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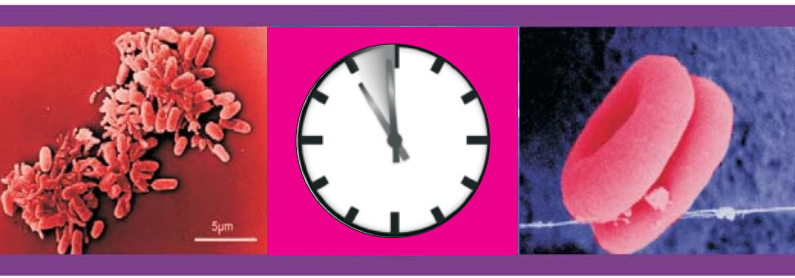
HELLENIC INSTITUTE FOR THE STUDY OF SEPSIS

HELLENIC SEPSIS STUDY GROUP

BOOKLET ON SEPSIS



DEFINITIONS-DIAGNOSTIC APPROACH-TREATMENT GUIDELINES

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INTRODUCTION

Since 2006 the Hellenic Sepsis Study Group (HSSG) keeps up intensive work focused on recording the incidence and the study of the particular mechanisms of the septic syndrome. This effort of the HSSG is internationally recognized as innovative in establishing a new personalized approach on treating the septic patient. This recognition comes out of 10 original papers in international medical journals, 3 of which provide for the first time evidence for the need for a personalized approach in the pathogenesis of sepsis[1-3]. Other research studies have also been completed and submitted for publication in international medical journals. In recognition of its contribution, HSSG is among the founding members of Global Sepsis Alliance **(www.globalsepsisalliance.com)**. On the same time one of its coordinators is member of the steering committee of the World Sepsis Day **(www.worldsepsisday.com)**.

Following the success of the two previous Booklets on Sepsis published by HSSG on 2008 and 2011, a fully updated Booklet is published on March 2014 including results of the statistical analysis of data of 3982 patients of the Greek Registry. This analysis is divided in two periods; 2006-2009 and 2010-2013. It should be emphasized that the majority of contents of the two previous Booklets referred to data of the study period 2006-2009. During the years 2010-2013, mortality of patients treated in Internal Medicine and Surgical wards with severe sepsis and septic shock was 39.0% and 70.9% respectively. Respective rates for patients treated in Intensive Care Units (ICU) were 34.4% and 55.3%.

Until now, 19 departments of Internal Medicine, 9 department of Surgery, 4 department of Chest Medicine and 24 ICUs throughout Greece and Cyprus participate actively in the HSSG. Each member of these departments becomes a member of HSSG. Active participation comes through the recording of clinical data of patients with sepsis. This process takes place through a well-standardized

registry protocol. Each patient is recorded only once. Regular communication of HSSG members is done via e-mail while three times each year meetings of HSSG members take place.

It should be outlined that analysis on antimicrobials provided in this booklet is based on the selection of antimicrobials done by the attending physicians. **Analysis comprised patients diagnosed with uncomplicated sepsis, severe sepsis or septic shock outside an ICU,** since more clinical data are available for these patients. It is evident that most of these patients should have been treated in ICUs, especially those in septic shock. However, the lack of ICU beds in Greece results either in delayed transfer of these patients in an ICU or sometimes transfer is not possible at all. As a consequence, most of these patients are hospitalized in the general ward. For this reason this Booklet aims to inform Greek physicians of all specialties about sepsis and the basic principles of treatment.

This Booklet is published under hope that the effort of the Greek Registry is going on and expands by the participation of even more departments and ICUs.

September 2014

C. Gogos

E.J. Giamarellos-Bourboulis

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SEPSIS DEFINITIONS

Uncomplicated sepsis

Any clinically or microbiologically documented infection accompanied by at least two of the following:

- Body core temperature >38°C or <36°C
- Heart rate >90/minute
- Breath rate >20/minute or $PaCO_2$* <32 mmHg
- White blood cells >12000/mm^3 or <4000/mm^3 or >10% blasts

Severe sepsis

Sepsis aggravated by at least one organ failure. Organ failures are defined as follows:

- ***Respiratory failure***: PaO_2/FiO_2**<300 and diffuse shadows on chest x-ray
- ***Acute renal failure***: urine output <0.5 ml/hour/kg body weight within the last two hours provided that negative fluid balance has been restored
- ***Metabolic acidosis***: pH <7.30 or base deficit > 5 mmol/l **and** blood lactate > 2 x upper normal limit
- ***Acute coagulopathy***: platelets <100.000/mm^3 or INR >1.5
- ***CNS dysfunction***: Sudden change of mental status
- Dysfunction of other systems/organs e.g. liver, gut etc

Septic shock

Severe sepsis aggravated by systolic arterial pressure < 90 mmHg necessitating the administration of vasopressors

*partial pressure of carbon dioxide

**ratio of partial oxygen pressure/fraction of oxygen in the inspired mixture

AVAILABLE THERAPEUTIC OPTIONS AND EVALUATON PROCESS

The need to elaborate proper management of the patients led to the initiative of many scientific societies for the creation of guidelines. This initiative, known as the "Surviving Sepsis Campaign"[1-3], led to the publication of guidelines regularly revised (last revision February 2012[3]).

