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HELLENIC INSTITUTE FOR THE STUDY OF SEPSIS

# HELLENIC SEPSIS STUDY GROUP
# BOOKLET ON SEPSIS

## DEFINITIONS-DIAGNOSTIC APPROACH-TREATMENT RECOMMENDATIONS


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# INTRODUCTION

The Hellenic Sepsis Study Group (HSSG) was formed in 2006 with the aim to resister the epidemiology and particular pathogenetic aspects of sepsis in Greece. This effort is internationally recognized as pioneer in establishing a personalized approach for sepsis management. The approval of Anakinra for the treatment of COVID-19 pneumonia by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) of the United Stade, based on the studies SAVE and SAVE-MORE, as well as the contribution of more than 120 original papers in international medical journals witness our success. HSSG is among the founding members of the Global Sepsis Alliance (www.globalsepsisalliance.com); one of HSSG coordinating members is also member of the steering committee of the World Sepsis Day (www.worldsepsisday.com) and Chairman of the European Sepsis Alliance.

Following the successful publishing of the previous Booklets in the years 2008, 2011, 2014 and 2017, a fully updated Booklet is published in 2023, including analysis of data coming from more than 7000 patients of the Hellenic Registry. The new Booklet contains:

- Recent advances in biomarker discovery for diagnosis
- Suggestions for antimicrobial treatment, based on the analysis of data of the Hellenic Registry
- Description of newer antimicrobial agents
- Recommendations for management according to the Surviving Sepsis Campaign
- Data on the latest HSSG scientific publications

During the COVID-19 pandemic, important and groundbreaking scientific publications made of HSSG an international leader in the field of precision immunotherapy. Under the coordination of the Hellenic Institute for the Study of Sepsis (HISS), the HSSG designs and runs more than 35 randomized clinical trials, aiming to improve the outcome of our patients. We hope that this effort will inspire and guide younger Greek physicians, and other health-care providers in their scientific carrier.

September 2023

C. Gogos EJ. Giamarellos-Bourboulis

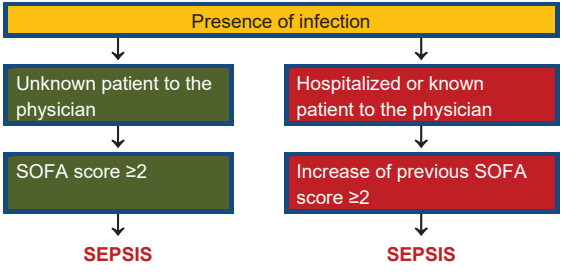
## DEFINITIONS

**Sepsis**
A life-threatening organ dysfunction caused by a dysregulated host response to an infection.

**Organ dysfunction**
**The acute increase in total SOFA score ≥ 2 points,** reflecting an overall mortality risk of approximately 10% in a general hospital population with infection.
*In patients without known pre-existing organ dysfunction, baseline SOFA score before the current incident is assumed to be zero*

Singer M, et al. *JAMA* 2016; 315: 801-810

## CRITERIA OF SEPSIS DIAGNOSIS



## SOFA SCORE

| Parameter | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| $PaO_2/FiO_2$ (mmHg) | ≥400 | <400 | <300 | <200 (in MV) | <100 (in MV) |
| Platelets (per $mm^3$) | ≥150 | <150 | <100 | <50 | <20 |
| Circulation | MAP ≥70 | MAP <70 | Dobutamine administration[1] | Adrenaline[2] or noradrenaline[2] administration | Adrenaline[3] or noradrenaline[3] administration |
| Glasgow Coma Scale | 15 | 13-14 | 10-12 | 6-9 | <6 |
| Bilirubin (mg/dl) | <1.1 | 1.2-1.9 | 2.0-5.9 | 6.0-11.9 | ≥12 |
| Creatinine (mg/dl) or 24h Urine output | <1.1 | 1.2-1.9 | 2.0-3.4 | 3.5-4.9 or <500ml/24h | ≥5.0 or <200ml/24h |

[1]any dose, [2]≤0.1μg/kg/min, [3]>0.1μg/kg/min
MV: Mechanical Ventilation
MAP: Mean arterial pressure (mmHg)

**Septic shock (Definition)**
A subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to subtantially increase mortality.

Singer M, et al. *JAMA* 2016; 315: 801-810

**CRITERIA OF SEPTIC SHOCK DIAGNOSIS**
ALL the following:

- Presence of sepsis (see diagnosis above)
- Mean arterial pressure less than 65mmHg despite adequate intravenous fluid administration
- Serum lactate level >2mmol/l
- Need for vasopressors

## EARLY RECOGNITION OF SEPSIS OUTSIDE THE ICU: qSOFA SCORE

HIGH SUSPICION OF INFECTION

+

At least 2 of the following clinical signs[1]:

- Altered mental status (Glasgow Coma Scale < 13)
- Respiratory rate >22/min
- Systolic arterial pressure <100mmHg

According to the analysis of the data of the Hellenic Registry, the presence of any of these clinical signs increases the risk for death in patients admitted for infection[2].

