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INITIAL EMPIRIC ANTIBIOTIC TREATMENT IN SEVERE BACTERIAL INFECTIONS

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ABSTRACT. The progress of diagnosis means of infections, the improvement of surgical techniques and large spectre antibiotic availability resulted in an important reduction of the morbidity and mortality produced by severe bacterial infections (SBIs) in the last century. Nevertheless, this pathology remains a major challenge for surgeons, internists, infectious diseases and microbiology specialists. The adequacy of initial empiric antibiotic therapy is life-saving. Progressive bacterial resistance and its spread within institutions limit the antibiotic treatment options and the patients' outcome. This phenomenon is more obvious in Gram-negative bacilli which are the main cause of SBIs in countries were the antibiotic treatment is based rather on general guidelines than on local susceptibility data. This presentation discusses criteria for choosing empiric antimicrobial therapy aiming to reduce the use of unnecessary anti -pseudomonas antibiotics and outlines available therapies for these infections.

Keywords: bacterial infections, anti-pseudomonas antibiotics, multidrug resistant organisms

INTRODUCTION

Severe bacterial infections remain a cause of morbidity and mortality among immunocompromised but also among immunocompetent patients. In USA, in 2013, 23,000 people died as a result of bacterial resistance alone (http://www.theverge.com /2013/9/17 /4740620/ antibiotic – resistant – diseases –cause – 23000 – deaths – per – year – in - us). The therapeutic progress of medicine, from cancer therapy to organ transplantation is threatened by bacterial resistance. This phenomenon is divers and is spreading, rendering antibiotics useless. Since they are a precious life-saving but limited resource, the medical community should direct its efforts toward a wise use of antibiotics. Delayed or ineffective initial therapy can produce longer hospital stay, increase expenses, increase risk of death, augmentation of multi drug resistant (MDR) organisms. The economic impact, the ultimate negative effects are increased absenteeism and low productivity.

Typically, patients with severe infections receive initial empiric antibiotic therapy with a broad spectrum regimen covering the most likely pathogens. This design is based on guidelines or on local surveillance data and on risk factors for infection with a resistant microorganism. This article aims to describe the problem pathogens and the approach to antibiotic treatment based on local epidemiologic data and on emergency laboratory findings. The doctors' attitude in this matter is driven by their education, the information on guidelines and local data, the antibiotic availability and support from the microbiology laboratory. The patients at especially high risk are those undergoing cancer chemotherapy, rheumatoid arthritis, complex surgery, dialysis for end-stage renal disease, organ and bone marrow transplants (http://www.cdc.gov/ drugresistance/ threat – report -2013/).

The MDR organisms are growing all over Europe. The EARS-net data show the increase in all countries. This narrows even more therapeutic options and drives the medical action toward a broad-spectrum antibiotic or an association of drugs aiming a wider range of resistance mechanisms. Although this habit of mind improves the likelihood of a life-saving outcome, use of broad-spectrum, highdose, empiric antimicrobial therapy produces increased pressure for the permissive effect (and quorum sensing) of resistant species and possibly exposing patients to adverse events or collateral infections such as *Clostridium difficile* pathology. Initial empirical therapy should be directed against the most likely pathogens and subsequently amended when the responsible pathogen is identified and its susceptibility to antimicrobials tested. De-escalation is a strategy that attempts to balance the competing aims of providing initial empiric therapy that is appropriate and covers the likely pathogens, and limiting antimicrobial exposure and increased risk for emergence of resistant pathogens. The de-escalation strategy is based on laboratory reports produced on cultures taken before initiating broadspectrum empiric therapy. This strategy allows the therapeutic switch to a narrow spectrum antibiotic 2–3 days later, if warranted by clinical status and culture results. Moreover, negative culture results and subsequent clinical review enables termination of antibiotic therapy. Laboratory reports enable more effective targeting of the causative pathogen(s), elimination of unnecessary antibiotics, a decrease in antimicrobial pressure for emergence of resistance, and cost savings. The initial therapy should be designed primarily on the nature of the source of infection, on the epidemiologic characteristics: nosocomial or community acquired, on the type of patient, the underlying disease and recent medical and surgical treatment. The microbial flora of hospitals varies greatly in type and susceptibility, often MDR. The dominant factor driving the antibiotic choice is the patient's clinical state. The ultimate therapeutic objective is life – saving. In this framework, the antibiotic therapy could take into account the algorithm:

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sampling- timely decision to treat broad spectrum (guidelines vs local susceptibility) data- de-escalation to narrow spectrum agents. The microbiology laboratory is able to provide urgent information regarding the presence of microbes (morphology, Gram stain) or fungi. In patients with signs and symptoms of invasive infections, because of the high morbidity and mortality associated with bacteraemia, prompt evaluation and appropriate empiric antibiotic treatment are of paramount importance, at least until molecular biology becomes widely available (Bearman *et al.*, 2005). Laboratory information on negative or false positive blood cultures support termination of antibiotic treatment.

