ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΧΗΜΕΙΟΘΕΡΑΠΕΙΑΣ
HELLENIC SOCIETY FOR CHEMOTHERAPY

ΕΛΛΗΝΙΚΟ ΙΝΣΤΙΤΟΥΤΟ ΜΕΛΕΤΗΣ ΤΗΣ ΣΗΨΗΣ
HELLENIC INSTITUTE FOR THE STUDY OF SEPSIS

HELLENIC SEPSIS STUDY GROUP BULLETIN ON SEPSIS

DEFINITIONS-DIAGNOSTIC APPROACH-TREATMENT GUIDELINES

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ATHENS-GREECE 2012

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INTRODUCTION

In September 2010 Global Sepsis Alliance was founded, an international initiative trying to create awareness that sepsis is a leading cause of death (www.globalsepsisalliance.com). Under this perspective, Hellenic Sepsis Study Group which participates in this international effort felt it necessary to publish the present booklet in Greece (www.sepsis.gr). The first booklet was published in October 2008 and it was accepted with a great deal of enthusiasm since more than 4000 free copies were distributed in Greek physicians in hospitals.

This booklet is revised since it provides data coming from the analysis of 2352 Greek patients with sepsis. Some of these data have already been published in international medical journals. Based on these data, mortality from severe sepsis and septic shock for patients hospitalized in the general ward is 35.3% and 61.2% respectively. Respective mortality rates for patients hospitalized in Intensive Care Units (ICUs) are 37.0% and 49.2%.

Twenty-two departments of internal medicine, 9 departments of surgery, 4 departments of chest medicine and 17 ICUs participate in the Hellenic Sepsis Study Group. All these participate intensively by registering clinical data from hospitalized patients through the usage of a common research protocol. Every patient is registered once. Communication between members of the Group is done through e-mails whereas regular meetings of all members are organized three times every year.

The combinations of antimicrobial agents that are mentioned in this booklet come from analyzed epidemiological data. They refer to patients with severe sepsis and/or septic shock developed outside the ICU because most of available data come from such type of patients. Analysis was subject of thorough discussion with a panel of experts during the *4th European Conference on Bloodstream Infections* that took place in Athens on the the 27th and 28th May 2010.

There is no doubt that these patients, particularly sufferers from septic shock, should have been hospitalized in an ICU environment. However, the lack of bed availability in our country mandates to create awareness for the proper management of these patients even in the general ward. Under this perspective, the present bulletin aims to help Greek physicians understand the basic principles of sepsis management.

This booklet is published in hopes that all efforts for registration of patients in Greece continues to expand with the participation of a growing number of departments of the general ward and of ICUs.

May 2012

Ch. Gogos E. J. Giamarellos-Bourboulis

SEPSIS DEFINITIONS

Uncomplicated sepsis

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

- 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% band forms

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 in chest x-ray
- **Acure renal failure**: urine output <0.5 ml/hour/kg body weight over the last two hours provided that the 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 e.t.c

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"[1,2], led to the publication of guidelines regularly revised (last revision January 2008[2]).

Proper management of sepsis patients 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 emergencies or at the general ward in parallel with search 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 severe sepsis/shock 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 recommendation according to the Surviving Sepsis Campaign 2008 guidelines is provided[1,2]. The GRADE system for recommendation is provided in Appendix 1.

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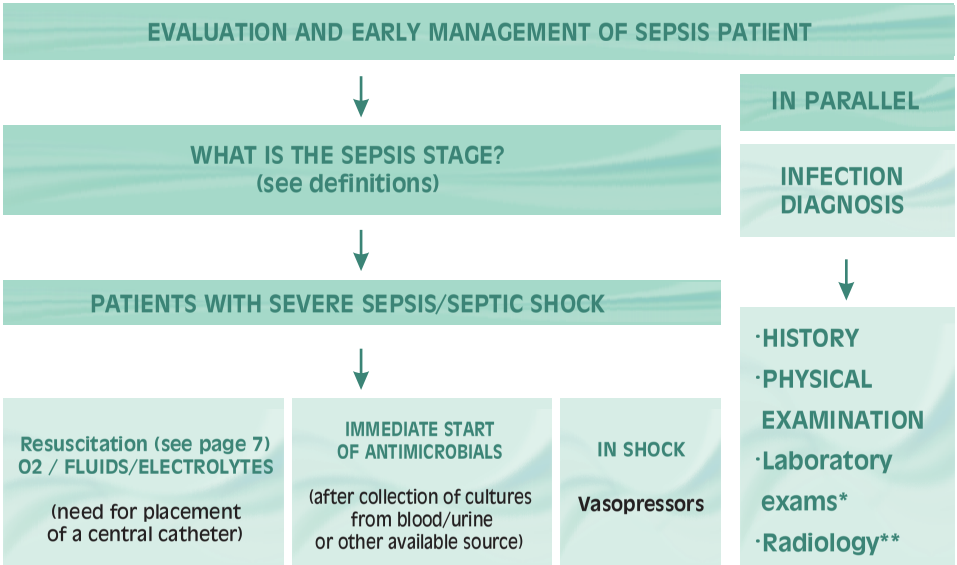

