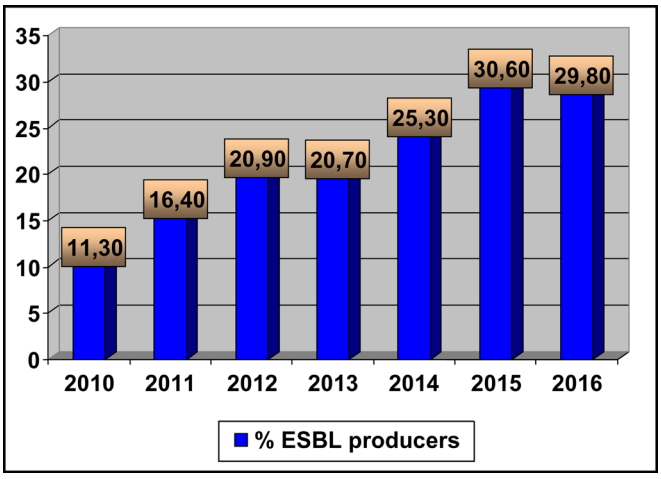
Majority of clinicians follow the guidelines, take microbiologic specimen before prescribing AB, make their best to tailor the therapy according to the result, reassess AB therapy on the 72 hours.

Despite the performed AS activities at MI, the AR rates are high (the first three problem MDR organisms, isolated from different clinical specimens in 2016 are shown in Table 1). For the majority of microorganisms AB R increases (incl. ESBL-producing *Enterobacteriaceae* (Fig. 1)). Newly introduced mechanisms of AB R have been recently identified: carbapenem-R *Enterobacteriaceae* (CRE) and *Acinetobacter baumannii* (introduced in 2014) and vancomycin – R *Enterococcus* spp (VRE) - in 2016.

Table 1. Problematic antibiotic resistant microorganisms by clinical specimens, in Medical Institute – Ministry of the Interior, 2016 (number, % of the total number of isolates)

Bloodcultures	Urines	Wounds	Sputum
61 Enterobacteriaceae –30 ESBL-producers (50 %)	343 Enterobacteriaceae – 106 ESBL-producers (28 %)	120 S. aureus – 11 MRSA (9%)	16 A.baumannii - 12 carbapenem resistant (XDR) (75 %)
9 A. baumannii – 7 carbapenem resistant (XDR) (78%)	98 P. aeruginosa – 19 carbapenem resistant (XDR) (19 %)	231 Enterobacteriaceae – 65 ESBL-producers (28 %)	8 P. aeruginosa – 2 carbapenem R (25 %)
20 E. faecalis – vancomycin resistant – 1 (VAN A) (5 %)	29 A. baumannii –19 carbapenem resistant (XDR) (65 %)	49 A. baumannii - 35 carbapenem resistant (XDR) (71 %)	11 K. pneumoniae – 3 ESBL-producers (27 %)

Fig. 1. Increasing rate of ESBL producing *Enterobacteriaceae* at Medical Institute – Ministry of the Interior, 2010-2016 (in percent)



AB consumption, although intended restrictive, was dynamic and even increased in 2016 (Table 2).

Table 2. Antibiotic consumption in Medical Institute – Ministry of the Interior (all hospital and Surgical Intensive Care Unit), 2011-2016 in DDD/100 bed-day

	All hospital	**Surgical Intensive Care Unit**
2011	**52,2**	**240,3**
2012	**53,4**	**251,3**
2013	**54,4**	**252,2**
2014	**47,2**	**215,1**
2015	**50,8**	**189,1**
2016	**72,5**	**204,8**

The first 5 top AB groups for 2016 were: combinations â-lactams + Inhibitor – 21.1 DDD/bed-day; third generation cephalosporins – 19.6 DDD/bed-day; first generation cephalosporins – 8.2 DDD bed/day; quinolones 5.4 DDD/bed-day; macrolides-lincosamides 5.1 DDD bed/day.

Participation in Point Prevalence surveys is very useful to compare the own practice with that of other institutions [8]. GLOBAL PPS – 2015 results for MI showed 24 % usage of ABs, 100 % registered reason for AB prescription and common tailoring to the microbiological result. Approaches in AB prescribing were similar to those of the other EU countries. However, the spectrum of the prescribed ABs was more limited, especially in the ICUs, ceftriaxone dominated.

