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MOJCA DOBAJA

RACIONALNA UPORABA ANTIBIOTIKOV; RE-EVALUACIJA ANTIBIOTIČNE TERAPIJE PRI 24-IH DO 72-IH URAH PO PRVI APLIKACIJI ZDRAVILA

RATIONAL USE OF ANTIBIOTICS; RE-EVALUATION OF ANTIBIOTHERAPY 24 TO 72 HOURS AFTER INITIAL APLICATION

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Diplomsko nalogo sem opravljala na Fakulteti za farmacijo, na Katedri za biofarmacijo in farmakokinetiko pod mentorstvom prof. dr. Aleša Mrharja, mag. farm. v okviru sodelovanja z bolnišnico Clocheville, v Tours-u v Franciji pod vodstvom somentorice Stéphanie Provôt mag. farm. spec..

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Izjava

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Mojca Dobaja

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Predsednik diplomske komisije: zasl. prof. dr. Aleš Krbavčič, mag. farm.

Član diplomske komisije: doc. dr. Tomaž Bratkovič, mag. farm.

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1. ABSTRACT

Antimicrobial agents, commonly called antibiotics, are substances used to kill or inhibit the growth of microorganisms. They have been used for decades to treat infection diseases and prevent infections. Overuse and misuse of antibiotics have favored the growth of resistant organisms, what presents a serious danger to public health and environment. Consequences are also increasing costs for health care and society.

There are several ways to fight this problem; from collecting standardized, harmonized and comparable data on antibiotic resistance and use, to improving strategies for hygiene, infection control and infection prevention.

We decided to focus on fundamental concept of rational use of antibiotics, which is re-evaluation of antibiotherapy 24 to 72 hours after initial application. The aim was to develop a standardized methodology to measure, compare and follow-up antibiotic use in hospitals.

Audit was conducted in the general hospital of Tours, France. We included 70 wards, where 885 patients were hospitalized. At the time of audit 240 patients were on antibiotherapy (27% of all hospitalizations), but 146 patients were matching criteria of inclusion.

The basis of our research was a questionnaire with which we were trying to find out whether the re-evaluation of antibiotherapy was made in selected time frame and which researches have been made to localize the site of infection and to identify bacteria causing it.

We also focused on the fact whether at the time of re-evaluation there were any notes about adverse effects, economical or practical reasons for changing antibiotherapy, clinical signs (increase or drop of body temperature, presence of pain at the site of infection) and whether opinion of infectologist was written in patient record. Regarding all of the criteria mentioned above, re-evaluation was considered as complete in 12%, partial in 65% and null in 9%. In 14% of cases re-evaluation was not done at all. Initially prescribed antibiotherapy was at the point of re-evaluation maintained in 28%, modified in 67% and stopped in 5% of the cases.

What is most important is the fact that in 82% of the re-evaluations that were ranked as complete, initial antibiotherapy was modified. In case of partial re-evaluations 66% of them were modified regarding antibiotic treatment, and only 62% of the re-evaluations that were ranked as null were modified. From this we can conclude that "complete" re-evaluation is often leading to the changes of initial antibiotherapy – to the optimization of antibiotic treatment.

2. RAZŠIRJEN POVZETEK

UVOD

Antibiotiki so zdravila, ki se uporabljajo za ubijanje bakterij ali pa za zaustavitev njihove rasti. So zdravila, ki so namenjena zdravljenju bakterijskih okužb. S prekomerno in neustrezno rabo se širi odpornost bakterij proti antibiotikom, kar pa v današnjem svetu predstavlja vedno večji problem za javno zdravje in okolje, v katerem živimo.

Obstaja več načinov, kako se lotiti problema odpornosti bakterij in neustrezne rabe zdravil na področju zdravljenja in profilakse infekcijskih bolezni. Nekateri pomembnejši izmed njih so zbiranje primerljivih podatkov o rezistenci bakterij in porabi antibiotikov na nacionalni in mednarodni ravni, izboljševanje strategij za higieno, kontrolo nad okužbami in preprečevanje širjenja le teh.

V Evropi je uporaba antibiotikov spremljana s strani ESAC-a (European Surveillance of Antimicrobial Consumption), ki centralno izvaja analizo podatkov o porabi antibiotikov v 34 evropskih državah, ki sodelujejo v projektu.

Podatki iz leta 2006 kažejo, da so države južne Evrope (Grčija, Francija, Italija) bile v samem vrhu porabe antibiotikov, medtem ko je bila poraba v severnem delu (Nizozemska, Rusija) bistveno nižja. Že leta 2008 je bilo opaziti upad v večini držav, ki so izstopale v prekomerni porabi antibiotikov.

Tudi na splošno lahko rečemo da je poraba antibiotikov v Evropi med 1999 in 2008 upadla na terciarni in primarni ravni. Upad lahko pripišemo predvsem uspehu raznih kampanj v splošni in strokovni javnosti in upoštevanju priporočil o racionalni uporabi antibiotikov.

V uvodu diplomske naloge smo se osredotočili tudi na omejevanje odpornosti bakterij, pravilno izbiro optimalne antibiotične terapije ter pomembnost re-evaluacije antibiotične terapije. Proučili smo tudi probleme, povezane z napačno uporabo antibiotikov ter regulatorni vidik racionalne uporabe antibiotikov v Franciji.

NAMEN

V okviru naše raziskave smo se predvsem osredotočili na primarni koncept racionalne uporabe antibiotikov, ki je pravzaprav re-evaluacija antibiotične terapije pri 24-ih do 72-ih urah po prvi aplikaciji zdravila. Cilj je bil oblikovati standardizirano metodo, kako meriti, ocenjevati in primerjati racionalno uporabo antibiotikov v bolnišnicah.

METODE

Raziskava je bila izvedena v splošni bolnišnici Tours v Franciji. Vključenih je bilo 70 oddelkov, kjer je bilo v času raziskave hospitaliziranih 885 bolnikov. Od vseh bolnikov jih je bilo v času raziskave na antibiotični terapiji 240, kar predstavlja 27 % vseh hospitalizacij. Na podlagi kriterijev vključitve je bilo v obravnavo vključenih 146 bolnikov.

Delo v okviru diplomske naloge smo zastavili na podlagi vprašalnika, s pomočjo katerega smo ugotavljali, ali je re-evaluacija antibiotične terapije bila narejena v predpisanem časovnem okviru ter katere mikrobiološke in druge preiskave so bile narejene, da se lokalizira mesto okužbe in odkrije morebitni povzročitelj. Prav tako smo s pomočjo vprašalnika ugotavljali, ali so bili ob re-evaluaciji zabeleženi neželeni učinki, ekonomski razlogi za spremembo antibiotične terapije, klinični znaki (povišanje ali padec telesne temperature, prisotnost bolečine na mestu okužbe,...) ali pa je ob re-evaluaciji bilo zabeleženo tudi mnenje specialista infektologa. Na podlagi zbranih podatkov smo ocenili, ali je re-evaluacija popolna, delna ali nezadostna. Prav tako smo pregledali, ali se je ob re-evaluaciji terapija spremenila, bila ustavljena ali pa je ostala nespremenjena. V kolikor se je terapija spremenila, smo opredelili tudi naravo spremembe (sprememba v načinu dajanja zdravila, sprememba v odmerjanju, ukinitev enega izmed antibiotikov ali uvedba dodatne terapije, menjava terapije,..)

REZULTATI

Na podlagi analize vprašalnikov smo prišli do sklepa, da je bil razlog za predpis antibiotične terapije naveden v 97 % vseh primerov, prav tako je v 90 % primerov bilo zabeleženo kateri zdravnik je zdravljenje predpisal, ter v 99 % kdaj se je z zdravljenjem pričelo.

Prav tako smo ugotovili, da so mikrobiološke preiskave bile narejene v 94 % primerov ter da je v 53 % primerov povzročitelj infekcije bil identificiran. Infekcija je bila lokalizirana v 92 % vseh primerov.

V času re-evaluacije so bili neželeni učinki antibiotične terapije zabeleženi pri 6 % bolnikov, ekonomski ali praktični razlogi za spremembo terapije so bili jasno označeni v 6 % primerov, klinični znaki omenjeni v 48 % ter mnenje specialista infektologa v 15 % vseh primerov.

Ob upoštevanju navedenih kriterijev smo re-evaluacijo označili kot popolno v 12 % vseh primerov, kot delno v 65 % in kot nezadostno v 9 %. Omeniti moramo tudi podatek, da re-evaluacija ni bila narejena pri 14 % vseh bolnikov. Prvotno predpisana antibiotična terapija je bila ob času re-evaluacije nadaljevana v 28 % primerov, spremenjena v 67 % in ustavljena pri 5 % bolnikov.

Rezultati analize podatkov kažejo, da je večina re-evaluacij dobro sledljivih. Podpis zdravnika na mestu re-evaluacije smo našli v 89 % vseh primerov, točen datum re-evaluacije pa v 98 % primerov.

Ugotovili smo tudi, da je razlog za spremembo v antibiotični terapiji ob re-evaluaciji v 38 % identifikacija povzročitelja infekcije ter uvedba ozkospektralnega ali učinkovitejšega antibiotika, v 28 % je prišlo do uvedbe dodatnega antibiotika ali ukinitve enega izmed njih, v 27 % je prišlo do spremembe v načinu dajanja antibiotika (PO/IV/SC) in v 7 % je bil prilagojen odmerek zdravila.

Prav tako smo prišli do podatka, da je v 97 % primerov po zaključku zdravljenja bil poslan potek zdravljenja osebnemu zdravniku, v katerem je v 94 % bila omenjena bakterijska infekcija ter v 91 % navedena tudi predpisana antibiotična terapija.

SKLEPI

Pomembna ugotovitev, do katere smo prišli tekom analize vprašalnikov, je, da je v 82 % pri popolni re-evaluaciji prišlo do spremembe v antibiotični terapiji. V primeru, ko je re-evaluacija bila označena kot delna, je do spremembe v prvotno predpisani terapiji prišlo v 66 %, v kolikor pa je re-evaluacija bila nezadostna pa v 62 % primerov. Iz ugotovljenega lahko sklepamo, da popolna re-evaluacija v veliki večini primerov vodi k spremembam prvotno predpisane antibiotične terapije, torej k optimizaciji zdravljenja z antibiotiki.

Na osnovi analize podatkov lahko prav tako sklepamo, da elektronsko vodeno predpisovanje antibiotične terapije bistveno pripomore k bolj sledljivi in kakovostni re-evaluaciji. Prav tako so bolje in lažje sledljive spremembe tekom zdravljenja z antibiotiki.

Tudi delež pacientov, pri katerih re-evaluacija ni bila narejena, je na nekaterih oddelkih še vedno visok. Z ozaveščanjem zdravnikov o pomembnosti re-evaluacije antibiotične terapije se lahko ta delež pomembno zmanjša.

Ugotovili smo tudi, da motiv za uvedbo spremembe v antibiotični terapiji velikokrat ni bil zabeležen, kar je pomanjkljivost, če želimo dobro re-evaluacijo. V prihodnje je tako potrebno zdravnike, ki predpisujejo antibiotike, vzpodbuditi tudi k navajanju razloga za spremembo obstoječe antibiotične terapije.

3. ABBREVIATIONS

ATC - Anatomical Therapeutic Chemical (Classification System)

CAI - (Commission des Anti-Infectieux) ; Anti-infection Agents Committee

CBU - (Contrat de Bon Usage) ; Agreement of proper use

CHRU - (Centre Hospitalier Régional Universitaire) ; Regional University Hospital Center

DDD - Defined Daily Dose

DPP - (Dossier Patient Partagé) ; Shared Patient Record

ER - Emergency Room

ESAC - European Surveillance of Antimicrobial Consumption

HAS - (Haute Autorité de Santé) ; French National Authority for Health

ICATB - (Indice Composite de bon usage des Antibiotiques) ; Composited Index regarding rational use of antibiotics

ICU - Intensive Care Unit

IV - intravenous application

MDRB - MultiDrug Resistant Bacteria

PO - *per os*, administration by mouth

SC - subcutaneous application

SSR - **(**Soin de Suite et de Rééducation); Care and Rehabilitation Unit

WHO - World Health Organisation

4. INTRODUCTION

In the first part of this chapter we introduce the general definition of antibiotics, historical background and its importance of discovery. Later we focus on consumption of antibiotics in Europe, growing resistance of bacteria and how to prevent it. We also discuss how to choose optimal antibiotherapy and diminish misuse of antibiotics. Rational use of antibiotics is also closely connected with re-evaluation of initially prescribed antibiotherapy, which was our main subject of research.

4.1. ANTIBIOTICS

4.1.1. DEFINITION

In common use, an **antibiotic** (from the Ancient Greek: *anti*, "against", and *bios*, "life") is a substance or compound that kills bacteria or inhibits their growth (1). In the strictest sense antibiotics are antibacterial substances produced by various species of microorganisms that suppress the growth of other microorganisms. Common usage often extends the term *antibiotics* to include synthetic antimicrobial agents such as sulfonamides and quinolones (2).

With advances in medicinal chemistry, most antibiotics are now semisynthetic; chemically modified from original compounds found in nature, as is the case with beta-lactams (which include the penicillins, produced by fungi in the genus *Penicillium*, the cephalosporins, and the carbapenems). Some antibiotics, such as the aminoglycosides, are still produced and isolated from living organisms. On other hand there are groups of antibacterials that have been created through purely synthetic means, like the sulfonamides, the quinolones, and the oxazolidinones. The synthesis of arsphenamin, also known as Salvarsan was beginning of a new path in the fight against many infectious diseases that were previously considered incurable. Antibiotics have increased life expectancy for nearly 15 years for those who have access to them (1).

In addition to this origin-based classification into natural, semisynthetic, and synthetic, antibiotics may be divided into two broad groups according to their effect on microorganisms; those that kill bacteria are bactericidal agents, whereas those that only impair bacterial growth are known as bacteriostatic agents.

The main goal of any antibiotic treatment is to help to the immune system in its fight against bacterial infection.

4.1.2. BACKGROUND AND IMPORTANCE OF THE DISCOVERY

Before the early twentieth century, treatments of infections were based primarily on medicinal folklore. Mixtures with antimicrobial properties that were used in treatments of infections were described over 2000 years ago. Many ancient cultures, including the ancient Egyptians and ancient Greeks used specially selected mold and plant materials and extracts to treat infections. They were using as well inorganic compounds (minerals) in which we can find *CuSO4, PbS, ZnO,* etc. which also have antibacterial properties.

The term *antibiosis* was introduced by the French bacteriologist Vuillemin as a descriptive name of the phenomenon exhibited by these early antibacterial drugs. Antibiosis was first described in 1877 in bacteria, when Louis Pasteur and Robert Koch observed that an airborne bacillus could inhibit the growth of *Bacillus anthracis*.

The term "antibiotic" was coined by Selman Waksman in 1942 to describe any substance produced by a microorganism that is antagonistic to the growth of other microorganisms in high dilution. This original definition excluded naturally occurring substances that kill bacteria, but are not produced by microorganisms (such as gastric juice and hydrogen peroxide) and also excluded synthetic antibacterial compounds (3).

4.2. CONSUMPTION OF ANTIBIOTICS

4.2.1. IN EUROPE

In Europe, the use of antibiotics is monitored by the European Surveillance of Antimicrobial Consumption (ESAC) that centralizes and analyzes data of consumption for 34 European countries, which are participating in the network (4).
To enable a comparison on international level, the consumption of antibiotics is commonly expressed as number of defined daily doses per 1000 inhabitants per day (DDD / 1000 inhabitants / day). In hospitals, the consumption is expressed in DDD per 1000 hospitalization days (DDD / 1000 HD).

Defined Daily Dose (DDD) developed by the World Health Organization (WHO), is defined as the average daily dose of a drug in its primary indication, to treat an adult weighing 70 kilograms. The value of DDD is defined for each drug by a panel of international experts within the WHO.

It is used to standardize the comparison of drug usage between different drugs or between different health care environments.

It should be emphasized that the defined daily dose is a unit of measurement and does not necessarily reflect the recommended or Prescribed Daily Dose. Doses for individual patients and patient groups will often differ from the DDD and will necessarily have to be based on individual characteristics (e.g. age and weight) and consideration of pharmacokinetic properties.

It is also a fact that with the DDD we can not measure the quality of therapy (5).

4.2.2. CONSUMPTION IN ESAC MEMBER COUNTRIES

The countries of southern part of Europe have the highest consumption of antibiotics (colored red and dark red on the map; Figure 1), while the consumption level is lower in the north and in Russia (colored green and yellow).

Greece, France, Italy and Belgium are the highest consumers of antibiotics. On the other hand countries like the Netherlands and Russia are the lowest consumers. Slovenia is in the lower middle (colored in yellow).