The Surviving Sepsis Campaign 2021 Guidelines question the sensitivity of the qSOFA score for early sepsis recognition[3].

↓

INITIATION OF TREATMENT ALGORITHM UNTIL FINAL DIAGNOSIS (see page 15)

**REFERENCES**


1. Singer M, et al. *JAMA* 2016; 315: 801-810
2. Giamarellos-Bourboulis EJ, et al. *Clin Microbiol Infect* 2017; 23: 104-109
3. Evans L, et al. *Crit Care Med* 2021; 49:1974-1982

# EARLY SEPSIS RECOGNITION USING ARTIFICIAL INTELLIGENCE: THE NEWS 2 SCORE

Several systems have been developed which use clinical signs integrated into an artificial intelligence algorithm. The NEWS2 (National Early Warning Score 2) is suggested by the Surviving Sepsis Campaign as a more sensitive tool than qSOFA for sepsis recognition in patients with suspected infection[1,2]. Points are assigned for each clinical sign according to the following Table and the sum of points allows early assessment of clinical deterioration.

HIGH SUSPICION OF INFECTION

+

Sum of points for each system:

| **Respiration rate (/min):** | **Points** | **Temperature (°C):** | **Points** |
|---|---|---|---|
| ≤ 8 | +3 | ≤35 | +3 |
| 9-11 | +1 | 35.1-36 | +1 |
| 12-20 | 0 | 36.1-38 | 0 |
| 21-24 | +2 | 38.1-39 | +1 |
| ≥25 | +3 | ≥39.1 | +2 |
| **Systolic Arterial Pressure (mmHg)** | **Points** | **Heart rate (/min):** | **Points** |
| ≤90 | +3 | ≤40 | +3 |
| 91-100 | +2 | 41-50 | +1 |
| 101-110 | +1 | 51-90 | 0 |
| 111-219 | 0 | 91-110 | +1 |
| ≥220 | +3 | 111-130 | +2 |
| | | ≥131 | +3 |
| **Altered mental status** | +3 | **Supplementary Oxygen administration** | +2 |

↓

IF SUM ≥6 INITIATION OF TREATMENT ALGORITHM UNTIL FINAL DIAGNOSIS (see page 15)

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# BIOMARKERS FOR EARLY DETECTION OF SEPSIS
# PRESEPSIN

In patients with bacterial infection, we suggest the use of presepsin WITH clinical assessment and routine laboratory markers for the early detection of sepsis, rather than presepsin alone.

Presepsin (sCD14) is a fragment of the N-terminal part of soluble CD14, a co-receptor expressed on the surface of macrophages/monocytes. It can recognize multiple ligands, like lipopolysaccharide (LPS) of Gram-negative bacteria. A meta-analysis of 11 clinical trials showed an overall 84% sensitivity and 73% specificity for sepsis diagnosis[1]. A study enrolling 176 Greek patients with acute pancreatitis, post-operative fever or clinical suspicion of infection indicated that presepsin can improve the diagnostic output of qSOFA score. More precisely, in patients meeting at least one of the qSOFA score criteria, blood presepsin greater than 350 pg/ml had sensitivity 80.2% for early sepsis diagnosis and specificity 91.5% for prediction of 28-day mortality. Results were validated in two additional independent cohorts; the first cohort enrolled 57 patients admitted at the Emergency Department with suspicion of infection; and the second cohort enrolled 115 patients with COVID-19 pneumonia. Blood presepsin concentrations greater than 350 pg/ml provide sensitivity 85.7% and 92.3% respectively for the prediction of 28-day mortality[2].


**REFERENCES**

1. Kondo Y, et al. *J Intensive Care* 2019; 7: 22
2. Kyriazopoulou E, et al. S*ci Rep* 2023; 13: 3814

## suPAR

**Blood suPAR levels can be used for early risk assessment TOGETHER with clinical assessment:**

- **Values lower than 4 ng/ml indicate very low risk for unfavorable outcome**
- **Values equal to or greater than 6 ng/ml indicate high risk for unfavorable outcome**

suPAR is the soluble urokinase plasminogen activator receptor cleaved by the cell membrane of neutrophils. After evaluation of data coming from a study of 1914 Greek patients and other published studies, a group of experts of the Hellenic Sepsis Study Group, suggested that blood suPAR, together with clinical judjment, should be interpretated as follows[1]:

- Values lower than 4 ng/ml indicate very low risk for unfavorable outcome and may allow discharge from the Emergency Department
- Values 6 ng/ml or more indicate high risk for rapid clinical deterioration, regardless of diagnosis
- Values 12 ng/ml or more in patients with infection and at least one point of the qSOFA score are highly suggestive of sepsis
- Values 12 ng/ml or more in patients with sepsis indicate high risk of death, even if APACHE II is low.