Proper management of sepsis relies on two major issues:

- Appropriate and early management of all bundles of Care[1,2]
- Start of antimicrobial therapy **within the first hour** and achievement of early therapeutic goals **within the first six hours** from diagnosis[3]. This mandates immediate start of care of the patient either at the emergency room (ER) or at the general ward and in parallel attempt for ICU admission.

The present booklet is emphasizing on the following:

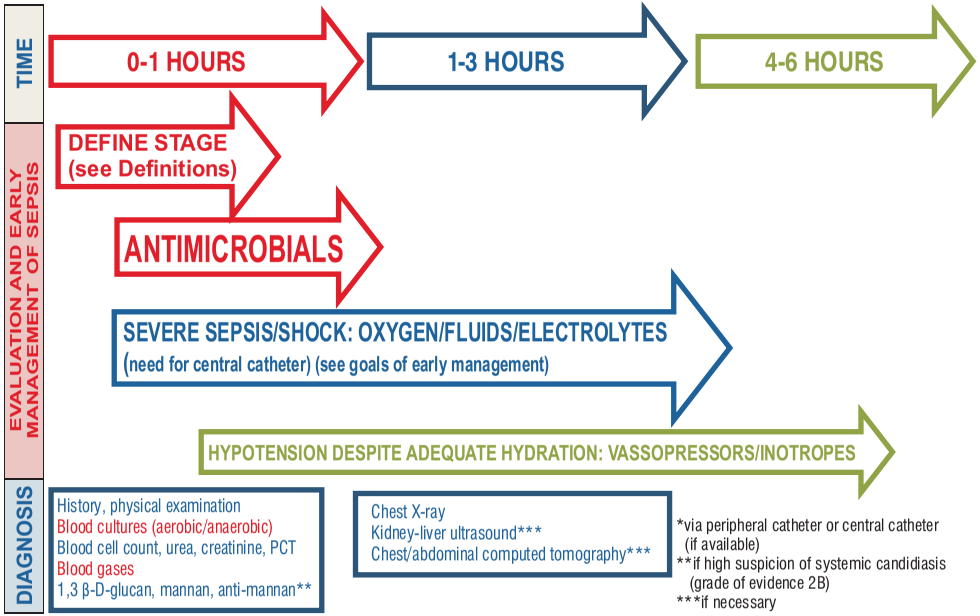
- Early goals of management
- Immediate start of antimicrobials and criteria of selection of the most appropriate antimicrobials
- Infection source control
- Data from the Greek registry of patients with emphasis on microbiology and resistance patterns
- Short reference of strategies of immunointervention for patients under severe sepsis/ shock.

For every therapeutic strategy the grade of recommendations according to the Surviving Sepsis Campaign 2012 guidelines is provided[1-3]. The GRADE system for recommendations is provided in Appendix 1.

REFERENCES

1.Dellinger RP et al. *Crit Care Med* 2004; 32: 858-873
2.Dellinger RP et al. *Crit Care Med* 2008; 36: 296-327
3.Dellinger RP et al. *Crit Care Med* 2013; 41: 580-637.

DIAGNOSTIC ALGORITHM AND INITIAL RESCUSITATION OF SEPTIC PATIENT



GOALS OF EARLY RESUSCITATION[1]

- Central venous pressure: 8-12 cmH_2O
- Systolic arterial pressure ≥90 mmHg or mean arterial pressure ≥65 mmHg
- Urine output ≥0.5ml/Kg body weight/hour
- Arterial blood O2 saturation ≥92%
- Mixed venous blood saturation through a catheter inserted in vena cava ≥70%

PRINCIPLES OF INFECTION SOURCE CONTROL[2, 3]

- Diagnosis of the underlying infection (grade of evidence 1B)
- Control/eradication of sepsis in the first 12 hours (grade of evidence 1B)
- Use of less invasive technique e.g. percutaneous versus surgical drainage where possible
- For intrabdominal/surgical infections, implementation of appropriate therapy based on available guidelines

REFERENCES

1.Rivers E, et al. *N Engl J Med* 2001; 345: 1368-1377
2.Dellinger RP, et al. *Crit Care Med* 2013; 41: 580-637
3.2013 WSES Guidelines. *World J Emerg Surg* 2013; 8: 3

Antimicrobials should start WITHIN THE FIRST ONE HOUR[1]:

- When signs of septic shock appear (grade of evidence: 1B) and
- When signs of severe sepsis without hypotension appear (grade of evidence: 1C)

In a retrospective analysis of data coming from 2731 patients with septic shock, final outcome was correlated with the time lapsing from diagnosis of hypotension until start of appropriate antimicrobials. Survival rate was 79.9% for patients administered appropriate antimicrobials within the first one hour. This was decreased by 7.6% for every hour of delay[2]. Selection of empirically administered antimicrobials relies on emerging resistance patterns in the community for community-acquired sepsis or in the hospital for hospital-acquired sepsis (see pg. 12)[1].