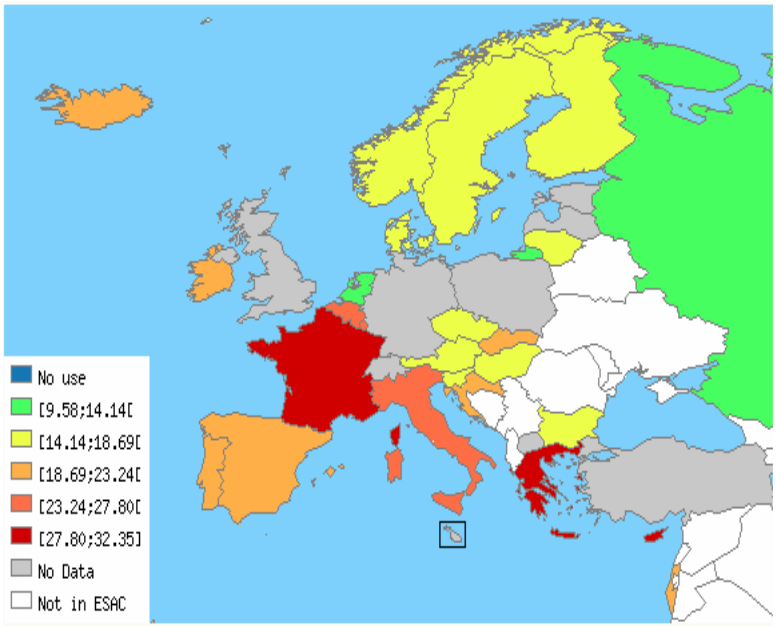

Figure 1: Consumption of antibiotics in Europe in 2006 (4)

However, between 2006 and 2008, we can already notice a decrease in antibiotic consumption in many countries, including France, Italy and Belgium (Figure 2) (6, 7).
In 2008, Greece was the only one remaining as biggest consumer of antibiotics in Europe.

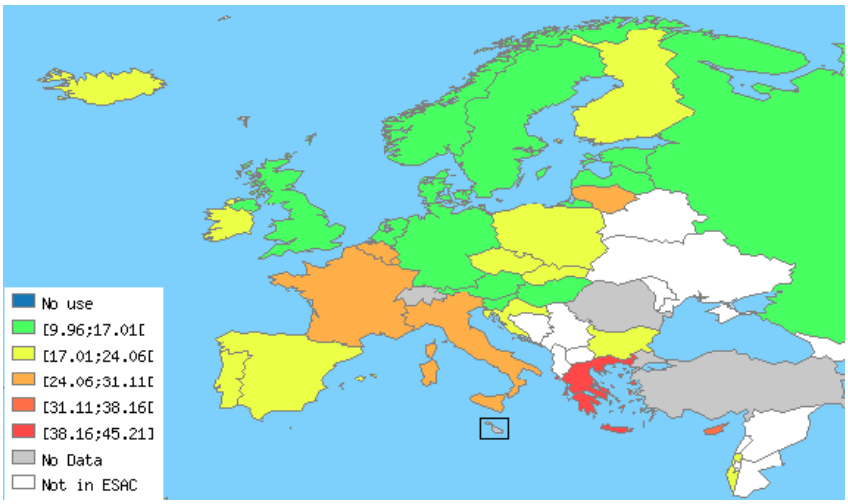

Figure 2: Consumption of antibiotics in Europe in 2008 (4)

4.2.2.1. CONSUMPTION IN THE FIELD OF AMBULATORY CARE

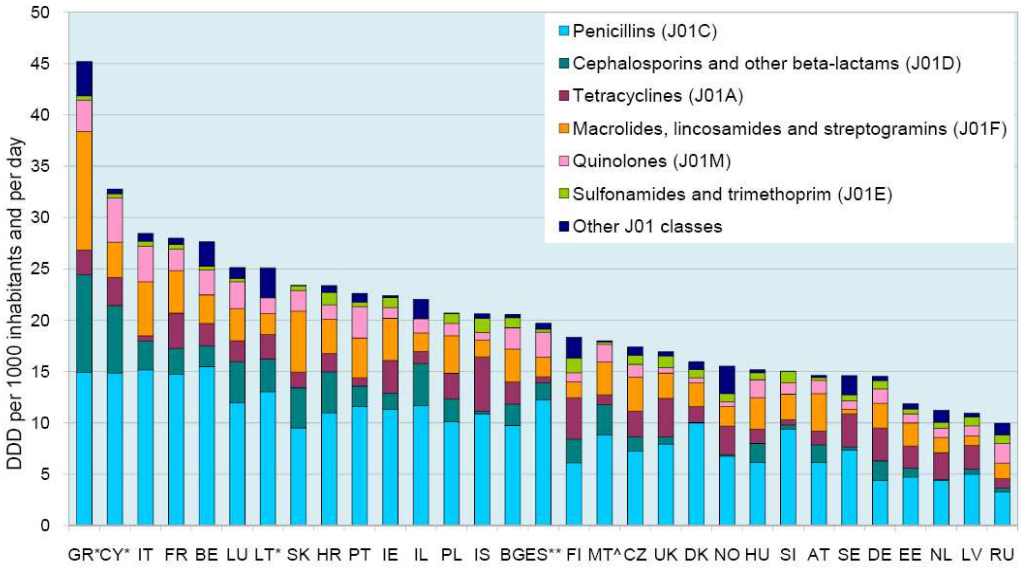

Figure 3: Consumption of antibiotics in the field of ambulatory care regarding different families of antibiotics - 2008 (ATC J01) (4)

* Cyprus, Greece, Lithuania: total use, including also consumption in hospital sector
** Spain: reimbursement data, which do not include over-the-counter sales without prescription ; ^ Malta: data for 2007

We can notice that consumption of antibiotics consumed in the field of ambulatory care between 1999 and 2008 slightly increased in low-consumption countries (Austria, Denmark, Netherlands, United Kingdom, etc.), while for countries that were using a lot of antibiotics (Belgium and France), we can see at first a drop in consumption between 1999 and 2004 and then again an increase in consumption between 2004 and 2008 (Table I).

Table I: Consumption of antibiotics in the field of ambulatory care between 1999 and 2008 (DDD / 1000 inhabitants / day) (DDD / 1000 inhabitants / day) (4)

Country	1999	2000	2001	2002	2003	2004	2005	2006	2007	**2008**
Austria	13.1	12.3	11.8	11.8	12.5	12.5	14.5	14.3	14.7	**14.6**
Belgium	26.2	25.3	23.7	23.8	23.8	22.7	24.3	24.2	25.4	**27.7**
Bulgaria[4)]	15.1	20.2	22.7	17.3	15.5	16.4	18.0	18.1*	19.8*	**20.6**
Croatia		18.4	18.5	22.6	23.4	23.0	23.4	21.2	22.5	**23.4**
Cyprus[1)]								31.9	33.9	**32.8**
Czech Rep.	18.6				16.7	15.8	17.3	15.9	16.8	**17.4**
Denmark	12.1	12.3	12.8	13.2	13.5	14.1	14.6	15.2	16.0	**16.0**
Estonia				11.7	11.1	10.4	11.7		12.7*	**11.9**
Finland	18.4	19.0	19.8	17.9	18.7	17.2	18.1	17.4	18.3	**18.4**
France	34.1	33.2	33.2	32.2	28.9	27.0	28.9	27.9	28.6	**28.0**
Germany	13.6	13.6	12.8	12.7	13.9	13.0	14.6	13.6	14.5*	**14.5**
Greece[1)]	30.7	31.7	31.8	32.8	33.6	33.0	34.7	41.1*	43.2*	**45.2**
Hungary	23.5	18.5	18.6	17.1	19.1	18.2	19.5	17.2	15.5	**15.2**
Iceland[2)]	21.7	20.5	20.0	20.6	20.3	21.4	23.2	20.0	20.1*	**20.6**
Ireland	18.0	17.6	18.7	18.7	20.1	20.2	20.5	21.2	23.0	**22.5**
Israel				19.6	20.1	19.6	20.5	22.2	20.2	**22.0**
Italy	24.5	24.0	25.5	24.3	25.6	24.8	26.2	26.7	27.6	**28.5**
Latvia				11.0		11.8	12.1	12.0	13.0	**11.0**
Lithuania[1)]								22.7*	24.11	**25.1**
Luxembourg	26.8	25.9	26.5	26.4	27.5	24.1	25.2	23.9	25.6	**25.1**
Malta									18.0*	
Norway			15.6	15.7	15.6	15.7	16.8	14.8*	15.5*	**15.5**
Poland	22.2	22.6	24.8	21.4		19.1	19.6		20.9*	**20.7**
Portugal	25.2	24.9	24.5	26.5	25.1	23.8	24.5	22.7	21.8	**22.6**
Russian Federation					9.8	9.3	9.1	9.6	10.2	**10.0**
Slovakia	25.7	27.6	29.1	26.7	27.6	22.5	25.1	22.5	24.8	**23.4**
Slovenia	19.8	18.0	17.4	16.3	17.0	16.7	16.3	14.7	16.0	**15.0**
Spain[3)]	20.0	19.0	18.0	18.0	18.9	18.5	19.3	18.7	19.9	**19.7**
Sweden	15.8	15.5	15.8	15.2	14.7	14.5	14.9	15.3	15.5	**14.6**
Switzerland						9.0				
The Netherlands	10.0	9.8	9.9	9.8	9.8	9.7	10.5	10.8	11.0	**11.2**
United Kingdom	14.8	14.3	14.8	14.8	15.1	15.0	15.4	15.3*	16.5*	**17.0**

1) Cyprus, Greece, Lithuania: total use, including the hospital sector.
2) Iceland: total use until 2005, outpatient use from 2006.
3) Spain: reimbursement data, does not include over-the-counter sales without prescriptions.
4) Bulgaria: total use until 2005, outpatient use from 2006. Change of data provider in 2006.
* updated data

Regarding consumption among the different families of antibiotics, there is predominance in use of penicillins (amoxicillin, amoxicillin/enzyme inhibitor ...) in all European countries (Table II).

Table II: Consumption of antibiotics in the field of ambulatory care in 2008 regarding different families of antibiotics (ATC J01) (DDD / 1000 inhabitants / day) (4)

Country	Penicillins (J01C)	Cephalosporins and other beta-lactams (J01D)	Tetracyclines (J01A)	Macrolides, lincosamides and streptogramins (J01F)	Quinolones (J01M)	Sulfonamides and trimethoprim (J01E)	Other J01 classes	Total J01
Greece*	14.92	9.51	2.41	11.54	3.05	0.42	3.35	**45.20**
Cyprus*	14.86	6.57	2.74	3.45	4.29	0.41	0.46	**32.78**
Italy	15.17	2.78	0.54	5.27	3.44	0.50	0.75	**28.45**
France	14.73	2.53	3.43	4.14	2.08	0.47	0.61	**27.99**
Belgium	15.48	2.02	2.19	2.78	2.41	0.38	2.39	**27.66**
Luxembourg	11.98	3.99	2.02	3.16	2.61	0.34	1.04	**25.13**
Lithuania*	13.04	3.20	2.36	2.04	1.56	0.01	2.89	**25.10**
Slovakia	9.53	3.89	1.54	5.93	2.00	0.48	0.04	**23.41**
Croatia	10.99	3.99	1.77	3.32	1.44	1.20	0.65	**23.37**
Portugal	11.60	1.98	0.82	3.87	3.05	0.43	0.85	**22.61**
Ireland	11.34	1.56	3.18	4.11	1.04	0.99	0.20	**22.42**
Israel	11.70	4.08	1.18	1.80	1.39	0.00	1.89	**22.04**
Poland	10.13	2.21	2.49	3.66	1.21	0.95	0.05	**20.69**
Iceland	10.88	0.26	5.29	1.61	0.77	1.35	0.48	**20.64**
Bulgaria†	9.75	2.08	2.16	3.20	2.08	0.99	0.30	**20.56**
Spain**	12.23	1.65	0.60	1.92	2.42	0.30	0.58	**19.70**
Finland	6.11	2.32	4.03	1.55	0.88	1.43	2.04	**18.36**
Malta^	8.81	2.99	0.93	3.22	1.71	0.20	0.14	**18.00**
Czech Republic	7.25	1.39	2.51	3.33	1.24	0.87	0.83	**17.41**
United Kingdom	7.95	0.71	3.72	2.47	0.52	1.13	0.42	**16.93**
Denmark	9.99	0.03	1.55	2.32	0.52	0.77	0.79	**15.97**
Norway	6,76	0,14	2,79	1,89	0,50	0,77	2,68	**15,53**
Hungary	6,14	1,86	1,39	3,06	1,75	0,69	0,29	**15,18**
Slovenia	9.37	0.44	0.52	2.47	1.11	1.12	0.00	**15.03**
Austria	6.17	1.70	1.33	3.65	1.31	0.29	0.20	**14.64**
Sweden	7.37	0.30	3.22	0.45	0.83	0.57	1.87	**14.60**
Germany	4.38	1.92	3.21	2.39	1.42	0.81	0.41	**14.54**
Estonia	4.73	0.85	2.17	2.25	0.88	0.47	0.52	**11.88**
The Netherlands	4.42	0.04	2.63	1.48	0.90	0.58	1.17	**11.24**
Latvia	5.01	0.49	2.28	0.95	0.98	0.84	0.39	**10.95**
Russian Federation	3.30	0.37	0.90	1.53	1.89	0.86	1.11	**9.96**

* Cyprus, Greece, Lithuania: total use, including the hospital sector.
** Spain: reimbursement data, does not include over-the-counter sales without prescription.
† Bulgaria: total use until 2005, outpatient use from 2006.
^ Malta: data for the year 2007.

4.2.2.2. CONSUMPTION IN HOSPITALS

Regarding consumption in hospitals in 2008 (Table III), the percentage in use of penicillin was 17.8% in Finland and 56.9% in France. Nine countries had a proportion in use of penicillins higher than one third. The proportion in use of cephalosporins was highest in Bulgaria (44.5%), while Ireland had the lowest (8.4%).

Highest proportion in use of tetracyclines was in Sweden (12.4%). The use of macrolides ranged from 3.2% in Lithuania and 15.7% in Malta, but for the quinolones ranged from 6.9% in Norway and 21.8% in Hungary. The proportion in use of sulfonamies was highest in Finland (6.5%) and lowest in Bulgaria (0.7%). Finally, also the use of other families was highest in Finland (22.0%) and in Russia (18.1%).

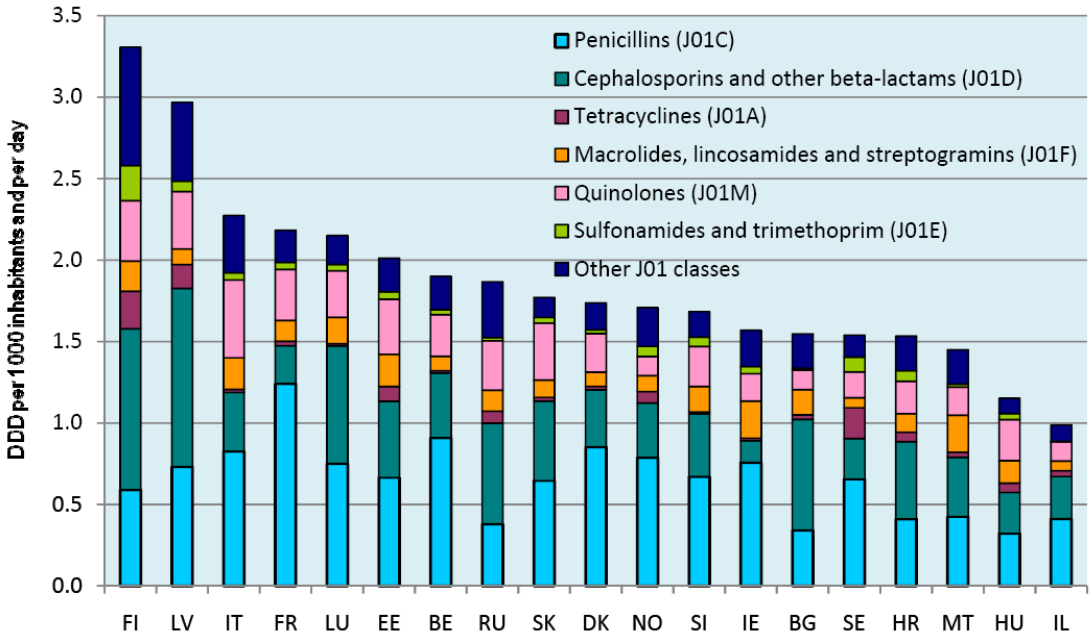

Figure 4: Hospital consumption of antibiotics according to the main families (ATC J01) – 2008 (4)

Table III: Hospital consumption of antibiotics according to the main families (ATC J01) – 2008 (DDD / 1000 inhabitants / day) (4)

Country	Penicillins (J01C)	Cephalosporins and other beta-lactams (J01D)	Tetracyclines (J01A)	Macrolides, lincosamides and streptogramins (J01F)	Quinolones (J01M)	Sulfonamides and trimethoprim (J01E)	Other J01 classes	Total J01
Finland	0.59	0.99	0.23	0.19	0.37	0.22	0.73	**3.31**
Latvia	0.73	1.09	0.15	0.10	0.35	0.06	0.48	**2.97**
Italy	0.83	0.36	0.02	0.19	0.48	0.04	0.35	**2.27**
France	1.24	0.23	0.03	0.13	0.31	0.04	0.20	**2.18**
Luxembourg	0.75	0.72	0.01	0.16	0.28	0.04	0.18	**2.15**
Estonia	0.67	0.47	0.09	0.20	0.34	0.05	0.21	**2.01**
Belgium*	0.91	0.40	0.01	0.09	0.25	0.03	0.21	**1.90**
Russian Federation	0.38	0.62	0.07	0.13	0.30	0.02	0.34	**1.87**
Slovakia	0.65	0.49	0.02	0.11	0.35	0.04	0.12	**1.77**
Denmark	0.85	0.35	0.02	0.09	0.24	0.02	0.16	**1.74**
Norway	0.79	0.34	0.07	0.10	0.12	0.06	0.24	**1.71**
Slovenia	0.67	0.39	0.01	0.16	0.25	0.06	0.16	**1.68**
Ireland	0.76	0.13	0.02	0.23	0.17	0.04	0.22	**1.57**
Bulgaria	0.34	0.68	0.03	0.15	0.12	0.01	0.21	**1.55**
Sweden	0.66	0.25	0.19	0.06	0.16	0.09	0.13	**1.54**
Croatia	0.41	0.48	0.06	0.11	0.20	0.06	0.21	**1.53**
Malta	0.43	0.36	0.03	0.23	0.17	0.02	0.21	**1.45**
Hungary	0.32	0.25	0.06	0.14	0.25	0.04	0.09	**1.15**
Israel	0.41	0.26	0.04	0.06	0.12	0.00	0.10	**0.99**

* Belgium: 2007 data

Antibiotic consumption in Europe overall decreased between 1999 and 2008, both in the field of ambulatory care or in the hospital. This decline can be explained with the success of various campaigns and recommendations implemented through the appropriate use of antibiotics in most European countries.

