THE BENEFITS OF INTRODUCING THE EUCAST SYSTEM FOR THE RATIONALIZATION OF HOSPITAL ANTIBIOTIC THERAPY

Korzyści z wprowadzenia systemu EUCAST dla racjonalizacji szpitalnej antybiotykoterapii

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ABSTRACT

On April 1, 2011, Poland adopted new EUCAST recommendations for microbial susceptibility testing, approved by the National Consultant for Microbiology. They contain important guidelines for microbiologists and many valuable data for physicians concerning antimicrobial drugs. The introduction of these recommendations to hospitals by microbiological laboratories involves changes in the interpretation of antibiograms. The breakpoints that determine the classification of strains into sensitive or resistant groups have been altered in most cases. Along with the new breakpoints, the dosage of many antibiotics has been updated, too. New EUCAST recommendations are fully accepted by the European Medicines Agency (EMA) as they are based on extensive research on infection pathogenesis and drug pharmacokinetics. The aim of the new recommendations is to standardize the rules concerning antimicrobial susceptibility tests and their interpretation as well as to increase the usefulness of the test results for the effective treatment of microbiological infections.

Keywords: EUCAST, antibiotic therapy, clinical efficacy

Słowa kluczowe: EUCAST, antybiotykoterapia, skuteczność kliniczna

INTRODUCTION

Infections are an inevitable consequence of the functioning of hospitals and necessitate the use of antibiotics and other antimicrobial medicines. The correct selection of medicines is not, however, easy, as it involves analysis of many factors determining treatment efficacy. Usually the only criterion is the price of the antibiotic, but cheap medicines do not always translate into low costs of the entire treatment of an infected patient, just as expensive medicines do not always guarantee clinical efficacy. The costs of infection treatment include not only the unit price of an antimicrobial drug, but also the frequency and route of administration, the number of medicines used (combination therapy, de-escalation therapy, sequential therapy), side effects, microbial drug-resistance, lack of clinical efficacy, and consequences of uncured infections.

DISCUSSION

Optimum treatment of infections, whose cost is adequate to the benefits gained, is based on:

1) basic knowledge of antimicrobial drugs, their properties, fate in the patient’s body (pharmacokinetics), ability to penetrate tissues, range of activity against microorganisms, and undesirable effects;

2) precise assessment of the patient’s clinical state, infection location, determination of probable etiological factors of infection, decision on the type of clinical samples to be microbiologically tested;

3) analysis of the epidemiological situation of the hospital unit based on reports from previous microbiological tests and on analysis of tests of the bacterial/fungal strains isolated from a given patient (including their sensitivity profiles);

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4) prompt and correct therapeutic decisions taking into consideration the three points above, especially in critically ill patients.

Given all the above, the choice of the most appropriate, safe, effective, and therefore cheap, therapy, is a difficult task, which is faced by doctors in every medical field.

Knowledge of antibiotics acquired during one's university education is insufficient as medicines are evolving: old antibiotics may have new dosage forms, generics are introduced, and new antibiotics are developed (e.g., linezolid, tigecycline, daptomycin). Furthermore, new data concerning antibiotic penetration into organs and their side effects continue to emerge; the same is true of information concerning microorganisms, their resistance mechanisms, and pathogenic action (e.g., the ability to produce hitherto unknown toxins, biofilm formation). The nomenclature of microorganisms is evolving, as are their interactions with the human body (colonization, carrier state, and infection). The clinical state of the patient, immunosuppression, extensive trauma, and invasive medical procedures may significantly influence the fate of a medicine in the patient's body and prevent the desired therapeutic effects. Nowadays, the physician choosing a therapy should receive support from both a microbiologist and a pharmacologist, or a hospital pharmacist, who, due to their specialization, have the most extensive knowledge of microorganisms and antimicrobial drugs. Therefore, just as a pharmacy has its place in a hospital, so does a microbiological laboratory. The proximity of a microbiological laboratory to well-educated personnel ensures close and fully competent contact between the diagnostician and the physician (exchange of information about the patient and microorganisms), enables a short specimen transport time to the laboratory, and facilitates prompt communication of immediate and final results. This has been emphasized by the National Consultant for Microbiology, Prof. Waleria Hryniewicz, who calls into question the utility of laboratories located outside the hospital, out of touch with the personnel and the patients. Apart from being located in close proximity of hospital facilities, a microbiological laboratory must have adequate tools for the entire diagnostic process to yield reliable and clinically useful results. To this end, laboratories increasingly often employ state-of-the-art testing techniques, develop precise testing procedures that facilitate the standardization of diagnostics, and apply appropriate interpretation guidelines recommended by relevant organizations. The interpretation of the results of microbiological tests, and especially antibiograms, is just as important as the process of testing itself, and is of particular relevance to treatment decisions.