Intraabdominal infections (IAIs) or other conditions which benefit from surgical approach may be managed by the source control and surgical sampling. Examination of the Gram stain provides important information especially on microbial morphology: anaerobes, *Enterobacteriaceae*, or *Pseudomonas* or *Acinetobacter*. The two latter are nosocomial pathogens. Since active antibiotics against these bacilli are becoming scarcer, the sparing anti pseudomonas drugs principle is very useful in preserving these ultimate agents against a deadly pathogen (Papagheorghe *et al.*, 2012). Urinary tract infections (UTIs) are frequent conditions encountered in hospital as well as outpatient and benefit greatly both from the Gram stain of the clean-voided urine sample and from the local susceptibility data.

The problem pathogens are:

Methicillin resistant Staphylococcus aureus (MRSA).

Hospital acquired (HA-MRSA) or community acquired (CA-MRSA) it is a deadly pathogen in bloodstream infections (BSIs) (Livermore, 2009) MDR coagulase negative staphylococci are increasingly reported in BSIs in immunocompromised patients, particularly with hematologic malignancies (Chen *et al.*, 2010). Both these strains of staphylococci are resistant to all β-lactams. Sparing anti fluoroquinolone antibiotics principle, in order to prevent selection of fluoroquinolone resistant Gram negative bacilli (Arslan *et al.*, 2005) conducts therapeutic options toward glycopeptides or other narrow spectrum anti- MDR staphylococcus (linezolid, quinupristin/dalfopristin, daptomycin, tigecycline, ceftobiprole, ceftaroline, telavancin, dalbavancin, oritavancin). Agents without anti pseudomonas activity are a better choice. The main problem is not therapeutic, since all these drugs are equivalently active, but the cost (Ratnaraja *et al.*, 2008).

The enterococci

They are less frequent but even more difficult to treat as a result of reduced therapeutic options. They are naturally resistant to cephalosporins and in severe infections only bactericidal antibiotics are useful. In many situations they produce infections by permissive effect, after cephalosporin treatments. Vancomycine resistant strains were not reported yet in Romania, thus glycopeptides are a good option. The high level aminoglicosyde resistance (HLAR) limits the association of gentamycine to therapy, especially in endocarditis. Daptomycin is bactericidal, but, at presently licensed dosages, is marginal against E. faecium (Livermore, 2008). Linezolid and tigecycline, have good in vitro activity against enterococci (including vancomycin-resistant strains) but are bacteriostatic, thus of uncertain value in terms of patient outcome in people with endocarditis or neutropenic patients (Livermore, 2009).

Gram negative bacilli

Enterobacteriaceae or non-fermenters are the most frequent pathogens in many severe cases, at least in BSIs, IAIs and UTIs. The initial empiric approach should be designed according to the risk of Pseudomonas / Acinetobacter risk factors or on Gram stain arguments. If the most likely pathogens are the *Enterobacteriaceae*, the initial therapy should tackle the most likely resistance mechanisms, the extended spectrum β-lactamases (ESBLs). Since these enzymes render inactive all β-lactams except carbapenems, these drugs are a good option (Hawser *et al.*, 2012). Since many situations, the ESBLs resistance plasmids carry resistance genes to fluoroquinlones and minoglicozydes (Livermore *et al.*, 2008). Local data are useful in informing upon the co-resistance to these latter drugs. combinations of β-lactam/ β-lactamase inhibitors are useful in ESBLs producers. Local data can provide information on prevalence of enzymes like AmpC which render these drugs unusable. These enzymes are present naturally in *Enterobacter* and *Serratia spp*. The wide use of third generation cephalosporins to treat these pathogens can trigger the production of AmpC and spread it to other *Enterobacteriaceae* by quorum sensing and increase the resistance to β-lactam/ β-lactamase inhibitors. The spread of these enzymes are a threat to public health since they render unusable both anti ESBLs drugs (amoxicillin/ clavulanic acid) and anti pseudomonas agents (ticarcillin/clavulanic acid and piperacillin / tazobactam). Tigecycline has low blood levels and its efficacy in severely-ill patients remains to be established unequivocally (Livermore, 2007). Non pseudomonas-active agents (like ertapenem) are a good choice to treat Gram negative bacilli ESBL positive infections. ECDC reports carbapenem resistance in Romania 13.7% (14/84), in *K. pneumoniae* in 2012 (http://www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/table_reports.aspx). Resistance to carbapenems is due to impermeability and carbapenemase production. Both can be acquired from *Pseudomonas* and *Acinetobacter*. Local data of the prevalence of these pathogens and their subsequent enzymes are useful in initial antibiotic scheme design. If carbapenem resistance is suspected, in severe cases, the last option is colistin associated to carbapenems. Although rare, colistin resistant *Enterobactericeae*