ATTENTION

- It is mandatory for antimicrobials to be administered within the first hour in the emergency room (ER). Collection of cultures should be done before start of antimicrobials.
- Antimicrobials available for bolus infusion should be administered first. Then antimicrobials requiring a certain infusion time should follow.

REFERENCES
1.Dellinger RP, et al. *Crit Care Med* 2013; 41: 580-637
2.Kumar A, et al. *Crit Care Med* 2006; 34: 1589-1596

SELECTED ANTIMICROBIALS SHOULD[1]:

- Be active against all probable pathogens* (grade of evidence 1B)
- Have efficient pharmacokinetics at the infection site (grade of evidence 1B)
- Be given at first at the maximum allowed dose
- Dose regimen should be adapted according to renal function (see Appendix 2).
- Be de-escalated according to the results of blood cultures (grade of evidence 1B)
- Not belong to the same group of antimicrobials administered to the patient over the last three months (grade of evidence 1B)

***Surveillance of emerging pathogens at the wards where the patients are hospitalized is mandatory**

[1]Dellinger RP, et al. *Crit Care Med* 2013; 41: 580-637

General Principles of Antimicrobial Treatment[1]

- Combination treatment is necessary in neutropenic patients with severe sepsis and in patients with severe sepsis due to species of *Klebsiella, Acinetobacter and Pseudomonas* (grade of evidence 2B)
- The total therapy duration is 7-10 days. Therapy should be extended to 14 days in case of infections from *Acinetobacter* and *Pseudomonas* or in immunocompromised patients, in neutropenic patients or in patients with bacteremia by *Staphylococcus aureus* or slow clinical improvement (grade of evidence 2C)

[1]Dellinger RP, et al. *Crit Care Med* 2013; 41: 580-637

DE-ESCALATION OF ANTIMICROBIAL TREATMENT[1]

This is defined as the change of administered antimicrobials depending on the microbiology of blood cultures.

This comprises:

- Change of a broad-spectrum antimicrobial into a more narrow-spectrum antimicrobial provided that the latter is active on the isolated pathogen
- Stop of any empirically administered antistaphylococcal or antifungal medication provided that staphylococcal and fungal pathogens are not isolated
- De-escalation strategy should be applied both for sepsis patients outside the ICU and for sepsis patients inside the ICU.

[1]Dellinger RP, et al. *Crit Care Med* 2013; 41: 580-637

TRAITS FROM PATIENTS' HISTORY IDENTIFYING INCREASED RISK FOR INFECTION BY MULTIDRUG-RESISTANT BACTERIA:

- Intake of broad-spectrum antimicrobials[1] over the past three months

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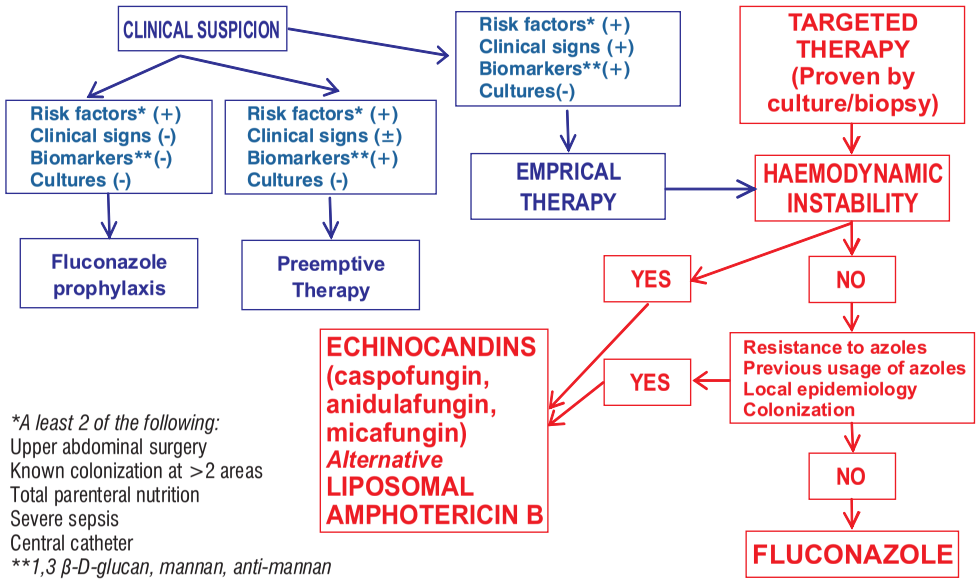
- Hospitalization for 2 days over the past three months
- Duration of present hospitalization 5 days
- Residence in long-term care facilities
- Close association to places of medical care[2]
- Stage IV chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis
- Regular hemodialysis over at least one month
- Immunosuppresion[3]

[1] 3rd or 4th generation cephalosporins, aztreonam, fluoroquinolones, piperacillin/tazobactam, carbapenems
[2] e.g. intravenous home therapy
[3] hematological disorders, neutropenia, chemotherapy for solid tumors, transplantation, intake of corticosteroids (>10 mg equivalent prednisone/day or >700 mg in total), intake of immunosuppressants

TREATMENT ALGORITHM OF CANDIDIASIS IN THE ICU

(Dimopoulos G, et al. *J Crit Care* 2013; 28: 717-727)