Other activities performed in AS were: periodic AB audit + feedback; educational seminars and posters issuing. Recent audits of AB prescriptions in surgical patients, in patients with bacteremia and with urinary tract infections revealed several cases of inappropriate AB treatment, related to infections with MDR organisms. The European AB day – 18 November- has been celebrated.

DISCUSSION

Antimicrobial stewardship is a complex multifactorial activity [1, 2, 5, 7, 8, 11, 16, 17, 18]. A lot of necessary requirements for rational AB policies have been accomplished at MI [2, 15, 19, 20]. Despite the availability of a sub-committee on AB policy and a Rational AB policy program, in recent years important indicators such as AB resistance rate and AB consumption were high and even increased. One explanation is the country's increased rate of AB resistance: an alarming rate of cephalosporins 3rd generation resistant *Enterobacteriaceae* from invasive infections was reported by EARS-Net project of the ECDC; the spread of ESBL – producers in the country, is endemic, despite the IC guidelines (issued by NCIPD more than 10 years ago). Majority of experts have agreed that implementation of AS programs requires strong awareness about the problems, good organization and support [6, 8, 10, 11, 16, 19]. Obtaining positive results is more difficult in the areas of increasing resistance, particularly of MDR bacteria [21]. A common problem in Bulgarian hospitals is the the low percentage of isolating rooms.

In addition, new resistance mechanisms such as XDR *A. baumannii*, CRE [21] and VRE have been introduced/ emerged last years. At MI after publishing by ESCMID guidelines for managing of XDR Gram-negative bacteria

(Tacconelli et al., 2014), adapted policy was prepared.

Rapid tests for Microbiology laboratories, such as MALDI-tof and multiplex real-time PCR, very important for the microbiologic diagnosis, especially in seriously ill patients [1, 3, 4, 7] are not yet available (nore point of care rapid tests).

Unfortunately, sometimes, when a physician wants to prescribe the best choice AB, it is not available. The National healthcare fund (NHF) covers no more than 60 % of healthcare patient expenditure [13]. It is therefore not surprising, that ABs known to be drivers of AB resistant bacteria, such as the cheap generic ceftriaxone are frequently used, opposite to the recommendations.

Other specific characteristics of the implementation of AS measures in Bulgaria are the leading role of microbiologists (see above in *Results* section), and that majority of medical personnel (at MI) is adherent to the Guidelines. This could be related to the traditionally good education in Antimicrobial Chemotherapy area [12], as well as because medical specialists actively participated in the discussion of AB policy program, and had an authorship in some of the Guidelines.

Many countries all over the world have already issued their strategic plans to contain AB resistance and to improve the AB usage [2, 4, 7, 8, 9, 11, 18]. In Bulgaria, a particular success was obtained with the Antimicrobial resistance surveillance and the mandatory requirement for hospital antibiotic policies. Some gaps exist, for example, the current Guidelines for AB therapy of the NHF are not consistent with the increased AB R rate and therefore do not allow adecuate empiric therapy based on the risk factors [7, 8, 10, 21]. There is an emergent need for the creation and implementation of Government supported and controlled AB stewardship program. Establishment of working programs with enough resources in all hospitals and in the ambulatory setting is required [1, 2, 3, 13, 16]. Much more work is required at MI and in the all system of healthcare: education, raising awareness of stakeholders and society to improve AB usage, to control infections and MDR strains.

CONCLUSIONS

Important activities in Antibiotic stewardship have been performed both at the institution (hospital) and country level. Antibiotic policy programs in Bulgaria are characterized by the leadership of microbiologists and generally good adherence of the other medical personnel.

Among the most important achievements till now are the system for Antimicrobial resistance surveillance BulSTAR and the requirements for hospital antibiotic policy.

Increasing rates of antibiotic resistance and antibiotic consumption, however, suggest for gapes both in the Control of infections and implementation of Antibiotic policy, mostly related to the subfunded healthcare. It would be necessary to introduce Government supported and controlled Antibiotic Stewardship program with better organization and more resources: people, financies, and responsibilities.

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