4.2.3. IN FRANCE

High consumption of antibiotics is also related to development of resistance of bacteria. Resistance is a global public health problem, but the rate of multidrug resistant bacteria (MDRB) is particularly high in France. This fact became of significant concern, but it is not irreversible. Indeed, the decline in use of antibiotic is associated with the recovery of the susceptibility of bacteria (8-10).

The overuse of antibiotics is a public health problem, if we want to preserve the effectiveness of these drugs, and also an economic concern for the health care system, since recently discovered antibiotic molecules are very expensive. Experts also criticize systematic prescription of certain antibiotics, especially in clinical cases, when infection is actually not bacterial, but viral.

4.3. THE GROWING RESISTANCE OF BACTERIA

Antibiotic resistance is a type of drug resistance where a microorganism is able to survive exposure to an antibiotic. Genes can be transferred between bacteria in a horizontal fashion by conjugation, transduction, or transformation. Thus a gene for antibiotic resistance, which had evolved via natural selection, may be shared. Evolutionary stress, such as exposure to antibiotics, then selects for the antibiotic resistant trait. Many antibiotic resistance genes reside on plasmids, facilitating their transfer. If a bacteria carries several resistance genes, it is called multiresistant.

The primary cause of antibiotic resistance is genetic mutation in bacteria. The prevalence of antibiotic resistant bacteria is a result of antibiotic use in human and veterinary medicine. The greater is the duration of exposure, the greater is the risk of the development of resistance. However, despite a push for new antibiotic therapies, there has been a continued decline in the number of newly approved antibiotics in past years (11).

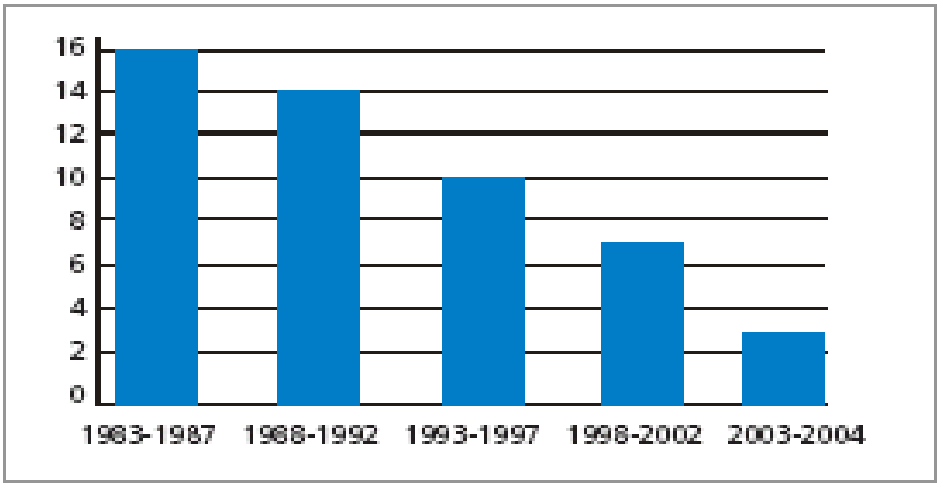

Figure 5: Number of antibacterial agents discovered between 1983 and 2004 (5-year Intervals) (12)

Actually more than 10,000 antibiotic molecules exist, but only a hundred, from which a quarter are representing beta-lactams, are effective and suitable for therapeutic use. Others are either too toxic, too unstable or they have poor bioavailability in human body.

Nowadays many antibiotics are used, but their overuse leads to resistance of some bacteria (e. g. *Staphylococcus aureus*, *Pseudomonas aeruginosa*), so diseases that were already treated successfully with antibiotics, are again becoming incurable. Antibiotic resistance therefore poses a significant problem (13).

4.3.1. WAYS TO PREVENT RESISTANCE OF BACTERIA

The most important ways to prevent resistance of bacteria are:

• to support vaccination campaigning

• to minimize unnecessary prescribing and overprescribing of antibiotics. This occurs when people expect doctors to prescribe antibiotics for a viral infection or when antibiotics are prescribed for conditions that do not require them;

• to complete the entire course of therapy with the prescribed antibiotic, so that antibiotherapy can be fully effective and not breed resistance;

• to practice good hygiene and use appropriate infection control procedures.

Especially in hospitals the practice of good hygiene is very important. Common ways, in which bacteria can be passed from patient to patient, include contact with contaminated hands of hospital staff, contact with contaminated surfaces or contact with contaminated equipment (14).

Other very important ways to prevent resistance of bacteria are also:

• avoiding usage of too low doses of antibiotics;

• adapting duration of treatment and avoiding treatments that are either too short (less than 8 days) or too long;

• diminishing the massive use of antibiotics in agriculture, veterinary medicine and livestock meat industry.

4.4. THE MISUSE OF ANTIBIOTICS

The misuse of drugs can also lead to serious adverse events, where outcome is hospitalization or prolonged hospitalization, life-threatening state, or even death (15).
The class of antibacterials is one of the classes of drugs that are strongly affected by adverse events in the field of ambulatory and also hospital health care.

Misuse of antibiotics can have various consequences:
- individual consequences: increased morbidity and mortality, adverse effects (diarrhea, allergies), the emergence of resistance as the cause of failure in treatment, superinfections, reason for cross-transmission, etc.
- collective consequences: increased bacterial resistance to antibiotics, encouraging the use of broad-spectrum antibiotics, etc.

These problems have various origins:
- multiple prescribers with unequal level of knowledge,
- routine in antibiotic prescribing, despite complexity and diversity of different clinical cases,
- lack of access to the information necessary for the prescription in everyday practice (clinical and therapeutic recommendations, results of microbiological researches and epidemiological information)
- incomplete and inadequate protocols in clinical practice (lack of information on dosages, methods of administration, duration of treatment, etc.) (16).

Therefore, many studies and actions have been conducted to fight the misuse of antibiotics. A policy regarding rational use of antibiotics should be defined within every health care facility.
The development, provision and use of protocols, the implementation of recommendations and organization of trainings also contribute a lot to improving of the quality of use of antibiotics in health care facilities.

4.5. HOW TO CHOOSE THE OPTIMAL ANTIBIOTHERAPY?

The choice of antibiotherapy usually depends on several criteria, such as:

• **the bacteria itself**; it is necessary to identify the site of infection for an accurate diagnosis. The agent causing the infection can be identified or not. If infection is proved, the choice of antibiotherapy will be made depending on susceptibility of tested bacteria to a panel of antibiotics. In case that bacteria is not identified and prescription of antibiotherapy is made in the absence of bacteriological information, treatment is probabilistic;

• **individual characteristics of the patient**; it has to be considered that some antibiotics require dosage adjustments or they are even contraindicated in patients with renal or hepatic insufficiency or failure. In addition, some people are allergic to some families of antibiotics;

• **properties of the antibiotic**; the families of antibiotics differ in their spectrum of activity against bacteria. The spectrum of activity of an antibiotic is a list of bacterial strains on which an antibiotic is active and it is unique for each antibiotic, but it can vary over time due to the emergence of bacterial resistance. Antibiotics can be divided in two classes; in one class there are narrow-spectrum antibiotics that are selective and active only against specific bacteria. Therefore, they are prescribed when the bacteria causing the infection are known. They are generally less hazardous to the human bacterial flora that is necessary for the health of the body than the second class of antibiotics. In other class there are broad-spectrum antibiotics that are active against a wide spectrum of bacteria. They are prescribed when the bacteria causing the infection is not known or when the infection is caused by several different bacteria. Unfortunately, these antibiotics also destroy the "good" bacterial flora of human body. Regarding properties of the antibiotic we also have to take into account the pharmacokinetics of the antibiotic and the fact that some antibiotics are known as "concentration dependent" while others are "time dependent". In addition, it is necessary to pay attention also to the diffusion of the antibiotic to specific sites (brain, bone, etc.).

We also shouldn’t forget, that all antibiotics can have side effects such as allergies, diarrhea or stomach pain;

• **correct route of administration**; sometimes patients are in very severe health conditions or they can not swallow, so the choice of appropriate route of administration plays important role;

• **initiation of antibiotherapy has to be on time**; this depends on the health conditions of the patient. If health conditions are not severe and the site of infection is not detected yet, it's better to localize infection first and make bacteriological researches to identify the germ and the site of infection. In many cases, due to severity of health conditions, we can not afford that and it is better to start probabilistic treatment as soon as possible. In this case the re-evaluation of initially prescribed antibiotherapy is even more important, since in most cases we can switch to narrow-spectrum antibiotic after completing the bacteriological research.

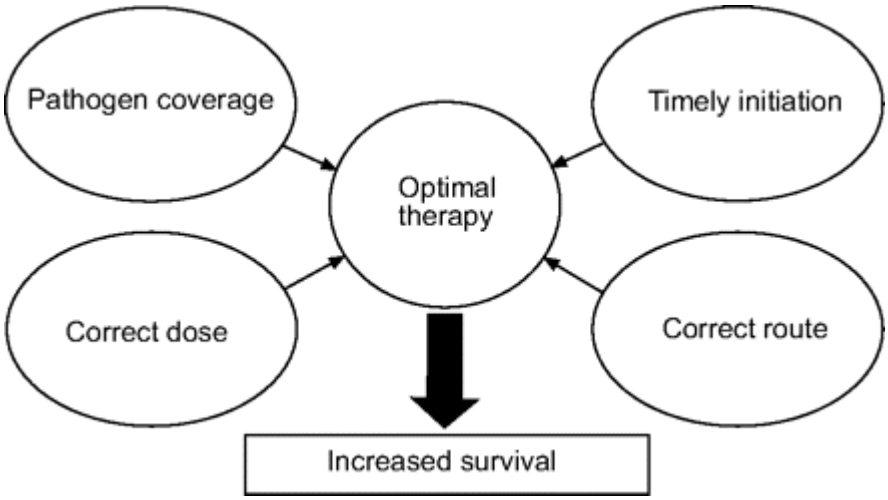

Figure 6: Factors that should be considered when choosing the optimal antibiotherapy

4.6. THE RATIONAL USE OF ANTIBIOTICS

The aim of rational use of antibiotics is to choose the best possible treatment for each patient, while also taking in consideration minimizing the emergence of resistant bacteria. It is based on team work of all health care professionals, trainings, monitoring of MDRB and monitoring of consumption of antibiotics.

4.6.1. OBJECTIVES OF RATIONAL USE

The rational use of antibiotics has many objectives:
- regarding the patient (effective cure usually means that treated patient can leave health care institution as soon as possible),
- regarding the prescriber (aim is to make his best in favor of the patient),
- regarding administration of health care institution (rational use of antibiotics affects also the costs related to treatment),
- regarding microbiologists and epidemiologists (they can contribute a lot to diminishing of emergence of MDRB)

4.6.2. RULES FOR RATIONAL USE OF ANTIBIOTICS

The appropriate use of antibiotics in curing infections and in using them as prophylaxis, depends on: (17, 18)
- early and accurate diagnostics,
- correct therapeutic indication,
- optimal treatment, that is justified and that respects optimal duration of treatment,
- the best benefit/risk ratio for the patient as an individual (avoiding adverse effects and choosing less invasive route of administration, if possible),
- a medical decision based on the best available scientific evidence,
- taking into account patient’s preferences,
- control of the emerging MDRB.

Similarly, the general practice of prescribing antibiotics can be summarized as:

1. To choose an active molecule for the identified or suspected bacteria.
2. To choose a molecule that diffuses as active and effective substance at sufficient concentrations to the site of infection.
3. To choose the optimal dose and dosing interval.
4. To optimize the duration of treatment.
5. Monitoring of possible toxic risks or allergic reactions due to selected treatment.
6. To evaluate the effectiveness of the treatment (in case of prophylaxis, possible appearance of post-operative infections and in case of curative antibiotherapy, we have to observe clinical signs and bacteriological results).
7. To choose equally effective and less expensive PO form as soon as possible.
8. To analyze possible failures and to investigate the causes.
9. To minimize influences on the environment.

On the other hand, the proper use of antibiotics has several constraints such as:
• ability of prescription of antibiotics by all clinicians;
• multiplicity of clinical cases, microorganisms and antibiotics;
• high expectation of quality of care from the patients' side;
• rapid evolution of science requires lifelong learning;
• scarcity of skilled clinicians, since extra educational courses are not obligatory and it depends on the interest of clinicians whether they want extra knowledge regarding rational use of antibiotics. However, there are also no criteria for identifying competence of prescribers.

Thus, many factors are involved in prescribing antibiotics (19).
In addition, many studies have shown the clinical benefit of appropriate choice of empiric antibiotic therapy. Indeed, inadequate antibiotic therapy may affect the prognosis of the patient and it can lead to bacteremia or death (20, 21), while an appropriate antibiotic therapy reduces mortality and length of hospital stay (22, 23).

4.7. RE-EVALUATION OF ANTIBIOTHERAPY 24 TO 72 HOURS AFTER INITIAL APLICATION

4.7.1. DEFINITION

Re-evaluation of antibiotherapy is a checkup that is done as soon as we have more information about certain clinical case. For the first re-evaluation it's important that we do it on time, but at the latest 72 hours after initial application of antibiotic treatment. It is in a way a second opportunity to choose optimal antibiotherapy.

4.7.2. IMPORTANCE OF RE-EVALUATION

The re-evaluation of antibiotherapy is important in promotion of rational use of antibiotics. Re-evaluation should be done systematically 24 to 72 hours after the initial prescription, depending on various criteria (clinical effectiveness, bacteriological results, adverse effects, etc.) to achieve a de-escalation of antibiotherapy if possible.

Re-evaluation can help us with further decision:

"- Necessity of maintenance of antibiotic treatment if bacterial infection is not confirmed or the presence of infection seems very unlikely (patient without clinical signs).
- Switch from a broad-spectrum antibiotherapy to a narrow spectrum antibiotherapy on the basis of antibiogram results, which is important if we want to diminish resistance of bacteria in general.
- If an combination of antibiotics had been initially selected, including an aminoglycoside with a beta-lactam, in most cases we can do de-escalation to monotherapy. On the other side, positive antibiogram for bacteria like *Staphylococcus aureus* or *Pseudomonas aeruginosa* can lead to change of monotherapy to combination therapy (24). "

The main goal of this re-evaluation is to reduce the emergence of bacterial resistance with diminishing use of antibiotics to a minimum by taking into account bacteriological and clinical criteria, while maintaining optimal treatment for the patient. With all these

decisions we can also reduce the financial costs of treatment by reducing use of antibiotics or by changing of the route of administration (switch from IV to PO).

4.7.3. THE IMPORTANCE OF CORRECT INITIAL PRESCRIPTION

The re-evaluation can be considered as significant only after correct initial prescription, which means having answers to the questions regarding:

- the suspected bacterial target,
- the pharmacokinetic or pharmacodynamic properties typical for the infected area or for the patient.

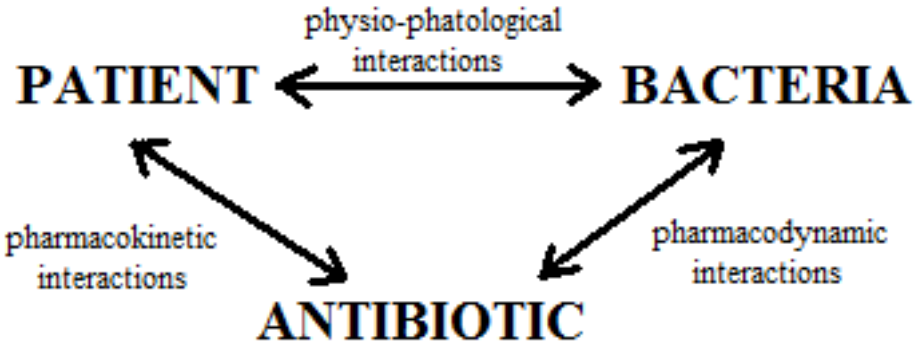

Figure 7 : Relationship between patient, bacteria and selection of optimal antibiotherapy

Correct initial prescription depends on medical knowledge of prescriber in the field of pathophysiology, clinical pharmacy, microbiology, epidemiology and pharmacotherapy. The prescribing physician has to link these different aspects to a whole at the time of initial prescription and at the time of re-evaluation.

The difficulty of prescribing optimal antibiotherapy seems especially important because:

- the target of antibiotics is a living organism, that has specific segments called regions of genomic plasticity (RGPs),
- the prognosis of the patient can quickly get worse, if initial treatment is not carefully selected and correct. Consequences of inappropriate initial treatment can often lead to the introduction of broad spectrum antibiotics treatment or to addition of another antibiotic (combination therapy), especially if general clinical state of the patient is severe.