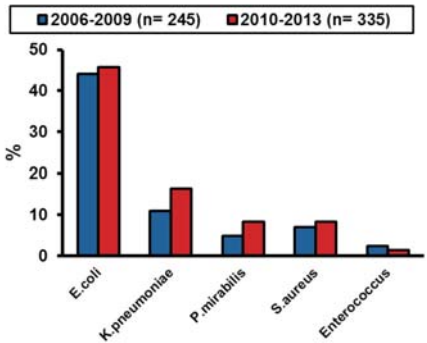
**A least 2 of the following:*
Upper abdominal surgery
Known colonization at >2 areas
Total parenteral nutrition
Severe sepsis
Central catheter
***1,3 β-D-glucan, mannan, anti-mannan*

DATA FROM SEPSIS REGISTRY IN GREECE

Registration of septic syndrome has started in 2006. Data were analyzed separately for years 2006 to 2009 (which are listed in the first two editions of the Booklet) and for years 2010 to 2013. Patients were divided into those who developed one sepsis episode outside the ICU and those who developed the first sepsis episode after ICU admission.

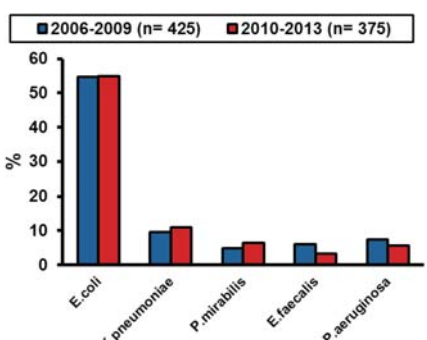
The most common pathogens and resistance to antimicrobials are provided. Administered antimicrobials associated with better survival outside the ICU are provided (overall data regardless of the infection site). Administered antimicrobials are selected by the attending physicians based on the infection site, the patient's history and other clinical criteria non-predefined by the current epidemiological study. As a consequence, association with better outcomes only signifies the appropriateness of choice. It is evident that the development of therapeutic guidelines for empirical antimicrobial treatment cannot solely rely on data coming from observational studies, since groups of patients under treatment are not comparable even if they do not differ in severity (according to the APACHE II score). As expected, analysis provided a vast number of combinations of administered antimicrobials. Survival of patients treated with the most common combinations of antimicrobials was analyzed since their number was large enough to allow statistical analysis.

BLOODSTREAM ISOLATES (%) FROM PATIENTS DEVELOPING SEPSIS OUTSIDE THE ICU

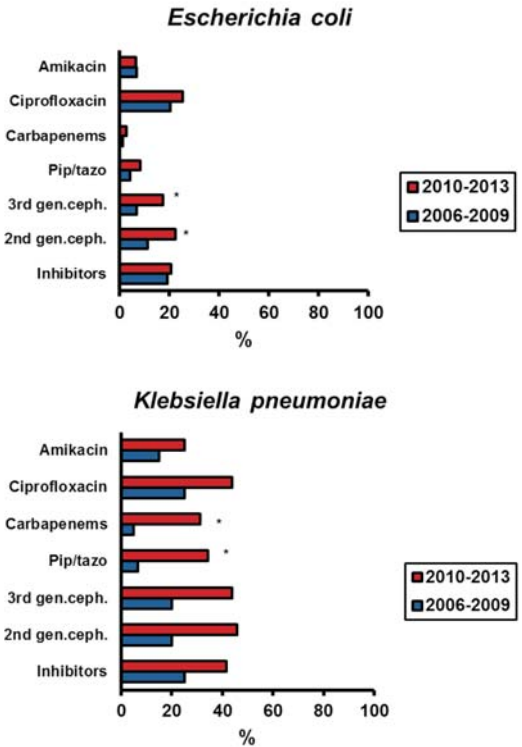


Koupetori M, et al. *BMC Infect Dis* 2014; 14: 272

URINE ISOLATES (%) FROM PATIENTS DEVELOPING SEPSIS OUTSIDE THE ICU



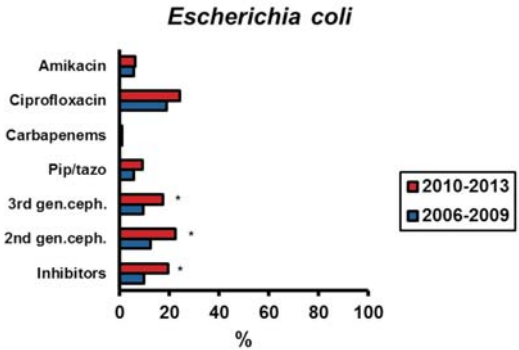
RESISTANCE (%) OF BLOODSTREAM ISOLATES OF PATIENTS DEVELOPING SEPSIS OUTSIDE THE ICU