*Hemogram, urine, creatinine, blood gases, coagulation tests, procalcitonin
**chest X-ray, kidney-biliary tract ultrasound, computed tomography of chest-abdomen if necessary

GOALS OF EARLY RESUSCITATION OF SEPSIS PATIENTS[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 saturation ≥92%
- Mixed venous blood saturation through a catheter inserted in the upper vena cava ≥70%

PRINCIPLES OF INFECTION SOURCE CONTROL[2]

- Diagnosis of the underlying infection
- Eradication e.g. an abcess
- Use of the minimal invasive technique when feasible e.g. transcutaneous than surgical interventions

REFERENCES
1. Rivers E, et al. *N Engl J Med* 2001; 345: 1368-1377
2. Dellinger RP, et al. *Crit Care Med* 2008; 36: 296-327

PRINCIPLES OF ANTIMICROBIAL THERAPY FOR THE SEPTIC PATIENT

- **Antimicrobials should start WITHIN THE FIRST ONE HOUR from signs of severe sepsis/septic shock**
- **Grade of evidence: 1B[1]**

In a retrospective analysis of data from 2731 patients at septic shock, final outcome was correlated with time between diagnosis of hypotension until start of appropriate antimicrobials. Survival 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]. The need for early start of treatment is profound even for combination of antimicrobials as shown is a recent retrospective analysis of 1223 patients at septic shock[3]. 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.

ATTENTION

- It is mandatory to administer antimicrobials within the first hour in the emergencies and not to wait patient transfer in the general ward or in the ICU. Sampling for microbial cultures (blood, urine etc) should be done before start of antimicrobials.

- Antimicrobials available for bolus infusion should be administered first. Then antimicrobials administered with a certain infusion time should follow.

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2. Kumar A, et al. *Crit Care Med* 2006; 34: 1589-1596
3. Kumar A, et al. *Crit Care Med* 2010; 38: 1773-1785

SELECTED ANTIMICROBIALS SHOULD:

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

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

DE-ESCALATION OF ANTIMICROBIAL TREATMENT

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.

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

- Intake of broad-spectrum antimicrobials[1] over the last three months
- Hospitalization for ≥2 days over the last three months
- Present hospitalization of ≥5 days
- Residence in long-term care facilities
- Close association with 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

TRAITS FROM PATIENTS' HISTORY SIGNIFYING INCREASED RISK FOR FUNGAL INFECTIONS[1]:

- Upper abdominal surgery
- Colonization of ≥2 sites
- Total parenteral nutrition
- Severe sepsis

[1]León C, et al. *Crit Care Med* 2006; 34: 730-737

ANTIFUNGAL THERAPY FOR PATIENTS WITH CANDIDEMIA:

- Echincandins* and fluoconazole are the first choice for infections by *Candida albiacans* in ICU patients
- For non-stable sepsis patients and when *Candida non-albicans* is isolated, echinocandins are the first choice.
- Liposomal amphotericn B is recommended when other drugs are not available or when resistance to other drugs emerges.

[1] caspofungin, anidoulafungin, micafungin

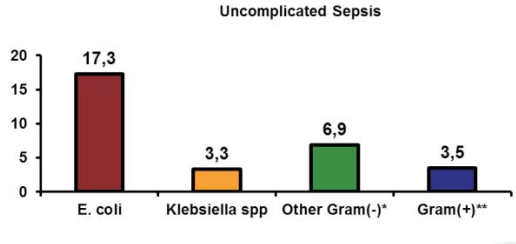
DATA FROM SEPSIS REGISTRY IN GREECE

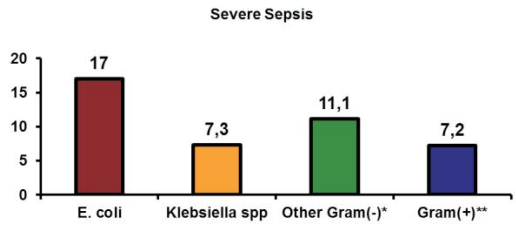
The described combinations of antimicrobial agents come from the analysis of data selected by Greek patients who have been registered by the protocol of the Hellenic Sepsis Study Group. They refer to patients with **severe sepsis/shock developing outside the ICU**. They represent findings of an epidemiological study and not proposed regimens for management.