Supervision and mentorship of experienced doctors to less experienced prescribers and them following the protocols regarding empirical antibiotherapy prescription, also plays an important role in reducing misuse of antibiotics and wrong diagnoses.

Prescription of probabilistic antibiotic treatment should be limited to maximum 3 or 4 days. We should also pay higher attention to the duration of antibiotic use for different indications.

4.7.4. WHY TO INSIST ON MAKING RE-EVALUATION?

According to recommendations of French National Authority for Health (Haute Autorité de Santé; HAS), the continuation of antibiotherapy at the time of re-evaluation should be supervised by senior physician (head of the department, infectologist, etc.) (25).

Re-evaluation of antibiotherapy often raises different questions from those at the point of initial prescription. It is recommended to answer them, even if sometimes we could be satisfied with an effective treatment or with the fact that isolated bacteria are sensitive to the prescribed antibiotic.

Many arguments can be used to favor one antibiotic treatment over another regarding sensitivity on the antibiogram. These arguments can have different points of view:

- Microbiological aspect:

For example, changes in treatment are recommended for treatment of pneumococcal meningitis based on values of minimum inhibitory concentrations of amoxicillin, cefotaxime and ceftriaxone if the isolated strain is *Streptococcus pneumoniae* (24).

- Pharmacological aspect:

Some infection sites, like meninges, eye or bone, are specific and because of this we have to pay attention to choosing antibiotics that have sufficient diffusion. Also in the case of prosthetic material we have to choose an antibiotic that is active against bacteria in stationary growth phase.

We must also take into account the relation between the pharmacokinetics (absorption, distribution, metabolism and elimination) and pharmacodynamics (the relation between concentration and antibacterial effect). If necessary, microbiological assays of antibiotics can be of help.
It is also necessary to adapt the dosage interval regarding pharmacokinetics of antibiotic to achieve desired concentrations.

- Aspect of rational use:

This criteria underlies the concept of recommendation regarding choosing certain antibiotics, that are considered as a reserve. Glycopeptides are, for example, antibiotics that are given to patients infected with Gram-positive bacteria, for which there is no alternative therapy due to resistance or allergy (e.g. when treatment with β-lactam antibiotics is not an option) (26).
Decision for prescribing an aminoglycoside is usually due to the need of rapid bactericidal activity. Due to this, clinical cases, where we find an aminoglycoside used in combination, are usually serious or there is a risk of progression to sepsis and/or septic shock. In these cases we can decide for de-escalation only at the point of re-evaluation, when we examine individual case once again with more detailed information.
Also, some recommendations state that at the time of the re-evaluation, the maintenance of any combination of antibiotics should be discussed. Usually, the maintenance of an combination should not be continued for more than three days, except in rare situations (25).

- Economic aspect:

The prescribing physician should also be aware of the amount of the daily costs, dosages and recommended duration of treatment for certain indication.
Usually we can significantly diminish unnecessary costs already with appropriate earlier switch from IV to PO therapy, without putting the patient at increased risk (27).
However, if the *per os* route is appropriate to treat some infections, the intravenous route is obligatory for others, like bacteremia, meningitis, endocarditis, etc. In general, it is unnecessary to begin the treatment of infection with most expensive antibiotics, unless life of the patient is endangered.

- Aspect regarding toxicity:

We have to observe possible side effects of the treatment and also follow laboratory results of blood concentrations of certain antibiotics.

The virtual disappearance of chloramphenicol use and the low use of lincosamides have significantly reduced the risk of toxicity to human body (hematotoxicity, pseudomembranous colitis). We can avoid this problem in most cases with withdrawing aminoglycosides after initial combination therapy after three days of treatment, when possible, or by monitoring residual serum levels to reduce nephrotoxicity. In any case, we have to follow patients' response to any antibiotic treatment.

- Use in practice:

At the point of re-evaluation, we should also focus on patients' response to initially established treatment (adherence to treatment: route of administration, dosing interval, number of pills that have to be swallowed, palatability, etc.). The role of nurses can also have a big impact regarding route of administration or preparation of the antibiotic that is given IV.

Ignorance of these concepts, their complexity or lack of supervision of prescribers can explain why 30% to 50% of hospital prescriptions of anti-infective agents are supposed to be inadequate (28, 29).

It is the role of the Anti-infection Agents Committee (Commission des Anti-Infectieux; CAI) and its multidisciplinary nature to distribute recommendations to less experienced prescribers by involving their members in the teaching of correct anti-infective therapy, especially in the field of "rational use of antibiotics". It’s also important that they present the importance of a re-evaluation as a basis for quality of treatment.

The recommendations regarding rational use of antibiotics are supposed to ensure that patients receiving antibiotic treatment are a part of re-evaluation of antibiotherapy 24 to 72 hours after initial application, and that further decision should be discussed or at least marked in patient’s medical record and in a nursing file.

In addition, information regarding antibiotic therapy should be also included in the patient's discharge paper (25).

4.8. REGULATORY ENVIROMENT

At the moment, calculation of ICATB (Composited Index regarding rational use of antibiotics ; Indice Composite de bon usage des Antibiotiques), V2010 certification and Agreement of proper use (Contrat de bon usage ; CBU) require the evaluation of the rational use of antibiotics in France.

Recommendations regarding rational use of antibiotics in hospitals recommend a re-evaluation of antibiotherapy 24 to 72 hours after initial application, when we already have the majority of the information regarding:

- results from antibiogram about bacteriological samples regarding bacterial strain and sensitivity,
- actual presence of the infection,
- clinical image about hospitalized patient and evolution of the infectious disease,
- tolerance or response to the treatment (25).

To encourage health care institutions to implement these recommendations about re-evaluation after 24-72 hours, several requirements have been drafted and indicators were developed.

4.8.1. RECOMMENDATIONS OF HAS

In April 2008, the Health care Authority (Haute Autorité de Santé, HAS) made professional recommendations called "Strategy of antibiotic therapy and prevention of bacterial resistance in health care" (25).

Concerning the general organization of the prescription of antibiotics in hospitals, these recommendations make clear that antibiotics should be prescribed and dispensed for each individual patient, also with information about expected duration of the prescribed

treatment. Computerization of prescribing and dispensing would enable better traceability, monitoring and analyzing of consumption of antibiotics.

4.8.2. ICATB (Composited Index regarding rational use of antibiotics ; Indice Composite de bon usage des Antibiotiques)

According to the national fight against nosocomial infections, the Ministry of Health has developed national indicators that have to be collected in France on an annual basis.

The list of 5 indicators regarding nosocomial infections:

- L'ICALIN (Composited Index of Activities of the fight against nosocomial infections; Indice Composite des Activités de Lutte contre les Infections Nosocomiales)
- L'ICSHA (Index regarding consumation of hydroalcoholic solutions; Indice de Consommation de Solutions Hydro Alcooliques)
- Le SARM (Indicator on Methicillin-resistant *Staphylococcus aureus* (MRSA); Indicateur relatif à *Staphylococcus aureus* Résistant à la Méticilline)
- Le SURVISO (Indicator for the existence of surveillance about surgical site infections; indicateur relatif à l'existence d'une SURVeillance des Infections sur Site Opératoire)
- L'ICATB (Composited Index regarding rational use of antibiotics; Indice Composite du bon usage des AnTiBiotiques)

The monitoring of ICATB is a part of comprehensive approach to improve the quality of health care. Annual calculation of ICATB for health care institutions is mandatory as a part of activities against nosocomial infections. The calculation methods are detailed in the ICATB document (30).

The improvement achieved with ICATB should result in reduction of misuse of antibiotics and thus reduce the unnecessary exposure of patients to antibiotics. This would also help to control the bacterial resistance to antibiotics and to preserve antibiotic effectiveness (31, 32).

The re-evaluation of antibiotherapy is also a part of ICATB and it is worth 2.5 points out of 20. To fulfill this requirement, audit about the rational use of antibiotics should be made in hospital at least once a year.

4.8.3. V2010 CERTIFICATION AND THE PROPER USE OF ANTIBIOTICS

Any health care facility should follow the recommendations and requirements of HAS. Requirements are described in a special certification manual (version 2010).
Criteria 8 h in this manual describe rules about importance of re-evaluation as well.

Regarding the appropriate use of antibiotics, the certification manual v2010 recalls that "the high consumption of antibiotics, the prevalence of bacterial resistance and the additional incurred costs are forcing health care institutions to follow the process to improve their practices. The appropriate use of antibiotics is part of national public health priorities" (33).

The certification manual states that the re-evaluation of antibiotherapy 24 to 72 hours after initial application is even more important in cases of a probabilistic treatment.

4.8.4. AGREEMENT OF PROPER USE ; Contrat de bon usage (CBU)

The University Hospital of Tours is like other health care facilities linked to its supervisory authorities by an Agreement of proper use (Contract de bon usage ; CBU).
The aim is to improve prescribing practices for a significant reduction of unjustified expenses.
Health care institutions have to follow commitments mentioned in the contract and take necessary action. In case of incompliance with commitments, the CBU is a financial penalty. Indeed, the rate of reimbursement for expenses and expensive medicaments may be reduced by the mandatory health insurance by 30% (34, 35).

4.8.5. FRENCH NATIONAL PLAN IN PRESERVING EFFECTIVENESS OF ANTIBIOTICS (2007 – 2011)

This is already the second phase of the national plan regarding preservation of the effectiveness of antibiotics and it follows the first one that was started in 2001 for the period of 5 years.

Actions taken in the first phase led to a significant decrease in antibiotic consumption. Results have shown that in the first 5 years, the consumption of antibiotics decreased by 23.4%, which is very close to the originally planned 25%. However, bacterial resistance still remains a big concern (36, 37).

The aim of the second phase is to diminish the emergence of bacterial resistance to minimum trough different actions like improving medical practices in the field of prescribing antibiotics and informing general public about the problem of resistance. Investigations in research field (new antibacterial agents and rapid diagnostic tests) are also considered as priority.

4.9. ACTIONS AT CHRU TOURS

The class of antibacterials is the only class of drugs, whose inappropriate use undermines the effectiveness by the emergence of resistance among bacterial pathogens. The cost of antibacterials, the emergence of new molecules, the awareness of the seriousness of nosocomial infections, the emergence of multidrug-resistant bacteria and aim to follow the good practice in use of antibacterials, have led to the establishment of Anti-infective Commission (CAI) at CHRU Tours in 1978.

4.9.1. GENERAL AIMS OF ANTI-INFECTIVE COMMISSION (CAI)

The CAI has to define the policy of antibiotic use at each health care institution. The necessary elements are:

- development of a list of available antibiotics;
- to coordinate the development of protocols that should serve as a reference to the prescriber and to dispensing pharmacist. A good protocol is supposed to be simple,

practical and adapted for each ward of the hospital. It should be also regularly updated and adapted in collaboration with prescribers;
- to ensure the quality of the information provided by the representatives of pharmaceutical industry and its compliance with the policy of the health care institution;
- coordination of educational trainings for everybody that is connected to antibiotherapy field (prescribers, dispensing pharmacists, nurses, etc.);
- to ensure the quality of the initial prescription of antibiotics and systematic re-evaluation after 24-72 hours and at day 7;
- to follow the aim that orders of reserve antibiotics should be for each patient individual and nominative;
- to work on establishing of computerized prescribing system that would be connecting wards, hospital pharmacy and the department of microbiology. This would be a great improvement that would allow individual prescription and dispensing for all patients and all antibiotics;
- monitoring of actions taken with clinical audits;
- monitoring of antibiotic consumption and frequency of bacterial resistance;
- contribution to researches in the field of anti-infective agents.

4.9.2. THE MAIN AIMS OF CAI AT CHRU TOURS

- Preparation of written recommendations and guidelines in form of protocols, newsletters and leaflets, that are regularly reviewed and posted on the Intranet of CHRU Tours;
- referencing of the new anti-infective agents;
- monitoring of the consumption of anti-infective agents;
- monitoring of MDRB (multidrug resistant bacteria).

However, until now not many of evaluation actions concerning the proper use of antibiotics have been undertaken. But as we have seen through the various recommendations (certification V2010, CBU, ICATB, etc.), it is necessary to evaluate good practice. The reference methodology for evaluation of practice is an audit. This is also a reason for choosing an audit regarding appropriate use of antibiotics (38, 39).
The main part of the audit focused on re-evaluation of antibiotherapy 24 to 72 hours after initial application of prescribed antibiotic.

5. AIMS AND OBJECTIVES

5.1. STUDY AIM

If we want to fulfill the rules of rational use of antibiotics, any established antibiotic therapy should be re-evaluated 24 to 72 hours after initial application of prescribed antibiotherapy.

In practice the re-evaluation is usually made by doctors or intern medical students, but not always marked in the patient record. Because of this, traceability of the re-evaluation of antibiotherapy was chosen as the theme of the audit.

5.2. STUDY OBJECTIVES

► The main objectives are:

- monitoring and evaluation of good practices, which recommend re-evaluation of initial antibiotic therapy 24 to 72 hours after initial application, which is important to ensure that hospitalized patients are receiving optimal antibiotic treatment,
- to ensure that this re-evaluation is marked in patient medical record and the reason of possible changes at the point of re-evaluation is written down, so changes in therapy can be traced.

► Secondary objectives are various:

- to improve the rational use of antibiotics,
- to implement the recommendations of good use of antibiotics,
- to educate prescribers and consequently improve their prescribing practices,
- to develop a tool for automatic and obligatory re-evaluation of antibiotherapy 24 to 72 hours after initial application,
- assessment of appropriateness of initial antibiotic therapy.

6. MATERIALS AND METHODS

6.1. THE HOSPITAL

The study was conducted in the general hospital in Tours: CHRU (Regional University Hospital Center of Tours, Centre Hospitalier Régional et Universitaire de Tours).
A public health institution, involving six hospitals (Bretonneau, Trousseau, Clocheville, Ermitage, Psychiatric clinic and Psychotherapeutic center) has a special place among other hospitals in the Central region of France. With its 2000 beds in its services, it has a capacity that allows accommodating 375 new patients every day. Each year more than 65,000 patients are treated at CHRU, which makes it the biggest and the most important hospital in the region. 27.8% of patients are residents of departments other than the Indre-et-Loire, which indicates the expertise and importance of CHRU (40).

6.1.1. WARDS

All wards from 4 hospitals were included, except the Operating units, ER (Emergency Room) and Psychiatry units.
The data on wards capacities, number of patients on antibiotherapy and the number of patients included can be found in the attachments section (Attachment 1).

6.2. DEFINITIONS

6.2.1. CLINICAL AUDIT

As we saw earlier, the aim of CAI is to evaluate the appropriate use of antibiotics. This mission is essential to fulfill regulatory requirements and to acknowledge the importance of implementing new practices at the wards.

Principles of appropriate antibiotic use prompted CAI to formalize its evaluation activities by setting up a retrospective audit regarding prescriptions of antibiotics within the services of CHRU. Indeed, the audit is an essential tool to evaluate the application of antibiotic policy.

► "Clinical audit is a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change. Aspects of the structure, process and outcome of care are selected and systematically evaluated against explicit criteria. Where indicated changes are implemented at an individual, team, or service level and further monitoring is used to confirm improvement in healthcare delivery."

or shorter :

"Clinical audit involves improving the quality of patient care by looking at current practice and modifying it where necessary. "

►"Clinical audit is essentially all about checking whether best practice is being followed and making improvements if there are shortfalls in the delivery of care. A good clinical audit will identify problems and lead to effective changes that result in improved patient care" (41).

► HAS (2004): "Clinical audit is a method of evaluation of practices compared to listed references. Its main feature is to measure the differences between observed and expected practice (usually expressed in the professional recommendations). It is an action-oriented method. Its purpose is to improve the quality of provided care. Conducting clinical audit in an integrated approach to improve quality or it may be the starting point" (42).

►General definition by WHO (1987): "Clinical audit is a scientific and systematic process designed with purpose to determine the extent to which an action or series of actions are successfully reaching a goal."

6.3. DESIGN

This audit was designed as a retrospective study, focused on the first prescribed antibiotic treatment of each patient.

6.3.1. PATIENT INCLUSION AND EXCLUSION CRITERIA

Criteria of inclusion:

Patients will be included in the study if they will match the following inclusion criteria:

- patients that are hospitalized with complete service,
- patients on antibiotherapy, which was started at least 3 days ago (antibiotherapy is in progress),
- patients that were taking antibiotherapy during hospitalization in audited unit (antibiotherapy was stopped),
- antibiotherapy was started in the audited unit or at the ER.

Criteria of exclusion due to objective reasons:

- surgical unit (where mainly patients with prophylactic treatment are hospitalized),
- ER (patients are normally transferred to appropriate ward as soon as possible),
- daily hospitalizations,
- hospitalizations only during the week (patient is “discharged” for weekend),
- psychiatry units of Psychiatric clinic and Psychotherapeutic centre (minimum use of antibiotics),
- nursing home for geriatric patients (long hospitalizations),
- patients on antibiotherapy that was initiated in some other unit or in another hospital than the audited one (except for patients for which antibiotherapy was started at ER).

6.3.2. SOURCES OF INFORMATION

The main source of data was the patients' medical record. This includes medical files, nursing file or the data written on computer and stored in online hospital database.

Data that was missing at the time of the survey were supplemented by examination of patients' records three months after the audit, with careful reading of reports in the Shared electronic patient record.