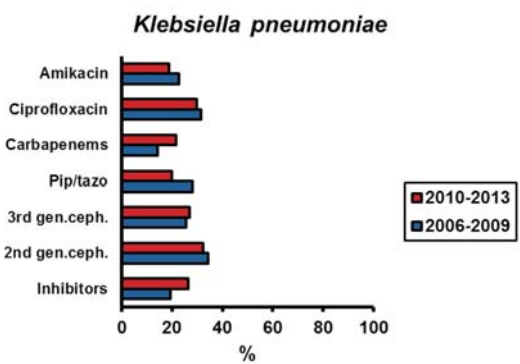


*significant increase between the two periods

Koupetori M, et al. *BMC Infect Dis* 2014; 14: 272

RESISTANCE (%) OF URINE ISOLATES OF PATIENTS DEVELOPING SEPSIS OUTSIDE THE ICU





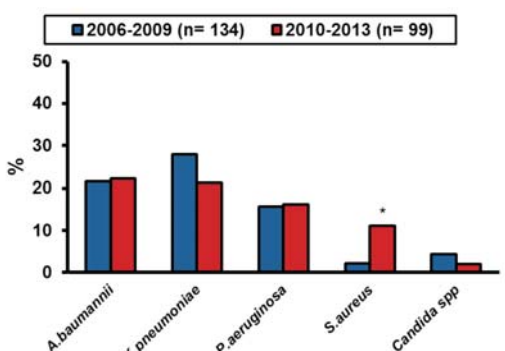
*significant increase between the two periods

RISK FACTORS FOR BACTEREMIA BY MULTIDRUG-RESISTANT PATHOGENS OUTSIDE THE ICU

Epidemiological registry
Major independent risk factors for bacteremia by multidrug-resistant pathogens were:

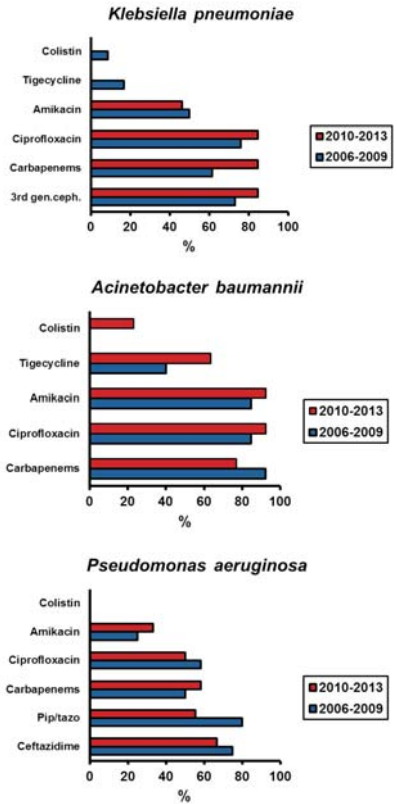
- Chronic Obstructive Pulmonary Disease
- Chronic haemodialysis
- Antimicrobial intake the last 3 months
- Residency in long-term care facilities

BLOODSTREAM ISOLATES (%) FROM PATIENTS DEVELOPING SEPSIS AFTER ICU ADMISSION



*significant increase between the two periods
Koupetori M, et al. *BMC Infect Dis* 2014; 14: 272

RESISTANCE (%) OF BLOODSTREAM ISOLATES OF PATIENTS DEVELOPING SEPSIS INSIDE THE ICU



non-significant differences between the two periods

Koupetori M, et al. *BMC Infect Dis* 2014; 14: 272

ANTIMICROBIAL THERAPY FOR PATIENTS WITH UNCOMPLICATED SEPSIS DEVELOPING OUTSIDE THE ICU

EPIDIMIOLOGICAL REGISTRY

From the prescribed antimicrobial combinations, the following are associated with better outcome*:

- 2nd generation cephalosporins +/- metronidazole
- Ciprofloxacin
- 3rd generation cephalosporins +/- metronidazole
- Piperacillin/tazobactam

*taking into consideration that no stratification was done regarding infection site, this finding is not conclusive and reported drug combinations cannot be considered as guidelines for all patients

PRINCIPLES OF ANTIMICROBIAL THERAPY (see also pages 9 to 12):

- De-escalation according to culture findings is recommended; survival analysis showed that de-escalation strategies did not impact on final outcome.
- Antimicrobials are indicated only for patients who have NOT been administered any antimicrobial of the same group during the last three months
- Metronidazole should be administered for intraabdominal infections
- Ceftazidime should not be administered for community-acquired pneumonia
- It is suggested to administer 3rd generation cephalosporins as a continuous 24-hour IV infusion and piperacillin/tazobactam at 4-hour IV infusions

ANTIMICROBIAL THERAPY FOR PATIENTS WITH SEVERE SEPSIS DEVELOPING OUTSIDE THE ICU

EPIDEMIOLOGICAL REGISTRY

From the prescribed antimicrobial combinations, the following are associated with better outcome*:

- 3rd generation cephalosporins +/-metronidazole
- Piperacillin/tazobactam
- Carbapenem[1]

[1]imipenem, meropenem or doripenem

*taking into consideration that no stratification was done regarding infection site, this finding is not conclusive and reported drug combinations cannot be considered as guidelines for all patients

PRINCIPLES OF ANTIMICROBIAL THERAPY
(see also pages 9 to 12):