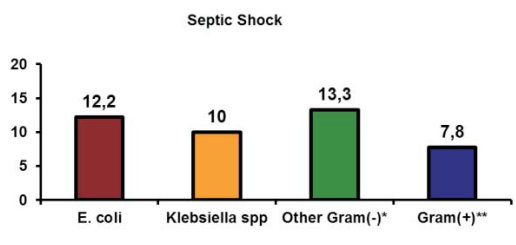
Analysis comprised this specific patient population due to the statistical power coming from their total number. As expected, registry provided a vast number of drug combinations. Survival analysis comprised those combinations for which adequate statistical power was available.

Drug combinations associated with survival benefit are reported herein for patients with severe sepsis/shock developing outside the ICU (cumulative data irrespective of the infection site). Selection of administered drugs was done by attending physicians by the infection site, the patients' history and by other criteria undefined by the research protocol. As such, connection with better outcome indicates the appropriateness of the choice. It is evident that formatting guidelines cannot solely be based on descriptive studies because groups of patients administered different regimens are not comparable (although APACHE II scores did not differ). It was considered important to provide these data to stimulate feedback thoughts. To this same end, results of blood cultures and resistance profiles are also provided.

ISOLATES (%) OF BLOOD CULTURES FROM PATIENTS DEVELOPING SEPSIS OUTSIDE THE ICU

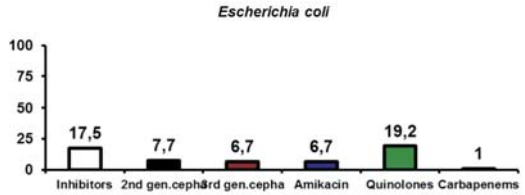


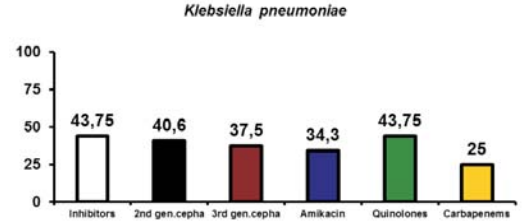




**Proteus spp, P.aeruginosa, P.stuartii, A. baumannii*
***Staphylococcus aureus, Enterococcus spp*

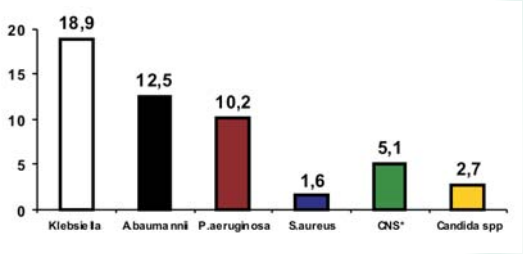
RESISTANCE (%) OF BLOODSTREAM ISOLATES OF PATIENTS DEVELOPING SEPSIS OUTSIDE THE ICU





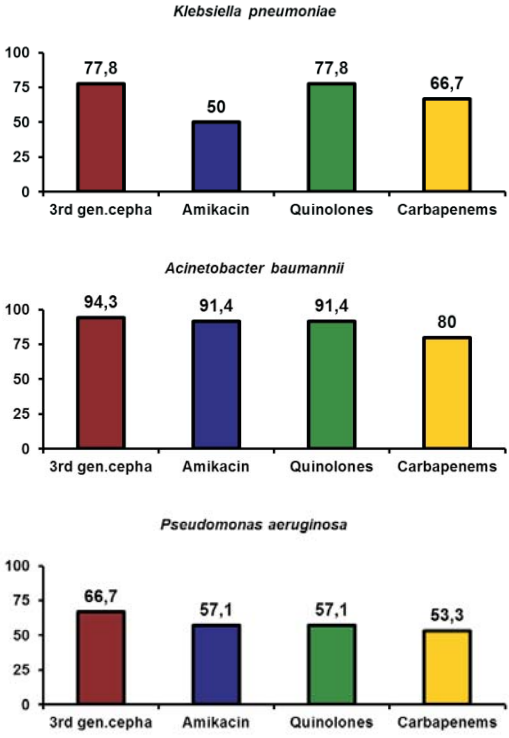
Resistance of Staph. aureus to methicillin (MRSA): 27.3%