6.4. DEVELOPMENT OF A DATA COLLECTION FORM

Data were collected with the help of a questionnaire proposed by Observatory of drugs, medical devices and Therapeutic Innovations (Observatoire des Médicaments, des Dispositifs médicaux et des Innovations Thérapeutiques ; OMéDIT), but we improved the content of collection grid during the various meetings with clinicians, who are members of CAI (Attachment 2).

Guidelines to facilitate and standardize the collection of data were also prepared (Attachment 3).

The data collection form consisted of various questions and squares to be checked.
We were collecting the following information: date of the audit, audited department, patient's history, prescribed antibiotic therapy (INN name, dose and administration route), whether diagnosis is written in the patient's folder, whether initial prescription is dated and signed, etc. Furthermore information about re-evaluation were collected: whether and which microbiological research was made, whether bacterial infection was identified, whether the site of infection was researched, whether diagnosis after re-evaluation was modified, whether there are any notes regarding re-evaluation on adverse effects, economical or practical reasons, clinical signs, whether opinion of infectologist or bacteriologist is written in patient's folder, etc.
Considering all of the criteria mentioned above, re-evaluation was considered as null, partial or complete. Also the traceability of the re-evaluation was checked (date, signature). In case antibiotherapy changed after re-evaluation, new antibiotherapy was written down (INN name, dose and administration route). Nature of initially prescribed antibiotherapy was also analyzed; whether antibiotherapy was maintained, modified or stopped. In case of modification, we also checked what kind of modification was made (changes in administration, dose modification, association or de-escalation of antibiotherapy, change of

drug substance or changes in duration of treatment). We also checked if hospital discharge paper was written and when.
On the base of working diagnosis and initially prescribed antibiotherapy we also ranked the initial antibiotherapy with assistance of an infectologist as Completely appropriate, Partially appropriate or Not appropriate.

6.5. CODIFICATION OF RE-EVALUATION

As already mentioned, the re-evaluation was codified as Null, Partial or Complete, according to criteria 3, 4, 5, 6, 7 and 8:
- Criteria 3: presence of microbiological research
- Criteria 4: investigations made to localize the site of infection
- Criteria 5: concepts of adverse effects
- Criteria 6: economic concepts
- Criteria 7: clinical concepts
- Criteria 8: presence of infectologist's opinion

The criteria for defining the nature of the re-evaluation were ranked according to their importance. We classified criteria as major (criteria 3 and 4) and as secondary criteria (criteria 5-8).

To define re-evaluation of antibiotherapy as Partial or Complete, at least microbiological research must have been done and site of infection must have been determined.

Four criteria were ranked as secondary criteria:

► Notes on adverse effects (that are very likely directly related to the prescribed antibiotherapy).
► Notes on practical or economical reasons (Switch IV/PO or IV/SC) with explanation that was found in patient record. Indeed, changing of administration to *per os* treatment reduces the risk of infection associated with injecting of antibiotic. Normally changing of

administration to PO or SC means also less invasive procedure for the patient and in most cases it is also less expensive from the economical point of view.
These economic concepts and practices may also result in lower dosages and shortening of treatment to optimal duration.
► Notes on clinical signs (here we were looking for information whether body temperature was still increased or was it back to normal; was pain still present, absent or increased; whether plasma level of aminoglycosides was in therapeutic values, etc.
► Notes on infectologist's, bacteriologist's or Intensive care unit (ICU) clinician's opinion were also found in some patient’s records.

If there were no notes regarding bacteriological research made, or if the focus of infection was not detected, the re-evaluation was automatically defined as Null.
We defined re-evaluation as Partial if these two main criteria were fulfilled and there was maximum of 1 secondary criteria marked as well.
Finally, we listed re-evaluation as Complete if two main criteria were present with at least 2 secondary criteria (notes on adverse effects, economic concepts, clinical signs or the opinion of the infectologist).

6.6. PILOT STUDY

We tested the questionnaire a few weeks before, at the ward of Infectious Diseases, to check if the questions are clear enough for the audit to be feasible and clear for analyzing the collected data.

The aim was to find marked re-evaluation of antibiotherapy in patients' records with as many information as possible, regarding the decision that was taken further on.

6.7. DATA COLLECTION

The audit was made for 10 consecutive days, from Tuesday 13th to Friday 24th of September 2010.

Each ward had to be audited from the beginning to the end on the same day, to assure reliable results regarding total number of hospitalized patients with antibiotherapy. Even though we could not include all of them in the audit because of exclusion criteria (presence of antibiotherapy for minimum 3 days, prophylaxis, etc.), we wanted to see what is the percentage of hospitalized patients with prescribed antibiotherapy.

Since it would be impossible to finish auditing the selected wards in 4 hospitals in 10 chosen consecutive days, we had some extra help from extern students of pharmacy, that were going through their practice at the hospital at that time.

We audited patients that were on broad-spectrum or narrow spectrum antibiotherapy, only patients on prophylaxis were excluded. Antibiotherapy had to be prescribed for at least 3 days before.

The evaluation was limited to antibiotics that are found on ATC list, code J01.

6.8. STATISTICAL ANALYSIS

The data gathered was analyzed with the help of descriptive statistic in Excel program.

7. RESULTS AND DISCUSSION

We audited 70 units in all four hospitals of Tours, which have 1112 beds and 885 patients were hospitalized during the audit. 150 questionnaires were filled in, but only 146 were exploitable, since we realized later that 4 patients were actually receiving prophylaxis antibiotherapy. We can conclude that 16.5% of the hospitalized patients were receiving antibiotherapy for minimum three days at the same unit. In total, 240 patients or 27.1% of all hospitalized patients, were receiving curative antibiotherapy on the day of the audit.

7.1. DISTRIBUTION OF PATIENTS INCLUDED IN THE AUDIT

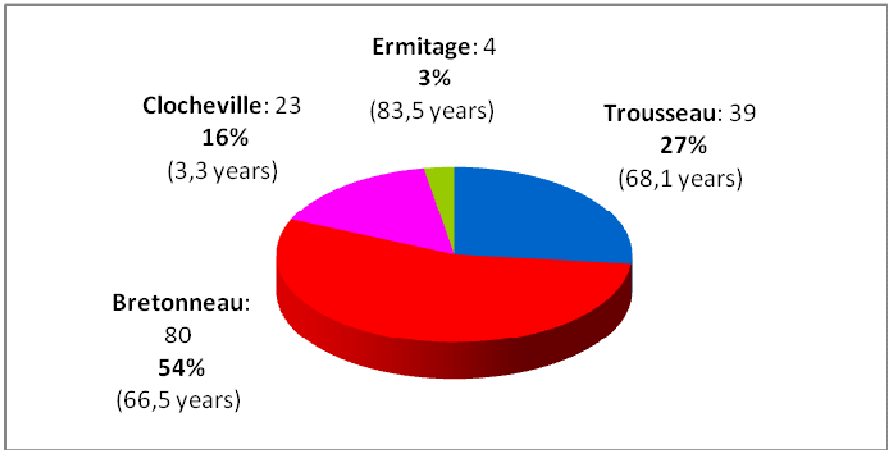

Figure 8: Distribution of included medical records regarding different hospitals (average age of enrolled patients is given in parenthesis)

The percentage of completed questionnaires in the hospitals of Tours was as follows:

• 27% in hospital Trousseau. The average age of enrolled patients was 68.1 years.

• 54% of the questionnaires were done in hospital Bretonneau.

The average age was 66.5 years.

• 16% in pediatric teaching hospital (hospital Clocheville).

The average age of children that were included in audit was 3.3 years.

• 3% or 5 patients were hospitalized in Ermitage hospital, which is actually a geriatric institution. The reason for a low number of completed questionnaires in Ermitage is the fact that patients are often transferred between units and therefore they were excluded from the survey. The average age was 83.5 years.

Regarding gender, 52.7% of patients, that we analyzed, were female and 47.3% were male.

7.2. DIVISION BY CATHEGORY

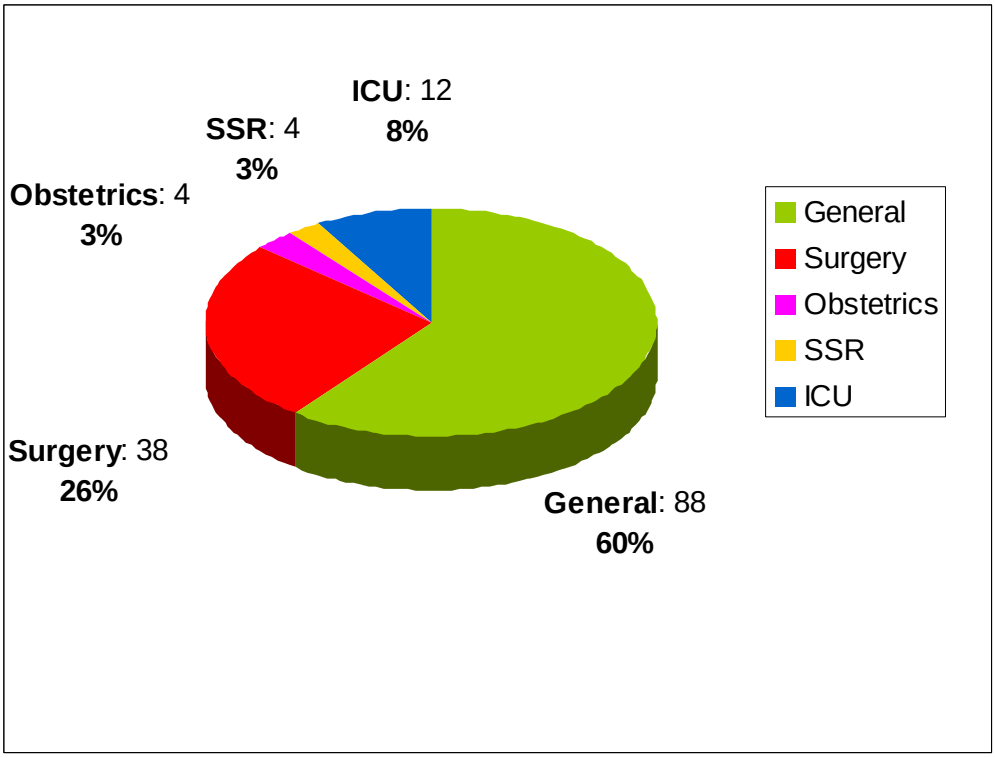

Figure 9: Distribution of included medical records depending on area

The questionnaires were done at different wards:

• 60% in general health services.

• 26% in surgical wards. This is primarily because of the therapy of secondary infections after operations. The antibiotic prophylaxis was not included in the survey on the basis of the criteria of exclusion.

• 8% at ICU (Intensive Care Unit).

• 3% in obstetrics wards.

• 3% in SSR (Care and rehabilitation units).

7.3. ANTIBIOTIC TREATMENT BEFORE ARRIVAL AT THE CHRU

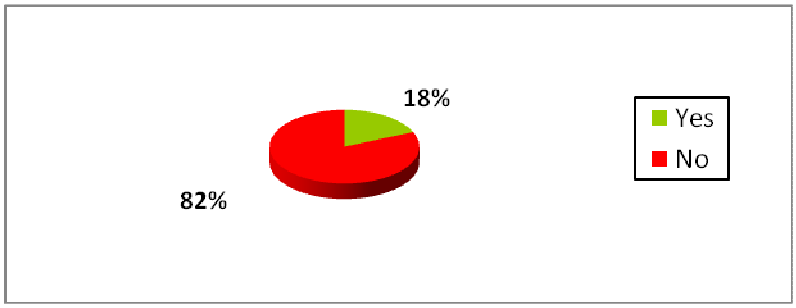

Figure 10: Presence of antibiotherapy before arrival at CHRU

18% of patients started with antibiotherapy before they were hospitalized at University Hospital of Tours. In all the cases but one antibiotherapy was modified at CHRU.

7.4. ADMISSIONS TROUGH THE ER

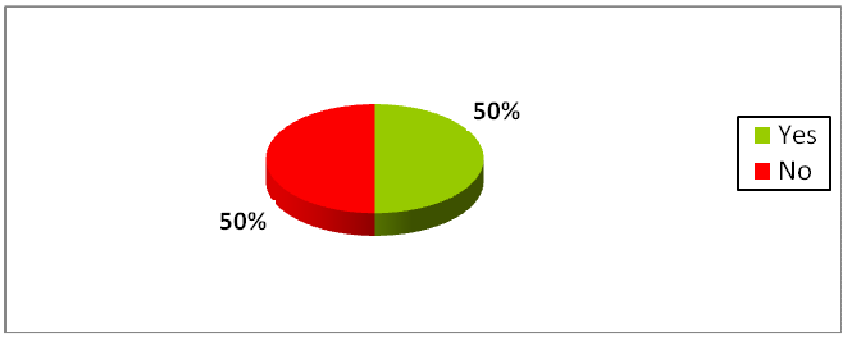

Figure 11: Admissions trough the ER

Exactly one half of the audited patients were admitted trough the ER.

7.5. INITIATION OF ANTIBIOTIC TREATMENT AT THE ER

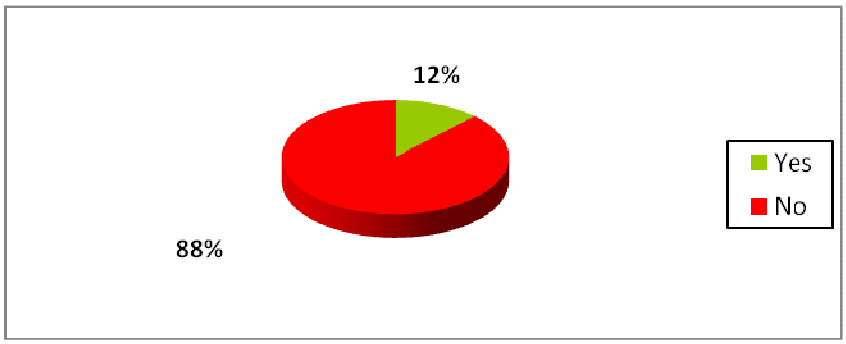

Figure 12: Initiation of antibiotic treatment at the ER

12% of the patients started with antibiotic treatment already at the ER. In 89% of these cases the prescribed treatment was probabilistic, but immediate beginning of antibiotherapy was needed due to severe health condition of the patients. However, usually bacteriological research is primarily done at the arrival of the patient to the ER.

7.6. INITIAL PRESCRIPTION OF ANTIBIOTHERAPY

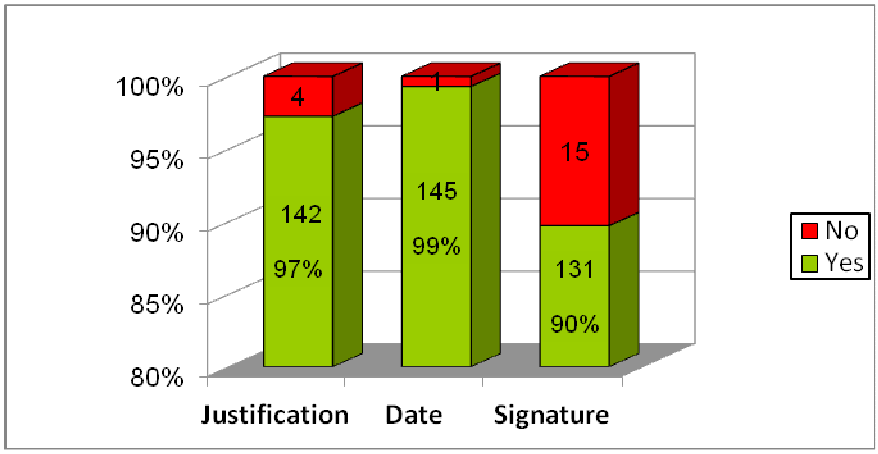

Figure 13: Traceability of the initial prescription

• The initial prescription is justified in the patients' records in 97% of cases. This justification is often written in comments as an initial diagnostics.

• Similarly, the initial prescription is dated in 99% and signed in 90% of cases. These two important data are found on special nurse's files.

Here we should also mention that department of Orthopedic Surgery for adults at Trousseau, Pneumology units at Bretonneau and Visceral Surgery at pediatric hospital Clocheville have better results due to computerized prescription software "Actipidos", where we can find all information regarding prescriber and date, also with exact time of prescription. In these cases, the traceability of the initial prescription is complete because the prescriber can not prescribe medicines without logging-in to the system.