- De-escalation according to culture findings is recommended; survival analysis showed that de-escalation strategies did not impact on final outcome.
- Metronidazole should be administered for intraabdominal infections
- Ceftazidime should not be administered for community-acquired pneumonia
- It is suggested to administer 3rd generation cephalosporins as a continuous 24-hour IV infusion and piperacillin/tazobactam at 4-hour infusions
- It is suggested to administer meropenem at 3-hour IV infusions and doripenem at 4-hour IV infusions
- Carbapenems are recommended for sepsis occurring during hospitalization or for infections by multidrug-resistant pathogens

ANTIMICROBIAL THERAPY FOR PATIENTS WITH SEPTIC SHOCK DEVELOPING OUTSIDE THE ICU

EPIDEMIOLOGICAL REGISTRY
From the prescribed antimicrobial combinations, the following are associated with better outcome*:

- Piperacillin/tazobactam
- Piparecillin/tazobactam + (glycopeptide[1] or linezolid or daptomycin)
- Carbapenem[2]
- Carbapenem[2] + (glycopeptide[1] or linezolid or daptomycin)

[1]vancomycin or teicoplanin
[2]imipenem, meropenem or doripenem
*taking into consideration that no stratification was done regarding infection site, this finding is not conclusive and reported drug combinations cannot be considered as guidelines for all patients

PRINCIPLES OF ANTIMICROBIAL THERAPY
(see also pages 9 to 12):

- De-escalation according to culture findings is recommended; survival analysis showed that de-escalation strategies did not impact on final outcome
- Linezolid is particularly recommended for patients with hospital-acquired pneumonia by MRSA
- Daptomycin is suggested for patients with MRSA bacteremia, endocarditis and SSTI
- Daptomycin should not be administered for pneumonia
- Administration of a combination of carbapenem + glycopeptides / linezolid / daptomycin is recommended for patients with sepsis developing during hospitalization or with probable infections by multidrug-resistant pathogens

PROCALCITONIN FOR THE MONITORING OF ANTIMICROBIAL THERAPY

- Decrease of serum procalcitonin may assist in decision-making of discontinuation of empirical antimicrobial treatment. This applies for patients with resolved signs of infection.
- Grade of evidence: 2C[1]

Increased procalcitonin (PCT) levels are found in the serum of patients developing a generalized septic reaction[2].

Results of our observational study on 289 patients[3] and of two randomized clinical studies enrolling 68 and 630 patients respectively[4, 5] corroborate the value of serial PCT measurements and end up with the following proposal for the use of PCT to monitor antimicrobial therapy:

- PCT should be measured upon diagnosis of sepsis and on follow-up days
- Decreases greater than 30% within the first 48 hours indicates favorable response to administered antimicrobials and favorable outcome.
- Decrease greater than 80-90% of the baseline value or levels ≤ 0.25 ng/ml accompanied by clinical improvement encourage discontinuation of administered antimicrobial treatment.

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3.Georgopoulou AP, et al. *J Crit Care* 2011; 26: 331.e1-e7
4.Nobre V, et al. *Am J Resp Crit Care Med* 2008; 177: 498-505
5.Bouadma L, et al. *Lancet* 2010; 375 : 463-474

suPAR is a reliable biomarker of the final outcome.
This applies even for patients with a low APACHE II score

More than 160 different protein molecules have been proposed to be used as biomarkers for the diagnosis and outcome prediction of sepsis. C-reactive protein (CRP) and procalcitonin (PCT) are most often used in everyday clinical practice. The following features are required for a molecule to be used as a surrogate biomarker in sepsis[1]:

- Concentration of the biomarker should reliably express the intensity of the inflammatory response of the host
- Concentrations should follow the change of the clinical state and reflect the final outcome.

A study of the Hellenic Sepsis Study Group in 1914 patients showed that concentration of suPAR (soluble urokinase plasminogen activator receptor) greater than 12 ng/ml are indicative of poor outcome even in patients with low APACHE II score. These results were confirmed in an independent group of patients from Sweden[2]

REFERENCES
1.Dellinger RP, et al. *Crit Care Med* 2013; 41: 580-637
2.Giamarellos-Bourboulis EJ, et al. *Crit Care* 2012; 16: R149

INTERNATIONAL GUIDELINES FOR IMMUNOTHERAPY OF SEVERE SEPSIS/SHOCK

Immunotherapy aims to attenuate the excess inflammatory reaction of the host

Despite improvement in antimicrobial therapy, mortality of severe sepsis/shock remains high ranging between 35% and 50%. Strategies of immunotherapy were developed after understanding the role of the excess inflammatory reaction of the septic host in response to an invading microbial pathogen. Several strategies have been evaluated in randomized clinical trials.

In the present booklet, a brief report is done to the following therapeutic strategies of immunotherapy:

- Hydrocortisone stress replacement
- Tight glucose control
- Immunonutrition
- Intravenous clarithromycin
- IV Immunoglobulin administration

Grade of evidence for every therapeutic strategy is provided, according to the Surviving Sepsis Campaign 2012 guidelines (GRADE system available in Appendix 1); wherever other grading systems of evidence have been used this is specifically stated.