For patients admitted with COVID-19 pneumonia, with or without need for supplementary oxygen administration, blood suPAR 6 ng/ml or more indicates high risk for progression to severe respiratory failure or death during the first 14 days[2].

**REFERENCES**

1. Velissaris D, et al. *Infect Dis Ther* 2020; 9: 407-416
2. Rovina N, et al. *Crit Care* 2020; 24: 187

## PROENKEPHALIN

### Proenkephalin A can predict progression to acute kidney injury in patients with sepsis

Proenkephalin A 119-159 (penKid) is the most stable and easily measurable product of the cleavage of preproenkephalin into opioid polypeptides containing enkephalin. Due to the low molecular weight, it is filtered through the glomerular membrane. In a retrospective study of 101 patients presenting to the Emergency Department with sepsis, blood proenkephalin A was associated with the presence and severity of acute kidney injury (AKI)[1]. A prospective study of 42 patients admitted with sepsis in the Intensive Care Unit revealed that values more than 66.97 pmol/L provided 100% sensitivity to predict progression into AKI[2]. A prospective study in two large cohorts of 2087 and 583 patients showed that high levels of proenkephalin can also detect subclinical AKI[3].


**REFERENCES**

1. Marino R, et al. *J Nephrol* 2015; 28: 717-724
2. Liu R, et al. *Crit Care* 2020; 24: 162
3. Dépret F, et al. *Am J Respir Crit Care Med* 2020; 202: 822-829

## IP-10/CRP/TRAIL

- In patients with respiratory tract infections, the combination of the biomarkers IP-10/CRP/TRAIL can distringuish between bacterial and viral infections
- Results should be interpreted TOGETHER WITH clinical assessment

A new diagnostic test evaluates the probability of bacterial or viral origin in respiratory tract infections. This test provides a simultaneous measurement of blood levels of three proteins:

- Interferon-gamma-induced protein-10 (IP-10) which is increased in viral infections.
- C-reactive protein (CRP) which is increased in bacterial infections, and
- Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), which is decreased in bacterial infections.

The values of these proteins are measured simultaneously and they are integrated into one final score ranging from 0 to 100. Score values between 0 and 35 suggest viral infection; and values between 65 and 100 suggest bacterial infection[1]. This score provides sensitivity 93.5% and specificity 94.3% to distringuish bacterial from viral infections which are greater than CRP and procalcitonin[2]. It is anticipated that the use of this diagnostic test may reduce inappropriate antibiotic prescription by 35%[3].

A study in Greek patients diagnosed with COVID-19 pneumonia showed that blood levels of IP-10 2000 pg/ml or more can predict risk of progression to severe respiratory failure and death[4].


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2. Ashkenazi-Hoffnung L, et al. *Eur J Clin Microbiol Infect Dis* 2018; 37: 1361
3. Papan C, et al. *Clin Microbiol Infect* 2022; 28: 723
4. Samaras C, et al. *Cytokine* 2023; 162: 156111

## RAPID SYNDROMIC MOLECULAR TESTING

- Allows early (<2 hours) pathogen identification in biological samples
- Provides information about detection of genes linked with antimicrobial resistance
- Should be interpretated TOGETHER WITH clinical assessment and should not replace conventional blood cultures

Syndromic testing refers to the simultaneous detection of multiple target-genes in biological samples (blood, cerebrospinal fluid, bronchial secretions, bronchoalveolar lavage, sputum) through multiplex molecular methods (multiplex PCR). Especially in the case of bloodstream infections, syndromic testing allows detection of the most common microorganisms along with genes linked with antimicrobial resistance, like *CTX-M, IMP, KPC, NDM, OXA-48, VIM, mcr-1, mecA/C* and *vanA/B*. Most available methods rely on positive blood cultures (with the exception of the T2MR system, which may apply directly on whole blood)[1]. Results are available within few hours (usually one to six hours). Diagnostic sensitivity and specificity are comparable to conventional methods[2].

Results should be interpreted according to the patient clinical state. This strategy may allow earlier initiation of appropriate treatment, even though there are no data coming from randomized clinical trials[3,4]. Especially for samples of sputum and bronchial secretion, interpretation should take into account the number of genome copies/ml of the pathogen[5].