7.7. THE MAIN CRITERIA OF THE RE-EVALUATION

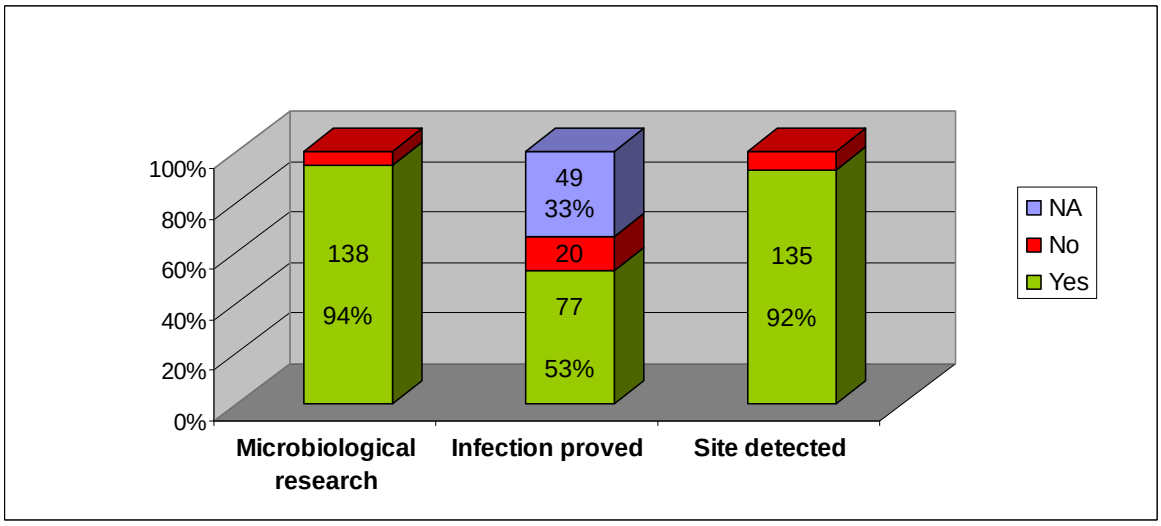

Figure 14: Main criteria that were taken as crucial at the time of re-evaluation

• The microbiological research was made in 94% of cases. At this point, we were looking for information whether some of the samples (blood, urine, stool, sputum, tissue or prosthetic material…) were taken and investigated.

This research is made with the aim to confirm infection. During the audit in 53% microbiological research identified the bacteria causing the infection. This information is important for choosing the most appropriate antibiotic treatment with optimal efficiency and fewer side effects. Also for switching from broad-spectrum antibiotherapy to a narrow-spectrum antibiotherapy this information is very important, especially if we want to contribute to diminishing of resistance of bacteria.

Here we should also mention that microbiological research can take up to 72 hours, so if re-evaluation was made after one or two days, maybe the results were not applicable yet. If we want to claim for sure that blood culture is negative, we have to isolate bacteria for five days and in this case we have not applicable results at the time of re-evaluation.

• The site of infection was detected in patient records in 92% of cases. Localization of the infection could be made with help of medical imagery (CT (Scanner), MRI, Ultrasound, Doppler...), relevant clinical diagnostic or with microbiologic research (e.g. positive urine culture or positive cerebrospinal fluid means the localization of infection site).

• For certain diagnoses like erysipelas, the diagnostics is often only clinical, so there is no microbiological research made. In this case, the antibiotherapy is already adapted to the suspected pathogen.

7.8. SECONDARY CRITERIA OF THE RE-EVALUATION

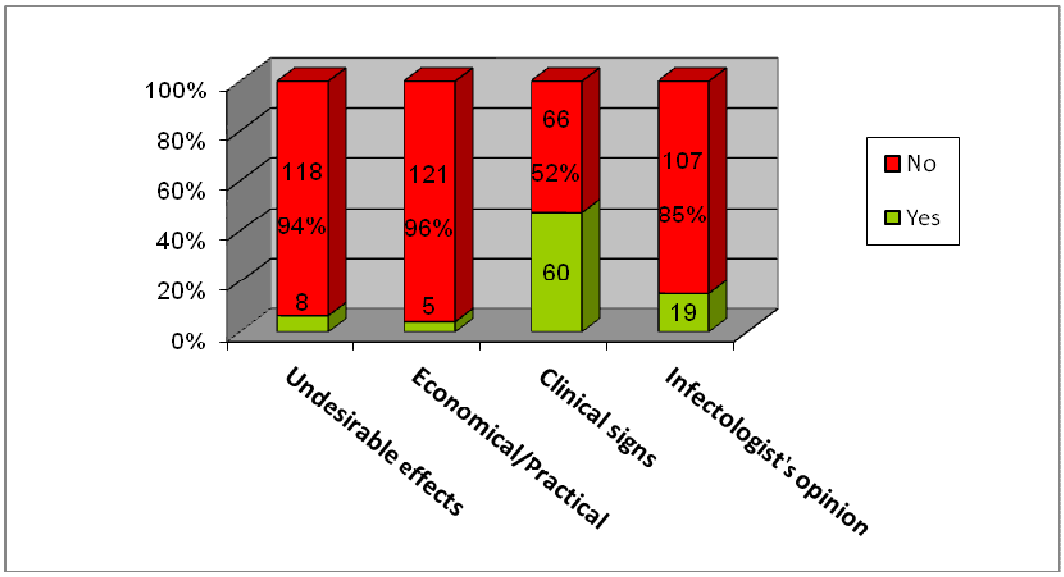

Figure 15: Secondary criteria taken in consideration at the time of re-evaluation

Regarding secondary criteria :

• 6% of unwanted effects related to antibiotic therapy were found written in patients' records.

• only in 4% of cases it was clearly marked that the change of route of administration was made because of economical or practical reasons. But in general this percentage was higher, just that the reason was not clearly marked and explained. However, we can also notice that less than 72 hours in some cases is too short to consider a change from IV to PO route.

• In 48% of audited patients clinical signs had been written down in medical record. This was mainly the persistence of fever or pain noted in the nursing file. In some patients' records we also found notifications about clearance and plasma level concentrations of certain antibiotics.

• The opinion of infectologist regarding antibiotherapy was found in 15% of analyzed cases.

7.9. CODIFICATION OF RE-EVALUATIONS IN GENERAL

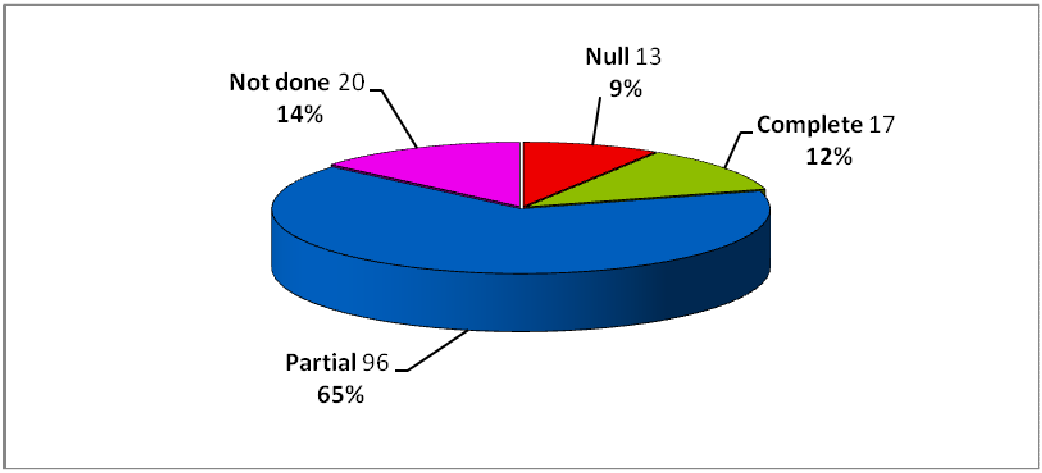

Figure 16: Codification of re-evaluations

Based on the primary and secondary criteria, the re-evaluation 24 to 72 hours after initial application of prescribed antibiotherapy had been codified. The re-evaluation was considered as Complete in 12% of cases, Partial in 65% and Null in 9% of cases. Re-evaluation was not done at all in 14% of cases.

For the re-evaluation to be Complete it was not enough to fulfill only the main criteria, but also at least half of secondary ones. Because of this, the majority of re-evaluations were Partial, since the microbiological research was done in most cases and also focus of infection was mostly found. Secondary criteria were usually not present, they were in most cases missing or we found less than two of them.

In 14% of cases the re-evaluation was not done at all. We should try to minimize this percentage with raising the awareness of prescribers that with making re-evaluation we can contribute to the optimization of antibiotic treatment.

7.10. CODIFICATION OF RE-EVALUATIONS REGARDING CATEGORIES

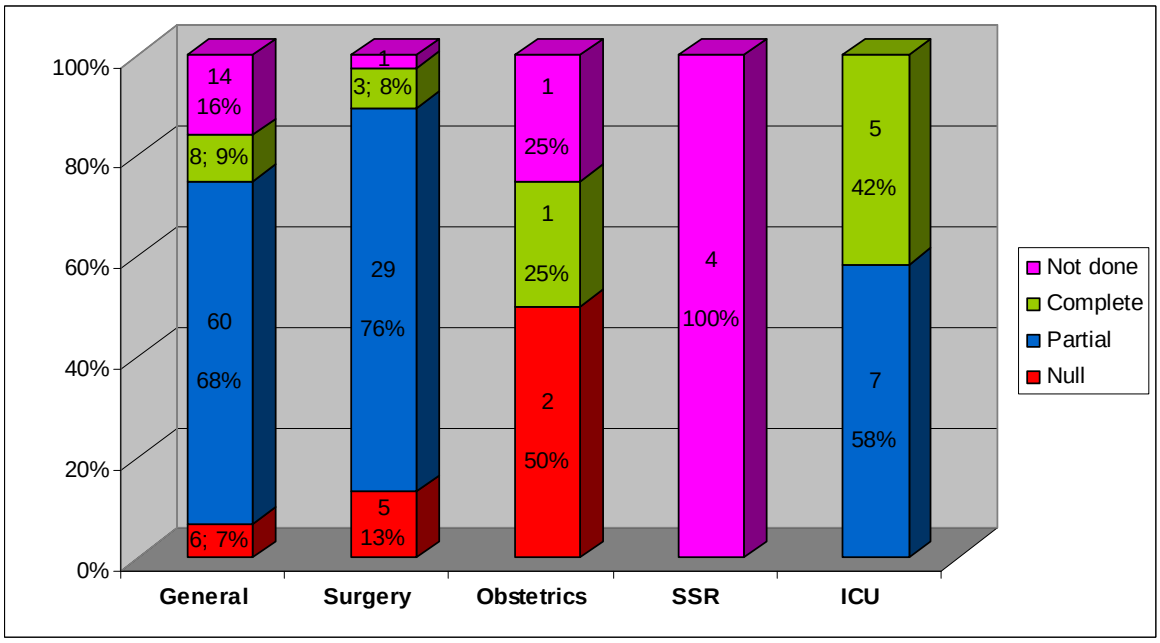

Figure 17: Codification of re-evaluations regarding categories

From this chart we can see that in ICU, where patients with serious clinical cases are hospitalized, percentage of "complete" re-evaluations is rather high comparing to other categories. There are also no cases at ICU with re-evaluations that would be considered as Null or Not done. This can be explained by ICU clinicians being experts in antibiotherapy.
On the other hand, percentage of re-evaluations considered Null is high at Departments of Obstetrics, but it is also true that the number of patients in this category is low and possibly not infected. In general here the problem was that re-evaluation was not done on time.
Also at SSR, the number of patients is relatively low, but we can notice that re-evaluation was not done at all for any of the patients. All of these cases were following some basic protocols regarding prescribing antibiotherapy. Duration of prescribed treatment was defined in all cases.

7.11. TRACEABILITY OF RE-EVALUATION 24 TO 72 HOURS AFTER INITIAL APPLICATION

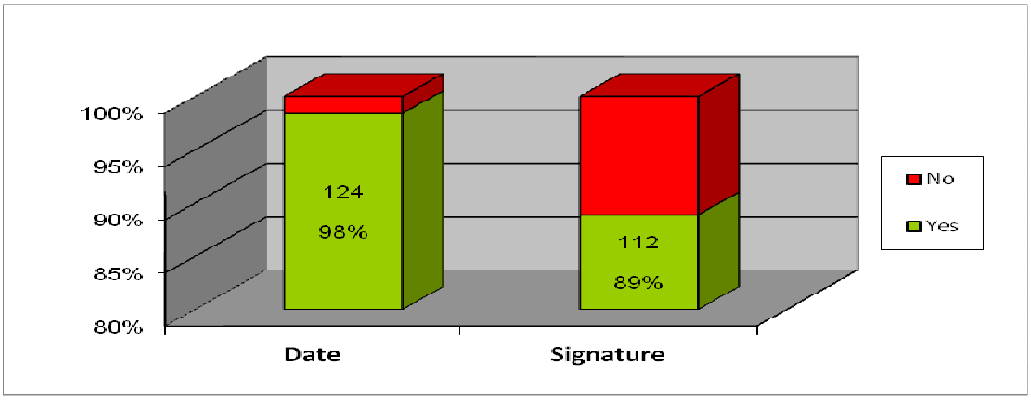

Figure 18: Traceability of re-evaluation 24 to 72 hours after initial application

The date of re-evaluation was written down in 98% of the cases and re-evaluation itself was signed in 89% of cases. Most of these data were found in nurses' files or in online hospital database. Also here we can notice the influence of computerized system at certain units that already use it.

7.12. THE NATURE OF CHANGES IN INITIALLY PRESCRIBED ANTIBIOTHERAPY

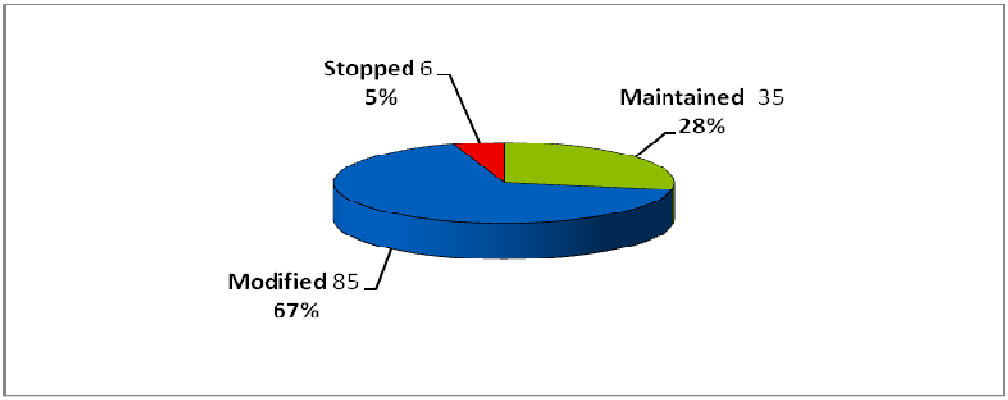

Figure 19: Nature of changes in initially prescribed antibiotherapy 24 to 72 hours after initial application

Regarding the nature of changes in initially prescribed antibiotherapy at the point of re-evaluation, antibiotherapy was maintained in 28%, modified in 67% and stopped in 5% of the cases.

7.13. THE NATURE OF CHANGES IN INTIALLY PRESCRIBED ANTIBIOTHERAPY REGARDING ITS CODIFICATION

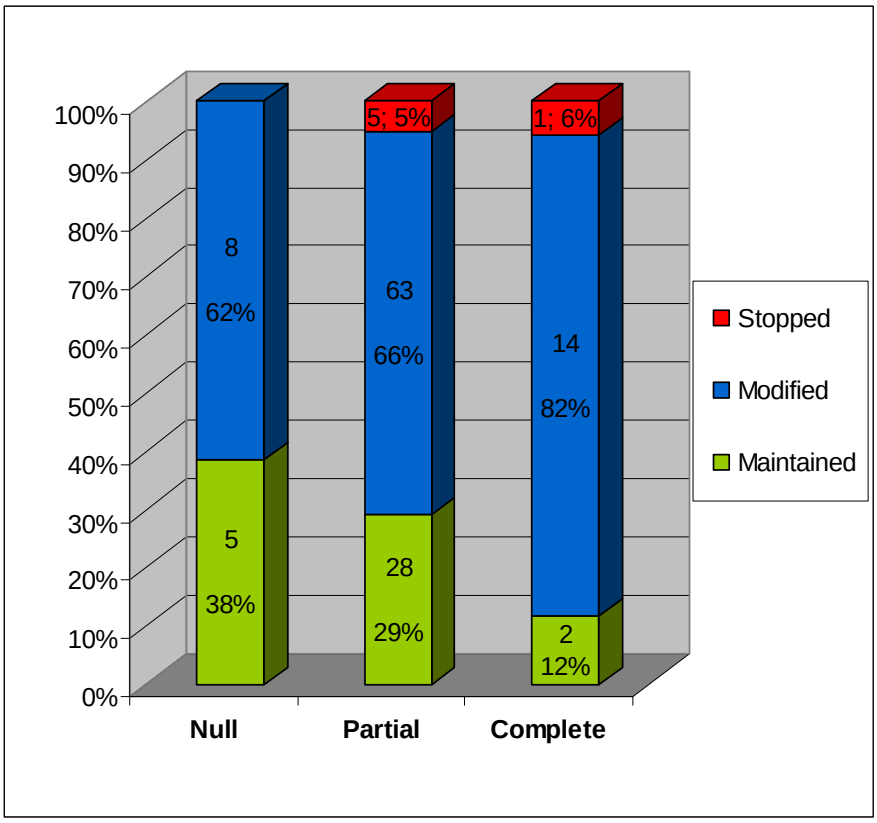

Figure 20: Nature of changes in initially prescribed antibiotherapy regarding its codification

In 82% of the initially prescribed antibiotherapies that were ranked as "complete", the initial antibiotherapy was modified. In case of "partial" re-evaluations, 66% of them were modified regarding antibiotic treatment, and only 62% of the re-evaluations that were ranked as "null" were modified.

Antibiotherapy was maintained in 12% of "complete" re-evaluations, in 29% of "partial" re-evaluations and in 38% of "null" re-evaluations.

From this we can conclude that "complete" re-evaluation is often leading to the changes of initial antibiotic treatment – to the optimization of antibiotherapy. This conclusion is very important, since it shows that making re-evaluation as detailed as possible helps us to follow rational and proper use of antibiotics, and consequently also helps in lowering of emergence of bacterial resistance.