STRESS HYDROCORTISONE REPLACEMENT IN SEPTIC SHOCK

- Administration of low-dose hydrocortisone is suggested in septic shock refractory to vasopressors
- Grade of evidence: 2C[1]

Almost 60% of patients with septic shock present with signs of functional adrenal insufficiency. This is manifested as refractory hypotension to the administration of fluids and vasopressors. Laboratory confirmation of this syndrome by synthetic ACTH (co-syntropin) administration test is not required.

The proposed **dose regimen** for patients is 200 mg of hydrocortisone daily as a continuous 24h IV infusion. The duration of treatment is 7 days and this is followed by gradual tapering[1].

An initial clinical trial in hospitals of France showed that this treatment led to prolonged survival of the patients[2]. Although later results of the CORTICUS randomized clinical trial in 499 patients did not confirm these findings, they showed that hydrocortisone replacement led to earlier discontinuation of the administration of vasopressors[3]. These two clinical trials differed considerably in the time window between start of vasopressors and start of hydrocortisone. One retrospective analysis from the Greek registry in 170 patients showed survival benefit when hydrocortisone replacement started within the first 9 hours from start of vasopressors. This was linked with a significant anti-inflammatory effect on circulating blood monocytes[4].

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1.Dellinger RP, et al. *Crit Care Med* 2013; 41: 580-637
2.Annane D, et al. *JAMA* 2002; 288: 862-871
3.Sprung CL, et al. *N Engl J Med* 2008; 358: 111-124
4.Katsenos C, et al. *Crit Care Med* 2014; 42: 1651-1657

TIGHT GLUCOSE CONTROL IN SEPSIS

In all patients with severe sepsis:

- Decrease of blood glucose is recommended by the intravenous infusion of insulin whenever blood glucose is found ≥180mg/dl in two consequent measurements. The target is blood glucose below 180 mg/dl (Grade of evidence: 1A[1])
- Blood glucose measurements should be repeated every one or two hours until blood glucose levels and insulin intravenous infusion rate become stable. (Grade of evidence 1C[1])
- Capillary blood glucose measurement should be performed and interpreted with caution. It is not a substitute for blood glucose measurement (Grade of evidence 1B[1])

Euglycemia in sepsis aims to maintain stable metabolic levels for the host. This is also accompanied by stimulation of the anti-inflammatory response of the host.

Hypoglycemia is a major hazard during the effort of preserving normal blood glucose with the intravenous infusion of insulin. Recent results of the randomized multicenter study NICE-SUGAR in 6104 patients, confirmed that tight control of blood glucose levels targeting values of 80-110 mg/dl was responsible for the incidence of severe hypoglycemia. This happened in 6-29% of patients and it was associated with increased mortality[2,3].

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Recommendations that apply for patients with severe sepsis and septic shock are:

- Gradual start with low calories (500 Kcal/day) oral (or per levin) feeding within the first 48 hours; gradual increase during the following days according to patient's tolerance (Grade of evidence 2C και 2B)[1]
- Enteral feeding should be supplemented by intravenous glucose administration during the first 7 days (Grade of evidence 2B)[1]
- Start parenteral feeding (total or supplementary) after day 7.
- Immunonutrition supplements and intravenous selenium are not recommended (Grade of evidence 2C)[1]

Initial clinical trials showed significant decrease of mortality and of the risk to progression into multiple organ dysfunction (MODS) as well as significant shortening of the time of mechanical ventilation and of ICU stay, after administration of EPA (eicosapentaenoic acid) and GLA (γ-linolenic acid) in septic patients[2]. Although the clinical trial OMEGA was prematurely stopped due to futility, it has been criticized for its design[3]. The most recent INTERSEPT clinical trial showed that enteral nutrition with EPA+GLA delayed progression into severe sepsis or septic shock, ***provided that it is used during the early stages of sepsis and not in patients already in MODS****[4].*

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INTRAVENOUS CLARITHROMYCIN AND SEPSIS

Intravenously administered clarithromycin

- Decrease significantly the relative risk for death by septic shock and multiple organ dysfunction following infections caused by Gram-negative pathogens
- Offers earlier resolution of Gram-negative infections accompanied by severe sepsis

IV clarithromycin was administered in one randomized clinical trial in 200 Greek patients with sepsis developing in the field of ventilator-associated pneumonia (VAP)[1]. Treatment led to earlier resolution of VAP and to significant decrease of the relative risk for death by septic shock and multiple organ dysfunction (MODS). These results were confirmed by a second randomized clinical trial in 600 patients with sepsis developing in the field of acute pyelonephritis, Gram-negative bacteremia and intra-abdominal infections[2]. In this second trial, clarithromycin treatment decreased hospitalization costs.

These two clinical trials mentioned above are not yet rated by the Surviving Sepsis Campaign. Based on results by retrospective studies, Surviving Sepsis Campaign provides Grade of evidence 2B for the administration of macrolides with other antimicrobials in patients with bacteremia by Streptococcus pneumoniae and septic shock[3].

The **recommended dose regiment** is 1gr once daily as 1-hour continuous intravenous infusion through a central catheter for four consequent days.