ISOLATES (%) OF BLOOD CULTURES FROM PATIENTS DEVELOPING SEPSIS INSIDE THE ICU



**coagulase-negative Staphylococcus spp*

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



No resistance to colistin was found
Resistance of Staph. aureus to methicillin (MRSA): 91.9%

ANTIMICROBIAL THERAPY FOR PATIENTS WITH SEVERE SEPSIS DEVELOPING OUTSIDE THE ICU

Epidemiological registry
From the prescribed combinations of antimicrobials, the following are connected with better outcome*:

- 3rd generation cephalosporins +/- metronidazole
- Ciprofloxacin +/- 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 page 9):

- 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 intra-abdominal infections
- Ceftazidime should not be administered for patients with community-acquired pneumonia
- Ciprofloxacin is indicated only for patients not administered any fluoroquinolone the last three months

ANTIMICROBIAL THERAPY FOR PATIENTS WITH SEPTIC SHOCK DEVELOPING OUTSIDE THE ICU

Epidemiological registry
From the prescribed combinations of antimicrobials, the following are connected with better outcome*:

- Piparecillin/tazobactam + (glycopeptide[1] or linezolid or daptomycin)
- 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 page 9):

- 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 recommended for patients with MRSA bacteremia
- Daptomycin should not be administered in patients with pneumonia

PROCALCITONIN FOR THE MONITORING OF ANTIMICROBIAL THERAPY

Procalcitonin (PCT) is an important aid for diagnosis and prognosis; serial measurements may safely guide antimicrobial decision-making.

PCT is increased in the serum of patients with generalized septic reaction. Its diagnostic and prognostic performance is superior that the other commonly used inflammatory markers[1]. A study of our group in 1156 patients showed that PCT >0.12 ng/ml the first 24 hours for sepsis developing outside the ICU and PCT >0.85 ng/ml for sepsis developing inside the ICU is related with unfavorable outcome[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 accompanied by clinical improvement encourage stop of administered antimicrobials.

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2. Giamarellos-Bourboulis EJ, et al. *J Hosp Infect* 2011; 77: 58-63
3. Georgopoulou AP, et al. *J Crit Care* 2011; 26,331.e1-331.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

INTERNATIONAL GUIDELINES FOR IMMUNOTHERAPY OF SEVERE SEPSIS/SHOCK

Immunotherapy aims to attenuate excess inflammatory reaction of the septic host

Despite improvements 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 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

For every therapeutic strategy, the grade of evidence according to the Surviving Sepsis Campaign 2008 guidelines is provided (GRADE system available in Appendix 1); when other grading systems of evidence have been used this is specifically referred.

STRESS HYDROCORTISONE REPLACEMENT IN SEPTIC SHOCK

- **Administration of low-dose hydrocortisone is suggested in septic shock**
- **Level of evidence: 2B**[1, 2]

Almost 60% of patients at septic shock present with signs of relative adrenal insufficiency. This is manifested as refractory hypotension to the administration of fluids and vasopressors. Laboratory confirmation of this syndrome is not required, although this is confirmed when plasma cortisol is increased by less than 9 mcg/dl after administration of 250 mcg of synthetic ACTH (co-syntropin) or when random plasma concentrations of cortisol are found below 10 mcg/dl.

The proposed **dose regimen** for patients at septic shock is 200 mg of hydrocortisone daily divided into 4 equal doses or a starting loading dose of 100 mg followed by 10 mg/hour infusion. The duration of treatment is 7 days and this is followed by gradual tapering[2].

The level of evidence of this strategy was underestimated in the 2008 Surviving Sepsis Campaign guidelines[1], based on results of the randomized CORTICUS trial on 499 patients showing the lack of survival benefit[3]. A published consensus of the American College of Chest Physicians/Society of Critical Care Medicine suggested a 2B grade stress hydrocortisone replacement for patients at septic shock refractory to the intravenous administration of fluids and vasopressors[2].