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were reported (Matthaiou *et al.*, 2008; Lia *et al.*, 2005; Evans *et al.*, 1999).

Currently, European framework FP7 is evaluating older antibiotic combinations with new methods in the AIDA project (Preserving old antibiotics for the future): (WP 1 Colistin vs Colistin + Carbapenem) for Gram negative bacilli non-susceptible to carbapenems (http://www.aida-project.eu/).

For UTIs, older drugs like nitrofurantoin and fosfomycin usually remain active in lower urinary infections but are not suitable in ascending infections. These drugs are under investigation in AIDA project: WP 2 Fosfomycin Trometamol vs. Nitrofurantoin.

Infections produced by non fermenters, *Pseudomonas* and *Acinetobacter* are mostly nosocomial, difficult to treat, life-treatening and with great impact on the society and public health. Local data on the susceptibility of these kinds of strains provide information whether we are dealing with MDR pathogens. In these cases, the only option is colistin with or without anti-pseudomonas carbapenems. Colistin resistant strains have been isolated in both species (Linden *et al.*, 2003).

CONCLUSION

Currently, pan-drug resistant strains have not been reported in Romania, nor is there a database regarding deaths produced by bacterial resistance alone. Untreatable infections are scarce, if any; death is presumably a result of comorbidities or/ and system ability to provide and manage microbial susceptibility, hospital antibiotic usage and patient outcome data (http://www.ecdc.europa.eu/en/publications/Publications/antimicrobial-antibiotic-consumption-ESAC-report-2010-data.pdf; http://www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/ esac-net-database/Pages/consumption-rates-by-country.aspx). Gram positive cocci infections benefit from many antibiotics, some new. For staphylococci infections our options are increasing; moreover, improved infection control has reducing the incidence of MRSA bacteraemia in Europe. Local data are useful in communicating the MRSA prevalence and the subsequent therapeutic approach becomes only a problem of antibiotic availability. Enterococci represent a higher risk, especially in deadly infections (e.g. endocarditis) where bactericidal activity is mandatory; however, the number of such infections is small and local data are of great importance. The real threat to the patient and to the public health is the Gram-negative pathogens. *Enterobacteriaceae* susceptible only to carbapenems, tigecycline and polymyxin are seen in many settings (http://www.ecdc.europa.eu/en/aboutus/organisation/Director%20Speeches/2013-Marc-Sprenger-EAAD2013-stakeholder-event) ; neither of these agents is ideal. In fact, adverse effects are known. Local data are of the utmost importance in these situations, since we are dealing with strains resistant to the last antibiotics. These drugs should not be used unless they are the only option; if emergency life-saving attitudes drove doctors' decision to one of these agents, but microbiology reports did not sustain its use, de-escalation to a narrow specter; non anti pseudomonas antibiotic should be the immediate option. On long term, the result of antibiotic use will be a slowly growing minority of infections that become technically untreatable. These strains will be seen more and more frequently in immunocompromised patients who receive antibiotic prophylaxis. These patients will no longer benefit and will end by receiving ineffective antibiotic as primary empirical therapy. And this, as numerous studies have shown, is associated with increased mortality. We strongly believe that the cumulative susceptibility local data is able to reduce local unnecessary antibiotic consumption, subsequent costs and prevent emergence of untreatable pathogens.

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