7.14. PRESENCE OF THE MOTIVE FOR NATURE OF THE RE-EVALUATION

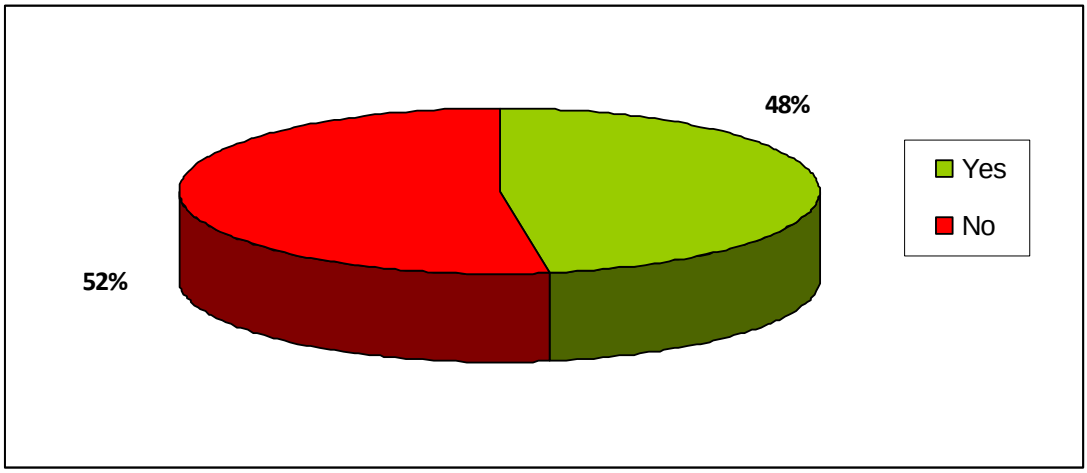

Figure 21: Presence of the motive of the nature of the re-evaluation

The motive for the modification, maintenance or stopping of the antibiotic treatment was found in 48% of patients' records. The reason was either marked in nurses' files or in online hospital database. We should encourage prescribers to write down the reason for changes, since it is important for traceability of antibiotic treatment.

7.15. PRESENCE OF MOTIVE DEPENDING ON THE NATURE OF CHANGES IN INITIAL ANTIBIOTHERAPY

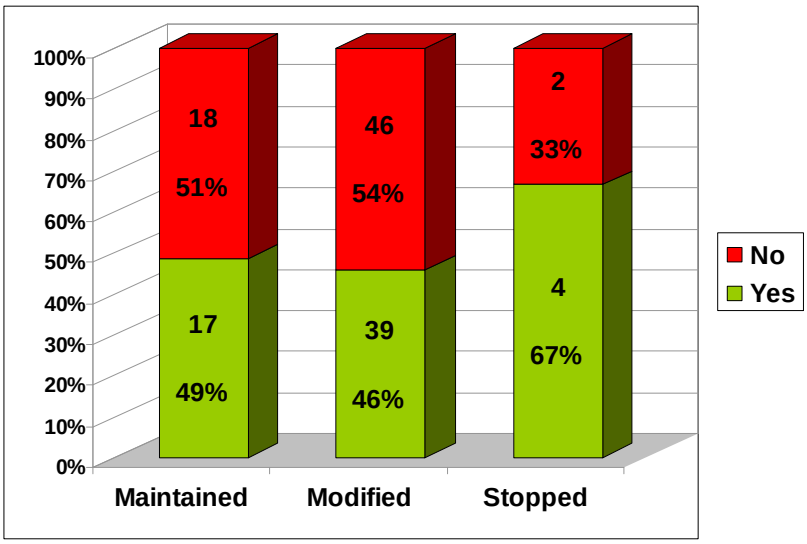

Figure 22: Motive depending on the nature of changes in initial antibiotherapy

The motive was found in 46% of cases where there was a modification of the treatment, in 49% when antibiotic treatment was maintained and in 67% in case of stopping of initially prescribed antibiotherapy.

Modification of initial treatment was often done because of the results of an antibiogram.

In cases when antibiotherapy was stopped, it was usually because of missing evidence of signs of bacterial infection.

7.16. NATURE OF THE MODIFICATION

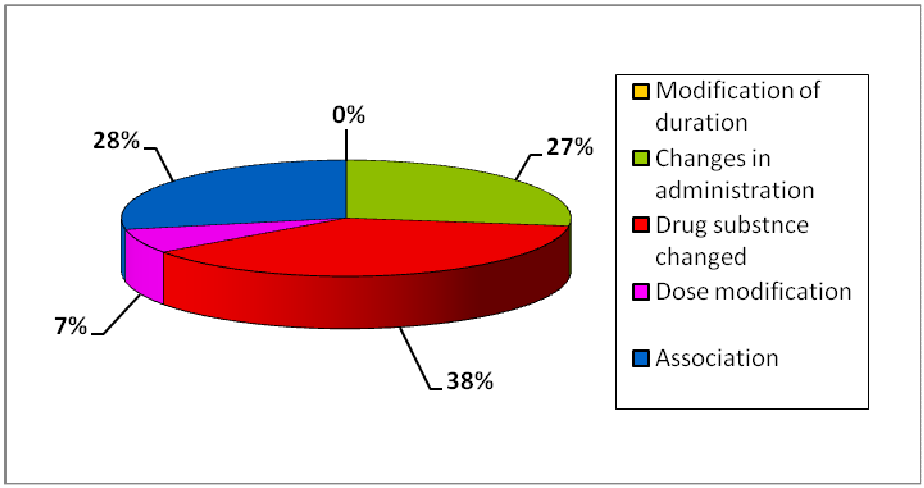

Figure 23: Nature of the modification of the initially prescribed antibiotherapy

The modification was either in:

► changes of administration: (e.g. from IV to PO or SC),

► dose modification: (e.g. in case of vancomycin loading dose is higher and then it is dropped down to a lower maintenance dose),

► association or de-escalation of antibiotherapy,

► change of drug substance (according to the results of antibiogram),

► changing of duration of treatment (this was not found because at the time of initial prescription duration of treatment is rarely indicated or there is a requirement "until further notice").

From Figure 23 we can see that in 38% initial drug substance was changed, in 28% they added or subtracted one of the antibiotics, in 27% changes in administration were made and in 7% dose was modified. We did not find any modifications in duration of treatment,

which was most probably due to the lack of information on expected duration of antibiotic treatment. Also this is one of the weak points of prescribers, since it is important to define the expected duration of treatment already at the point of initial prescription.

7.17. DISCHARGE PAPER OF THE HOSPITALIZATION

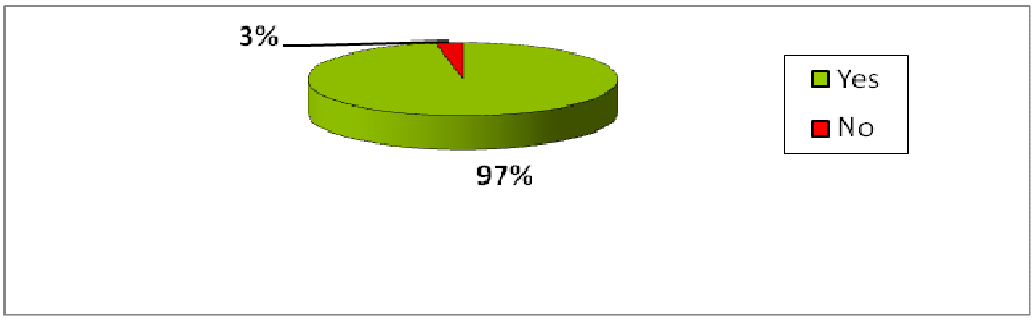

Figure 24: Presence of Discharge paper of the hospitalization

It is important that hospital staff informs personal physician also about patient's hospitalization and about medications prescribed during hospital stay. Since we wanted to get objective results, the presence of Discharge paper of the hospitalization was checked retrospectively for each patient in the Shared Patient Record (Dossier Patient Partagé ; DPP). In 97% of cases we found Discharge paper 3 months after concluding the audit at the latest.

7.18. DOCUMENTATION OF INFECTION IN DISCHARGE PAPER

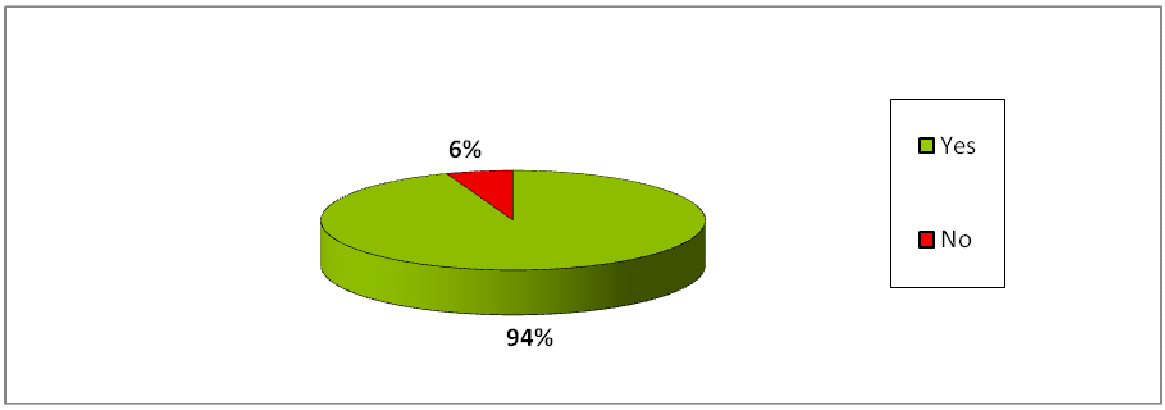

Figure 25: Documentation of infection in Discharge paper

In case of presence of Discharge paper, the infection was documented in 94% of cases. This shows that in general personal physicians are well informed about presence of infection during patient's hospital stay.

7.19. DOCUMENTATION OF PRESCRIBED ANTIBIOTHERAPY IN DISCHARGE PAPER

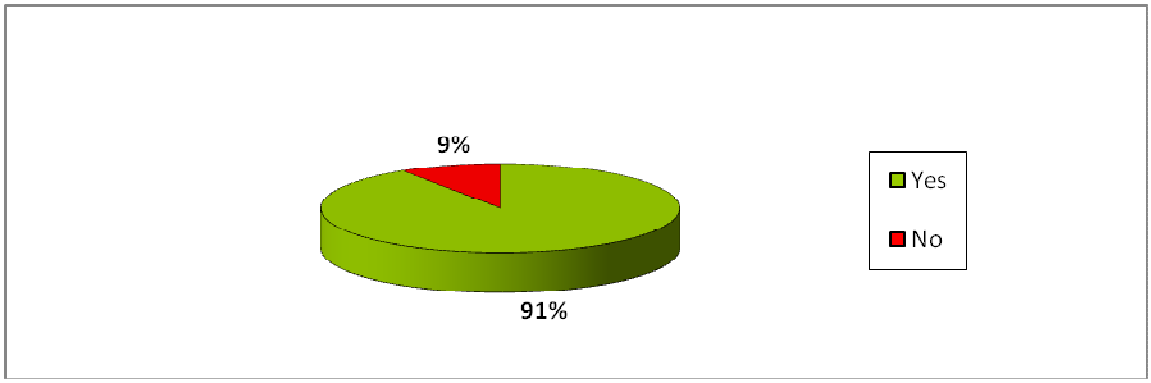

Figure 26: Documentation of prescribed antibiotherapy in discharge paper

In case of presence of Discharge paper, prescription of antibiotherapy was documented in 91% of cases.

In some cases, when patients died during hospitalization, the discharge paper was not written in details regarding presence of antibiotherapy during hospitalization.

7.20. APPROPRIATENESS OF INITIALLY PRESCRIBED ANTIBIOTHERAPY

As we already stated in the introduction, appropriate initial prescription of antibiotherapy is important for good re-evaluation. Because of this we decided to check clinical case of each patient and to rank initial prescription as Completely appropriate, Partially appropriate or Not appropriate. Since wide medical knowledge in the field of pathophysiology, clinical pharmacy, microbiology, epidemiology and pharmacotherapy is needed for this, we decided to rank appropriateness of initially prescribed antibiotherapy with the assistance of infectologist. We were able to analyze 140 of 146 patients, since we did not have all information needed for all the patients.

We came to the conclusion that the majority of initially prescribed antibiotherapies were either Completely appropriate (72%) or at least Partially appropriate (27%). Only 1% of initially prescribed antibiotherapies were Not appropriate. This results show that there was good basis for making efficient re-evaluation.

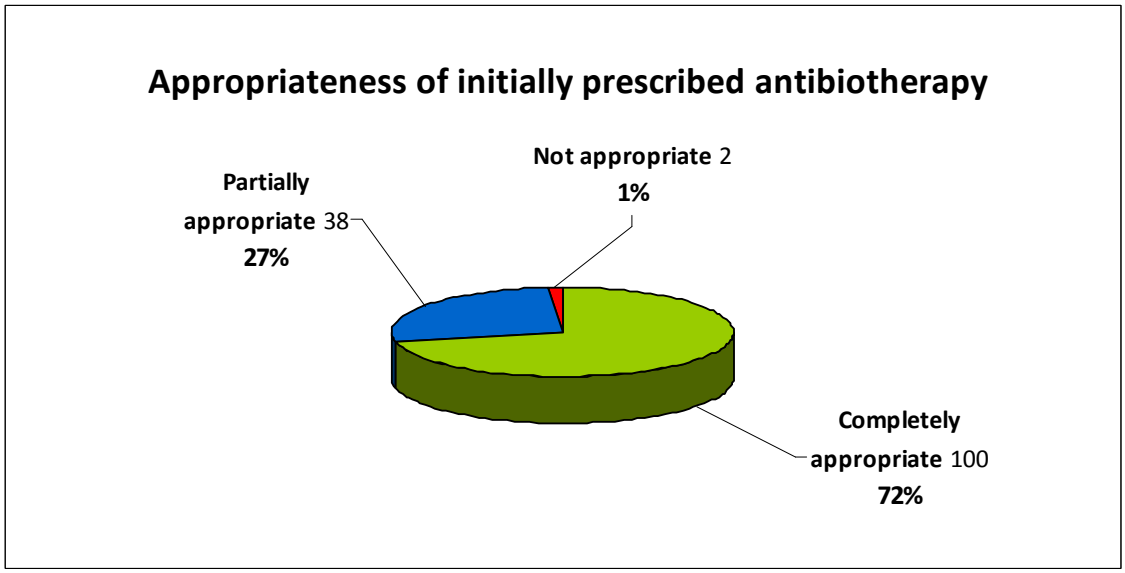

Figure 27 : Appropriateness of initially prescribed antibiotherapy

Here we also have to mention that appropriateness was ranked on base of working diagnosis and initially prescribed antibiotherapy, what does not mean that re-evaluation after 24 to 72 hours is not needed or that initial antibiotherapy will not be changed at point of re-evaluation even if antibiotherapy was ranked as completely appropriate at the beginning of treatment. The fact is that at the point of re-evaluation, when we have more information regarding microbiological research, site of infection and severity of health condition of the patient, modifications in antibiotherapy are still common, since we want to achieve optimal treatment with antibiotics.

7.21. RECOMMENDATIONS FOR IMPROVEMENT

During auditing different units, we noticed that in certain units, where computerized DPP was used on daily basis and also updated regularly, we could find a wealth of important information related to antibiotherapy and re-evaluation. Especially in units where they also use computerized prescription software "Actipidos", traceability of initial prescription and traceability of re-evaluation was complete. In few years when all wards will work with computerized prescriptions, results on traceability of re-evaluation will be even better.

We also discussed that it would be good to think about upgrading computerized prescription software in a way that an automatic alert would appear 24 to 72 hours after initial application of antibiotherapy, that would be a reminder to doctors that re-evaluation has to be made. Short version of our questionnaire could automatically open and basic facts about re-evaluation should be filled in, if doctor would want to progress in the program and to continue with computerized prescription. Possibly another alert would appear at day 7 after initial prescription and we could analyze second re-evaluation as well.

Computerized prescription of medicines is also a good way to follow and also diminish consumption of antibiotics.

For better results in future collaboration and support of all prescribers is also very important. They are the ones that play significant role in rational use of antibiotics and in diminishing emergence of resistance of bacteria. At the same time we have to assure that they do not take re-evaluation as something that is creating doubt about their knowledge regarding prescribing, but something that is essential for optimization of antibiotic treatment and rational use of antibiotics.

The next audits are planned on yearly basis to evaluate the correcting actions impact.

In future we recommend to monitor also clinical outcomes and to see what is the link between them and re-evaluations being ranked Complete, Partial, Null or Not done at all. This could be one of the ways, which would prove how important re-evaluation of antibiotherapy really is.

8. CONCLUSIONS

We have conducted a retrospective clinical audit, focused on the first re-evaluation of initially prescribed antibiotic treatment and traceability of antibiotherapy.

The study showed that :

- Modification of antibiotherapy at the point of re-evaluation is more common if re-evaluation is codified as Complete.

- Computerized prescription of antibiotherapy enable us better traceability of re-evaluation and changes in antibiotherapy during treatment.

- Percentage of clinical cases, where re-evaluation is not done, is still high in some units.

- Motive for changes in antibiotic treatment is not written down in half of clinical cases.

- Correct initial prescription of antibiotherapy is important for efficient re-evaluation.