The importance of interpretation for the correct results has been shown by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), established in 1997 and restructured in 2002, which sets standards for many countries. Until March 2011 all Polish laboratories based their result interpretations on the American CLSI recommendations with certain modifications proposed by the National Reference Center for Antimicrobial Sensitivity (KORLD). However, on March 1, 2011, the Polish National Consultant for Microbiology introduced the guidelines for result interpretation recommended by EUCAST. These recommendations have also been adopted in other European countries. The European recommendations were developed as a response to a growing number of clinical failures following administration of antibiotics and linked to a lack of correlation between antibiogram results and the therapies chosen based on those results (Chart 1).

The introduction of new recommendation was also motivated by the need to unify the interpreta-
The benefits of introducing the EUCAST system for the rationalization of hospital antibiotic therapy

While Poland had used American recommendations for many years, numerous countries had used their own guidelines defined by national committees on antimicrobial sensitivity, such as the British Society for Antimicrobial Chemotherapy (BSAC) in Great Britain, the Norwegian Working Group on Antibiotics (NWGA) in Norway, the Swedish Reference Group for Antibiotics (SRGA) in Sweden, the Deutsches Institut für Normung (DIN) in Germany, and the Comité de l’antibiogramme de la Société Française de Microbiologie (CA-SFM) in France. As a result of the existence of many recommendations containing different breakpoints for classification of strains as susceptible or resistant to a given antibiotic, the same results could have been interpreted as belonging to both categories. While physicians in one country were told that a microorganism was sensitive, those in another were informed that it was resistant to a given medicine (Table 1).7

The EUCAST recommendations have not only unified the breakpoints, but also revised them for

### Table 1. Breakpoints for piperacillin with tazobactam according to different national committees for microbial sensitivity

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>BSAC</th>
<th>CA-SFM</th>
<th>NWGA</th>
<th>SRGA</th>
<th>CLSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>16/16</td>
<td>8/64</td>
<td>8/16</td>
<td>16/16</td>
<td>16/64</td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>16/16</td>
<td>16/64</td>
<td></td>
<td>16/16</td>
<td>64/64</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>16/16</td>
<td>16/64</td>
<td></td>
<td></td>
<td>16/32</td>
</tr>
</tbody>
</table>

National committees for microbial sensitivity:
BSAC – Great Britain, CA-SFM – France, NWGA – Norway, SRGA – Sweden, CLSI – USA

Source: The European Union Committee on Antimicrobial Susceptibility Testing – EUCAST Internet: www.eucast.org (access: 20.06 2011)

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many antibiotics, making them the basis for reliable in vitro evaluation of strain sensitivity, well-correlated with treatment efficacy. It has been found that erroneously determined breakpoints led in the past to false reports of penicillin resistance of Streptococcus pneumoniae strains isolated from the lower respiratory tract. Following many publications, scientists conducted a new study of the criteria of interpreting antimicrobial sensitivity tests.