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1. Dellinger RP, et al. *Crit Care Med* 2008; 36: 296-327
2. Marik PE, et al. *Crit Care Med* 2008; 36: 1937-1949
3. Sprung CL, et al. *N Engl J Med* 2008; 358: 111-124

TIGHT GLUCOSE CONTROL THROUGH INSULIN INFUSION

- **It is suggested to infuse insulin intravenously to patients with severe sepsis/shock following early resuscitation of the patient**
- **It targets to maintain capillary glucose <150 mg/dl**
- **Grade of evidence: 2C**[1]

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

Tight glucose control (TGC) aims to maintain capillary glucose within 80-110 mg/dl through the continuous infusion of insulin via a pump. Conventional glucose control (CGC) refers to the intravenous infusion of insulin whenever capillary glucose exceeds 215 mg/dl in order to decrease to below 180 mg/dl. In two single-center randomized clinical trials, TGC singlificanlty decreased mortality compared with CGC. However, multicenter NICE-SUGAR study on 6028 patients concluded that TGC was connected with increased risk for death compared with CGC due to events of hypoglycemia[4]*. It is thus suggested that capillary glucose should be maintained < 150 mg/dl*[1]*.*

The American College of Physicians does not suggest TGC but CGC targeting to maintain capillary glucose between 140 and 200 mg/dl[5]*.*

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Enteral feeding with γ-linolenic acid/eicosapentaenoic acid:
- **Is suggested for sepsis patients with acute lung injury/acute respiratory distress**
- **Reduces risk of progression to multiple organ dysfunction**

Two randomized clinical trials in limited number of patients at the ICU with acute lung injury (ALI)/respiratory distress syndrome (ARDS) showed benefit from enteral feeding with a combination of γ-linolenic acid (GLA)and eicosapentaenoic acid (EPA). Benefit consists of significant decrease of length of ICU stay and of risk of progression to multiple organ dysfunction[1,2].

Enteral feeding with GLA+EPA has not been evaluated by the 2008 Surviving Sepsis Campaign. American Society of Chest Physicians/Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition have evaluated this treatment strategy and they have provided grade A of recommendation[3].

Daily energy needs are calculated by the Harris-Benedict formula, so that amount of GLA+EPA equal to a) 50% of daily energy needs are given the first 24 hours; b) 75% of daily energy needs are given daily for the next three days; and c) 100% of daily energy needs are given daily on the following days.

It should be underscored that the large scale randomized OMEGA trial studying the role of enteral feeding with GLA+EPA was prematurely stopped for futility[4].

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2. Singer P, et al. *Crit Care Med* 2006; 34: 1033-1038
3. McClave SA, et al. *JPEN* 2009; 33: 277-316
4. Rice TW, et al.*JAMA* 2011; 306: 1574-1581

INTRAVENOUS CLARITHROMYCIN AND SEPSIS

Intravenously administered clarithromycin
• Offers earlier resolution of ventilator-associated pneumonia irrespective of sepsis stage
• Decreases significantly relative risk for death by septic shock and multiple organ dysfunction

Clarithromycin was intravenously administered in a randomized clinical trial enrolling 200 Greek patients suffering from ventilator-associated pneumonia (VAP) and sepsis[1]. Treatment resulted in significantly earlier resolution of VAP and decrease of the relative risk for death by septic shock and multiple organ dysfunction without affecting all-cause mortality at 28 days. Benefit from clarithromycin treatment is accompanied by reversal of immunoparalysis of circulating monocytes[2].

The proposed **dose regimen** is 1g once daily within one hour of continuous infusion through a central catheter for three consecutive days.

The grade of evidence of intravenous clarithromycinin sepsis has not yet been evaluated by other panels of experts. It is, however, a novel very promising strategy with minimum side effects.

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2. Spyridaki A, et al. Antimicrob Agents Chemother 2012; May7 Epub

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 interpretated as follows:

- A: evidence based on well-conducted randomized clinical studies without methodological limitations or 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

The criteria of evidence are specified before any Consensus Conference taking into consideration not only available clinical studies but the importance of recommendation for the total or part of the patient population. Finally the benefit/risk ratio is defined.

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GRADE SYSTEM OF EVALUATION OF THERAPEUTIC STRATEGIES

Grade of evidence	Cost/benefit ratio	Available evidence	Interpretation
1A	Benefir >>> Risk	RCTs* without methodological limitations and restrictions or un-doubtable 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 change
2A	Benefit ≥ Risk	RCTs* without methodological limitations and restrictions or un-doubtable 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 g 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	2 g 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	
Vancomycin	1g x 2	1g x 1	1g/24-96 hours	1 g/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)	6 mg/kg x 1	6 mg/kg x 1	3 mg/kg/12 hours	2 mg/kg/18 hours	6 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

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