In general we can conclude that with results of this audit it is hard to say how big the contribution of making re-evaluation of initially prescribed antibiotherapy for the better quality of antibiotic treatment actually is. With enlarged audit and linking the re-evaluation and clinical outcomes we could claim with higher reliability what is the actual importance of re-evaluation. But for sure we can say that with modification of antibiotherapy to narrow-spectrum antibiotics, de-escalation of antibiotherapy, adjusting doses and changing of administration of antibiotic we contribute to diminishing of emergence of bacteria and unnecessary costs, what is also very important.

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10. ATTACHMENTS

ATTACHEMENT 1: UNITS INCLUDED IN THE AUDIT

	UF	UNIT	Number of beds	Number of hospitalized patients	Number of patients with antibiotherapy	Number of patients included
B R E T O N N E A U	1020	MEDECINE INT.A HC	20	20	4	2
	1062	MEDECINE INT.INF.HC	20	20	11	9
	1070	HEMATOLOGIE ET TH. CELLULAIRE	19	17	2	1
	1072	ONCO. UNITE STERILE	8	7	4	3
	1091	ONCOLOGIE MED. HC	17	13	3	0
	1100	PNEUMOLOGIE II HC	20	19	16	10
	1102	PNEUMOLOGIE I HC	20	18	14	11
	1670	USI NEPHROLOGIE TRANSPLANTATION	15	10	5	4
	1160	NEPHROLOGIE HC	/	/	/	/
	1200	NEURO. CHARCOT HC	21	19	3	3
	1210	NEURO. BABINSKI HC	20	18	3	2
	1211	NEUROVASCULAIRE SOINS INTENSIFS HC	6	4	0	0
	1230	REANIMATION MEDICALE I HC	10	2	1	1
	1240	REANIMATION MEDICALE II HC	10	5	3	1
	1250	REANIMATION MEDICALE III HC	6	4	3	2
	1261	UNITE DE SURV. CUNTINUE MED	/	/	/	1
	1360	UROLOGIE HC	20	16	4	2
	1411	NEUROCHIRURGIE CLOVIS VINCENT HC	20	18	/	1
	1421	NEUROCHIRURGIE SOINS INTENSIFS	12	9	4	2
	1431	NEUROCHIRURGIE CUSHING HC	28	19	2	2
	1440	OPHTALMOLOGIE HC	10	5	0	0
	1480	O.R.L. HC	18	13	2	4
	1500	GYNECOLOGIE HC	22	14	1	0
	1520	GROSSESSES PATHOLOGIQUES HC	20	14	4	2
	1521	OBSTETRIQUE A HC	25	18	1	2
	1531	OBSTETRIQUE B HC	25	18	0	0
	1561	SURVEILLANCE NEONATALE B1B HC	8	7	3	0
	1640	MEDECINE INT. B HC	22	/	/	5
	1671	TRANSPLANTATION HC	15	12	5	5
	1672	USI NEPHROLOGIE TRANSPLANTATION	/	/	/	/
	1880	MEDECINE INTERNE GERIATRIQUE HC	25	24	5	6
	1970	CORAD HC	15	13	0	0

	UF	UNIT	Number of beds	Number of hospitalized patients	Number of patients with antibiotherapy	Number of patients included
TROUSSEAU	2020	CARDIOLOGIE B HC	30	28	2	0
	2060	GASTRO ENTERO A HC	16	16	4	2
	2082	HEM. DIGESTIVES HC	3	3	3	0
	2080	GASTRO ENTERO C HC	16	15	4	3
	2110	DERMATOLOGIE C HC	24	24	7	2
	2120	RHUMATOLOGIE HC	26	26	6	2
	2150	CHIR.VASCULAIRE HC	19	17	5	3
	2170	ORTHO-TRAUMA 2A	26	19	6	2
	2190	ORTHO-TRAUMA 2C	26	23	6	3
	2202	CHIRUR. DIGESTIVE A	34	31	15	7
	2212	CHIR. THORACIQ. HC	15	13	1	0
	2222	CHIR.GEN.DIGEST. HC	27	24	13	2
	2240	CHIRURGIE MAIN HC	27	26	4	2
	2250	ORTHO-TRAUMA 1 HC	/	/	/	/
	2262	CHIR. PLASTIQUE RECONS.HC.	27	15	2	0
	2274	CHIRURGIE MAX.STOMATO.HC	/	/	/	/
	2140	REA.CHIRURGICALE	14	14	11	5
	2160	CHIR.CARDIO.VASC.REA.	10	6	2	0
	2440	BRULES TR HC	10	9	2	2
	2700 P	USCI PERIPHERIQUE	17	13	1	1
	2740	CARDIOLOGIE A HC	18	18	0	0
	2900	CHIR.CARDIAQUE HC	12	9	0	2
	2931	NEURO-TRAUMA INT.	13	8	4	0
	2291	NEURO-TRAUMA.HC	12	8	2	1
CLOCHEVILLE	3560	REA.NEONAT.CL HC	9	9	6	4
	3120	REA.PED.CL HC	7	3	0	0
	3660	NEUROLOGIE PED.HC	6	4	0	0
	3052	CHIR.CARDIO. PED HC	4	4	1	0
	3100	NEONAT. SOINS INT. HC	12	11	3	0
	3180	CHIR.PED.VISCER.HC	18	18	10	6
	3240	BRULES PEDIATRIQUES	3	1	0	0
	3750	SPECIALITES PEDIATRIQUES	28	20	8	4
	3220	CHIR.ORTHO.PED.HC	15	15	4	3
	3730	CHIR.PED.TETE ET COU HC	15	12	4	3
	3800	ONCOLOGIE PEDIATRIQUE HC	6	3	0	0
	9500	SOIN DE SUITE MED.PED.HC	8	6	4	4
ERMITAGE	80002	UNITE SOINS SUITE 2EME ETAGE	48	45	7	4
	80003	UNITE SOINS SUITE 3EME GAUCHE	14	13	1	0
TOTAL			**1112**	905	251	**148**

ATTACHEMENT 2: DATA COLLECTION FORM

Clinical Audit

Rational use of antibiotics: Re-evaluation of the antibiotherapy 24 to 72 hours after initial application

Data collection form

Date:	**Department:**
N° of the sheet:	**Unit:**
Name of the auditor: ……	**Hospital:**

Patient's label

Included patient :

IPP : ……

Male □ Female □ Child □

Birth date : ……

Patient's history in the Hospital:

* Admitted in ER : Yes □ No □ If Yes, admission date : …..…..

* Admitted in hospitalization department : Hospitalization date : ……....

General department □ : adult □ pediatric □

Surgery department □ : adult □ pediatric □

Obstetric department □

- Reanimation department □ : adult □ pediatric □

- SSR □ : adult □ pediatric □

- Other □ …….

Antibiotherapy : present □ stopped □ (treatment duration in days : ……)

- Antibiotherapy at the arrival to the hospital : Yes □ No □

N°	Name / INN	Dose / Preparation	Administration route
1			
2			
3			

Modified in the hospital ? : Yes □ No □

- Antibiotherapy prescribed in the hospital:

Department that initiated the antibiotherapy :……...…….
Date of initiation : …….....

Which antibiotherapy was initially prescribed ? Broad spectrum treatment?: Yes □ No □

N°	Name / INN	Dose / Preparation	Administration route
1			
2			
3			

	Criteria	YES	NO	NA	Comments
	INITIAL PRESCRIPTION				
1	The diagnostic leading the antibiotherapy is written in the patient's folder.	□	□		Initial diagnostic:
2	Traceability of the prescription: The prescription is: - dated - signed	□ □	□ □		Date: Prescriber:
	RE-EVALUATION BETWEEN 24-72 HOURS				
3	a) Microbiological research is written down in the patient's folder:	□	□		Nature of the research:
	b) If Yes, is it a proved bacterial infection? (bacterial origin, bacteria identified, antibiogram,…)	□	□	□	Bacteria(s) identified:
4	a) Was the site of infection detected?	□	□		Research done:
	b) Diagnostics has been modified?				Re-evaluated diagnostics:
5	Can you find in the patient's folder notes on: - undesirable effects (allergy, renal insufficiency,…) at the point of the re-evaluation?	□	□		If yes, comment:
6	Can you find in the patient's folder notes on: - economical or practical reasons (change to per os, …) at the point of the re-evaluation?	□	□		If yes, comment:
7	Can you find in the patient's folder notes on: - clinical signs (fever, pain,…) at the point of the re-evaluation?	□	□		If yes, comment:
8	Can you find in the patient's folder the infectologist or bacteriologist opinion at the point of the re-evaluation?	□	□		If yes, comment:

<table>
<tr><td colspan="6">CODIFICATION OF THE RE-EVALUATION BETWEEN 24 AND 72 HOURS</td></tr>
<tr><td>9</td><td>Regarding the criteria n°3a, 4, 5, 6, 7, 8,
the re-evaluation is considered as:
- Null
- Partial
- Complete</td><td>

□
□
□</td><td></td><td></td><td></td></tr>
<tr><td>10</td><td>Traceability of the re-evaluation:
The re-evaluation is: - dated
- signed</td><td>
□
□</td><td>
□
□</td><td>
□
□</td><td>Date :
Prescriber :</td></tr>
<tr><td>11</td><td colspan="5">Antibiotherapy after re-evaluation:
<table><tr><th>N°</th><th>Name / INN</th><th>Dose / Preparation</th><th>Administration route</th></tr><tr><td>1</td><td></td><td></td><td></td></tr><tr><td>2</td><td></td><td></td><td></td></tr><tr><td>3</td><td></td><td></td><td></td></tr></table></td></tr>
<tr><td></td><td colspan="5">If the re-evaluation is «Null» after 24-72 hours, it was done:
Not done □ Before than in 5 days □ After 5 days □</td></tr>
<tr><td colspan="6">NATURE OF THE RE-EVALUATION BETWEEN 24-72 HOURS</td></tr>
<tr><td>12</td><td>The antibiotherapy was maintained after 72 hours following the initiation?
Is the reason written down in the patient folder?</td><td>□
□</td><td>□
□</td><td></td><td>Reason:</td></tr>
<tr><td>13</td><td>Modification of the initial treatment?
Nature? :
- administration preparation
- dose modification
- association : Added □ Subtract □
- drug substance change
- duration modification
- other
Is the reason written in the patient’s folder?</td><td>□

□
□
□
□
□
□
□</td><td>

□</td><td></td><td>If yes, comment:

Reason:</td></tr>
</table>

14	Was antibiotherapy stopped? Is the reason written in the patient's folder?	□ □	□		Reason:

Hospital discharge paper was written: Yes □ No □
Date of the paper: ……....
Date of the paper's reading:……...……..

ATTACHEMENT 3: GUIDELINES FOR COLLECTING DATA

Criteria of inclusion:

- Patients that are hospitalized with complete service.
- Patients on antibiotherapy that was started minimum 3 days ago (antibiotherapy is in progress).
- Patients that were taking antibiotherapy during hospitalization in audited unit (antibiotherapy was stopped).
- Antibiotherapy was started in the audited unit or at the ER.

Notes:

- Limit re-evaluation only on 24-72 hours (other later re-evaluations do not matter).
- For patients that had several periods of antibiotic treatment during the hospitalization, first antibiotic therapy prescribed should be analyzed.
- Patients who passed between several departments or hospitals may be included.
- Regarding patients whose antibiotic therapy was initiated by a general practitioner, include those whose treatment was changed upon arrival to the ER or the audited unit.

Criteria of exclusion:

- Patients that are hospitalized at:
    - Operating unit
    - ER
    - Daily hospitalizations
    - Hospitalizations only during the week (patient is “discharged” for weekend)
    - Psychiatry unit
    - Patients that are hospitalized for long term (several weeks)
    - Patients on antibiotherapy that was initiated in some other unit or other hospital than the audited one (except for patients whose antibiotherapy was started at ER)

Audit checklist:

Note all useful comments for comprehension.

1st page :

- Date of the audit (each audited unit should be finished in the same day).
- Do not fill in the “Checklist number” - this number will be given later.
- IPP : the IPP (Permanent Patient Identity ; information that you will find on the patient’s label) is the number given to a patient for his very first hospitalization. The aim of this number is to easily find the patient through informatics system in order to access his/her hospitalization summary (hospital discharge paper), in case it was not available during the audit day.
- SSR (Care and rehabilitation unit): it refers to two departments of Ermitage hospital (elders) and Clocheville hospital (children).

- Patient history: aim of this information is to identify the department, which initiated the antibiotic treatment, and to find out if the patient arrived directly in the audited unit or if he/she was admitted through ER before.
- Write down the prescribed antibiotherapy in the hospital: date of first intake, INN name, brand name, dosage, preparation and route of administration.
- If the treatment is broad spectrum, (bacteria was not identified when treatment was started), check YES.

Criteria n°1 :
The diagnostics leading the antibiotherapy is written in the patient's folder (observation sheet, prescription's notebook, electronic folder, healthcare folder...).
Clearly write down the diagnostics in the comments (look at OMH or medical summary in the patient's folder).

Criteria n°2 :
The antibiotherapy is dated: check YES (add the date to the comments).
The name of the prescriber is in the patient's folder: check YES (add the name to the comments).

Criteria n°3 a:
If you can find in the patient's folder or in the hospital database some microbiological research in the first 72 hours after the treatment was started: check YES (even if the results are under process, add it to the comments).
If no research was done, or if the results were not found in the first 72 hours: check NO.

Criteria n°3 b:
If NO was checked at 3a criteria, check NOT APPLICABLE.
If the results are in process in the hospital database, check NOT APPLICABLE and add it to the comments.
If the results are known after 72 hours, check NOT APPLICABLE.
If the results of the microbiological research is not confirming a bacterial infection (negative culture, viral, fungal or parasitic infection,...) check NO.
If the results of the microbiological research is confirming a bacterial infection, check YES (add the name of the identified bacteria in comments).

Criteria n°4 a:
If the site of infection is detected through medical imagery (CT (Scanner), MRI, Ultrasounds, Doppler,...), relevant clinical diagnostic, microbiologic research (ex: urine culture positive, cerebrospinal fluid positive, which allows to find the infection site) and if the site is localized, check YES.
If the infection site is not found despite the research, check NO.
If the infection site was not detected, check NO.
Ask somebody from the department for the access to the PACS (Picture Archiving and Communication System) report.

Criteria n°4 b:
If after this localization research, the diagnostics is modified or has more details than the initial diagnostics, add it to the comments.

Criteria n°5 :
If you find some notes about undesirable effects due to the antibiotherapy, leading to an antibiotherapy modification, check YES.

Criteria n°6 :
If you cannot find any undesirable effect following the antibiotherapy, or if the patient had a renal insufficiency, or any other pathology when he/she arrived, without any direct link with the antibiotherapy, check NO.

If you can find any economical or practical notes in the patient folder, check YES.
Example: Route change (relay IV/PO)
Patient, who is not receiving IV infusion anymore, and can swallow
The drug substance is different (few IV substances cannot be taken PO)

If drug substance is changed, dose has to be adapted (add it in the comments).

Criteria n°7 :
If you can find any notes about clinical signs in the patient folder as fever, pain,… check YES (add it in the comments).

Criteria n°8 :
If an infectologist opinion (Frédéric BASTIDES, Louis BERNARD, Jean-Marc BESNIER, Patrick CHOUTET, Guillaume GRAS, Leslie GUILLON-GRAMMATICO) or bacteriologist (Alain GOUDEAU, Rolland QUENTIN, Marie-Frédérique LARTIGUE, Laurent MEREGHETTI, Philippe LANOTTE, Nathalie VAN DER MEE, Claire DE GIALLULY, Virginie SAUSSIER-MORANGE, Anne-Sophie VALENTIN , Gaëlle BATY, Eve HAGUENOER) is found in the patient folder, check YES (add it in the comments).

Criteria n°9 :
The re-evaluation is considered Null, Partial or Complete regarding criteria 3a, 4, 5, 6, 7 and 8. These criteria have different weightings regarding their importance:
-If criteria n°3a and/or 4 are checked NO, the re-evaluation is considered as Null
-If criteria n°3a AND 4 are checked YES and maximum one of criteria 5, 6, 7 or 8 is checked YES, the re-evaluation is considered as Partial
-If criteria n°3a AND 4 are checked YES and maximum two of criteria 5, 6, 7 or 8 are checked YES, the re-evaluation is considered as Complete
Check the right square.

Criteria n°10 :
The antibiotherapy re-evaluation is dated: check YES (add the date in the comments)
The name of the doctor who did the re-evaluation is written: check YES (add his/her name in the comments).
If the criteria 3a, 4, 5, 6, 7 and 8 are checked NO, check NOT APPLICABLE.

Criteria n°11 :
Write down the antibiotherapy prescribed 24-72 hours after the initial prescription (drug substance(s)/brand name(s), dose, preparation and route of administration.

Check the square according to the nature of the antibiotherapy re-evaluation (criteria 12, 13 or 14); maintained without any modification, modified or stopped.

Criteria n°12 :
If, regarding the patient folder, you notify that the antibiotherapy was maintained after the 72 hours following the initiation, check YES.
If the reason is written in the patient folder, check YES (add reason as a comment).

Criteria n°13 :
If, regarding the patient folder, we notice at least one modification of the antibiotherapy during the 72 hours following the initiation, check YES.
Check the square according to the nature of the modification; more than one square can be checked.
If the reason is written in the patient folder, check YES (add it as a comment).

Criteria n°14 :
If, regarding the patient folder, the antibiotherapy was stopped during the 72 hours following the initiation, check YES.
If the reason is written in the patient folder, check YES (add reason as a comment).

If the hospital discharge paper is available, read it and check YES.
Write down the hospital discharge paper's date and the date when you read it.