According to the estimates presented by Prof. W. Hryniewicz, pursuant to the new recommendations, the percentage of penicillin resistant pneumococci isolated from the lower respiratory tract should decrease from about 20% to 2%. The new recommendations also take into account the different nature of pneumococcal infection of the central nervous system (CNS) and provide separate breakpoints for strains isolated from the cerebrospinal fluid. The new breakpoints for Streptococcus pneumoniae isolated from the CNS may in turn lead to a higher percentage of penicillin resistant strains, even up to 30%. Thanks to the EUCAST guidelines, the results of penicillin sensitivity tests for pneumococci from infections of the lower respiratory tract and the CNS are much more clinically useful and better reflect the effects of the administered medicines on the pathogens in the patient’s organism. New, revised breakpoints have also been set for the sensitivity of Gram-negative bacteria to the majority of beta-lactams, including penicillin, cephalosporins, carbapenems, monobactams, as well as other groups of antibiotics, such as fluorquinolones and aminoglycosides. Assessment of the sensitivity of staphylococci to vancomycin has also been revised in response to the decreasing efficacy of the glycopeptide in the treatment of severe infections. It is estimated that the European recommendations will generally lead to reporting higher antibiotic resistance in bacteria. However, such results will be more clinically useful, as the choice of antibiotics for the treatment of particular sensitive pathogens will much more often correlate with clinical efficacy. Test results interpreted on the basis of the EUCAST recommendations will also limit the use of medicines which are bound to fail due to pharmacokinetics or microbial resistance. The ability of laboratories to produce more reliable results is linked to the introduction of more frequent use of new testing methods, and especially quantitative sensitivity tests. Thanks to technological progress, such tests are not as labor-intensive as the dilution methods that had been used for years. Over a similar time (as compared to qualitative methods), they make it possible not only to determine whether a strain is sensitive, resistant, or has reduced sensitivity, but also to evaluate the degree of sensitivity as expressed by MIC (minimal inhibitory concentration). MIC is a very important parameter that is taken into account both in antibiotic selection and in choosing a dosage appropriate for a given patient. Analysis of MIC in conjunction with selected pharmacokinetic parameters enables prediction of the probability of clinical success and modification of the dosage, if necessary (the more sensitive the strain, the higher the likelihood that a smaller dosage will be effective, thus reducing the risk of side effects). According to the EUCAST rules, laboratories should always determine MIC values in the following situations: vancomycin for staphylococcus strains; penicillin and cephalosporins for resistant pneumococci; beta-lactams for extended spectrum beta-lactamase (ESBL) and metallo-beta-lactamase (MBL) producing Gram-negative bacteria; colistin, tigecycline (except Escherichia coli) and daptomycin; antibiotics for anaerobic bacteria; and certain antibiotics prescribed for critically ill patients in intensive care units, hematological units, transplant units, dialysis stations, and others in whom treatment has been unsuccessful or the infection itself is life-threatening. The European recommendations have also systematized the principles of administration of antimicrobial medicines and indications for different dosage forms of antibiotics. EUCAST

10 The European Committee on Antimicrobial Susceptibility Testing – EUCAST Internet: www. www.eucast.org (access: 20.06 2011); Rotaub R. op. cit.
stresses the close correlation between the degree of antibiotic sensitivity of a strain and its dosage in the patient. To facilitate the choice of medicine dosage, for most antibiotics it has been estimated what dosage will be optimal and effective depending on the degree of sensitivity of the pathogen isolated from the patient.\(^{11}\)

It should be emphasized that strain sensitivities determined in vitro are valid only for particular antibiotic dosages. For instance, in Enterobacteriaceae infections, cefuroxime should be administered intravenously at 1.5 g × 3, cefepime at 2 g × 3, and imipenem 1 g × 4, sensitivity to aminoglycosides is met at a dosage of once a day (in Poland this group of medicines is still often administered 2 or 3 times a day – such a dosage does not ensure a correlation between the sensitivity found from a microbiological test and the efficacy observed following medicine administration).

**SUMMARY**

New recommendations provide valuable information for microbiologists, pharmacists, and physicians. Multicenter studies on the pharmacodynamics and pharmacokinetics of antimicrobial medicines conducted at the stage of recommendation development led to systematizing and updating knowledge of antibiotics. All guidelines proposed by EUCAST are free of charge and publicly available at www.eucast.org.\(^{12}\) The web site contains both files with instructions for microbiologists and for physicians, including systematic information on particular medicines (dosage, pharmacokinetic parameters, assessment of efficacy depending on MIC, indications for use – “rationale document” files). There is also a Polish translation available at www.korld.edu.pl,\(^{13}\) which is the official web site of the National Reference Center for Antimicrobial Sensitivity.

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