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INTRAVENOUS IMMUNOGLOBULIN ADMINISTRATION IN SEPSIS

- Intravenous treatment with IgG preparations does not prolong survival of septic patients[1]
- A meta-analysis demonstrated decrease of relative risk of death of infants and adults with the use of IgM-enriched preparations[2]
- A decrease of circulating IgM is found when patients progress into shock and this is connected with poor outcome[3]

Results of randomized clinical trials are controversial concerning IV immunoglobulin treatment in patients with severe sepsis or septic shock[1]. As a single exception, a meta-analysis demonstrated decrease of the relative risk of death with the intravenous administration of IgM-enriched preparations[2].

A recent publication of the Hellenic Sepsis Study Group in 332 patients showed a significant decrease of circulating IgM when patients with severe sepsis progress into septic shock. Reduced total body distribution of IgM was associated with increased 28-day mortality and total hospital mortality[3]. Even though IgM measurement can become a biomarker indicating the need for the start of treatment, prospective randomized clinical trials are still necessary.

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APPENDIX 1

According to the GRADE* system of recommendations adopted by the Surviving Sepsis Campaign, the grade of evidence is provided by a number and a letter.

Numbers are interpreted as follows:

1. It is recommended to follow the therapeutic strategy in most patients
2. It is suggested to follow the therapeutic strategy in well-selected patients

Letters A, B and C refer to the qualitative evaluation of available studies based on pre-defined criteria and they are interpreted as follows:

- A: evidence based on well-conducted randomized clinical studies without methodological limitations or on un-doubtable observational studies
- B: evidence based on conducted randomized clinical studies with certain methodological limitations or strong evidence coming from observational clinical studies
- C: evidence based on observational studies or on experts' opinion

Before each Consensus Conference concerning issues of therapeutic approach, evaluation criteria are pre-determined not only for all available trials but also for the clinical significance of their results. It is discussed if the criteria apply to all patients or part of them. Additionally, for each therapeutic strategy the benefit-risk ratio is co-estimated. After taking all the above parameters under consideration, the committee of experts participating to the Consensus Conference defines the grade of evidence of a certain practice or a therapeutic approach, as indicated in the following table.

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GRADE SYSTEM OF EVALUATION OF THERAPEUTIC STRATEGIES			
Grade of evidence	**Cost /benefit ratio**	**Available evidence**	**Interpretation**
1A	Benefit >>> Risk	RCTs* without methodological limitations and restrictions or undoubtable observational studies	Strong recommendation for all patients
1B	Benefit >>> Risk	RCTs* with methodological limitations and restrictions or strong recommendation by observational studies	Adequate recommendation for all patients
1C	Benefit >>> Risk	Observational studies	Adequate recommendation subject to changes
2A	Benefit ≥ Risk	RCTs* without methodological limitations and restrictions or undoubtable observational studies	Weak recommendation
2B	Benefit ≥ Risk	RCTs* with methodological limitations and restrictions or strong recommendation by observational studies	Weak suggestion
2C	Undefined benefit / risk ratio	Observational studies	Very weak suggestion

*RCTs: randomized clinical trials

ANTIMICROBIAL DOSE REGIMENS ACCORDING TO CREATININE RENAL CLEARANCE (ml/min)					
Antimicrobial	Normal	50-<90	10-<50	<10	CVVH*
Ceftriaxone	2g x 1	2g x 1	2g x 1	2g x 1	2g x 1
Cefotaxime	2g x 3	2g x 2	2g x 2	2 g x 1	2 g x 2
Ceftazidime	2g x 3	2g x 2	2g x 2	2.25g x 1	2 g x 2
Piperacillin/tazobactam	4.5g x 4	4.5g x 4	2.25g x 4	2.25g x 3	2.25g x 3
Imipenem	1g x 3	0.5 g x 4	0.5 g x 2	0.25 g x 2	0.5-1g x 2
Meropenem	0.5g x 3	2 g x 3	2 g x 2	1 g x 1	2 g x 2
Doripenem	0.5g x 3	0.5 g x 3	0.25 g x 3	No available data	
Tigecycline	50mg** (100mg loading dose)	50mg** (100mg loading dose)	50mg** (100mg loading dose)	50mg** (100mg loading dose)	50mg** (100mg loading dose)
Colistin	[BW/7.5] mU loading dose, [creatinine clearance/10 + 2] mU in 2-3 doses				5 mU x 2
Vancomycin	1g x 2	1g x 1	1g/24-96 hours	1g/4-7 days	0.5 g/24-48 hours
Teicoplanin	10 mg/kg x 1	10 mg/kg x 1	10 mg/kg x 1	10 mg/kg/48 hours	10 mg/kg x 1
Linezolid	600 mg x 2	600 mg x 2	600 mg x 2	600 mg x 2	600 mg x 2
Daptomycin (CPK weekly measurements)	8-10 mg/kg x 1	8-10 mg/kg x 1	8-10 mg/kg/48 hours	8-10 mg/kg/48 hours	8-10 mg/kg/48 hours
Ciprofloxacin	600 mg x 2	600 mg x 2	400 mg x 2	300 mg x 2	400 mg x 1
Metronidazole	500 mg x 3	500 mg x 3	500 mg x 3	250 mg x 3	250 mg x 3

*Continuous veno-venous hemofiltration **100mg (200mg loading dose when MIC>0.25 µg/ml)

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