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2. Rhoads DD, et al. *J Clin Microbiol* 2023; 61: e0189122
3. Verroken A, et al. *PLoS ONE* 2019; 14: e0223122
4. Sparks R, et al. *Pathology* 2021; 53: 889-895
5. Hanson KE, et al.*Clin Infect Dis* 2020; 71: 2744-2751

# INTERNATIONAL GUIDELINES FOR SEPSIS MANAGEMENT

Surviving Sepsis Campaign publishes guidelines every 4 years (latest edition November 2021[1-4]). According to the guidelines, sepsis management has two major pillars:

- Early and proper management of all patient conditions
- Initiation of antimicrobial treatment within **the first hour** and achievement of the main therapeutic goals within **the first 6 hours** from sepsis onset[4]. Therefore, early management of the patient is required, and should start either at the Emergency Department or in the ward, pending transfer to the Intensive Care Unit, which should be done as soon as possible.

This Booklet briefly describes the following:

- Goals of initial resuscitation
- Criteria of selection of antimicrobials
- Hellenic registry data on empirical antimicrobial treatment and the most common pathogens isolated from blood cultures and resistance profiles.
- Strategies of immunotherapy
- Relevant scientific publications of the Hellenic Sepsis Study Group.

The level of evidence of the Surviving Sepsis Campaign 2021 Guidelines is provided for each recommendation[4]. The quality of evidence is graded as described in Appendix 1.


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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
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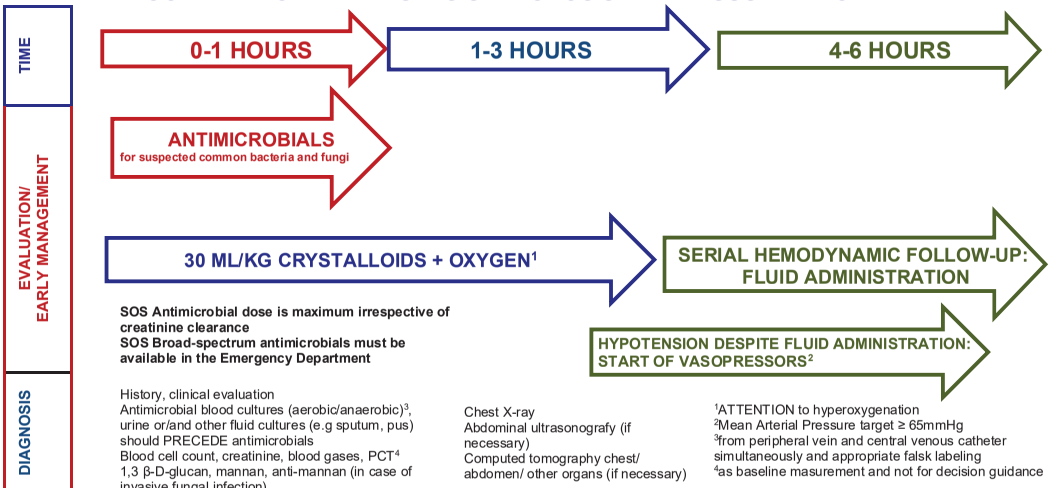
ALGORITHM FOR EARLY SEPSIS DIAGNOSIS AND RESUSCITATION
TIME
EVALUATION/ EARLY MANAGEMENT
DIAGNOSIS
0-1 HOURS
1-3 HOURS
4-6 HOURS
ANTIMICROBIALS
for suspected common bacteria and fungi
30 ML/KG CRYSTALLOIDS + OXYGEN[1]
SERIAL HEMODYNAMIC FOLLOW-UP: FLUID ADMINISTRATION
HYPOTENSION DESPITE FLUID ADMINISTRATION: START OF VASOPRESSORS[2]
SOS Antimicrobial dose is maximum irrespective of creatinine clearance
SOS Broad-spectrum antimicrobials must be available in the Emergency Department
History, clinical evaluation
Antimicrobial blood cultures (aerobic/anaerobic)[3], urine or/and other fluid cultures (e.g sputum, pus) should PRECEDE antimicrobials
Blood cell count, creatinine, blood gases, PCT[4]
1,3 β-D-glucan, mannan, anti-mannan (in case of invasive fungal infection)
Chest X-ray
Abdominal ultrasonografy (if necessary)
Computed tomography chest/ abdomen/ other organs (if necessary)
[1]ATTENTION to hyperoxygenation
[2]Mean Arterial Pressure target ≥ 65mmHg
[3]from peripheral vein and central venous catheter simultaneously and appropriate falsk labeling
[4]as baseline masurement and not for decision guidance

## GOALS OF EARLY SEPSIS RESUSCITATION[1]

- Crystalloids are the fluids of choice for early resuscitation and intravascular volume expansion in patients with sepsis and septic shock (weak recommendation, low quality of evidence)
- Use of balanced crystalloids (e.g., Ringer's Lactate, Plasmalyte) is recommended instead of 0.9% NaCl (weak recommendation, low quality of evidence)
- Albumin administration is recommended in patients having already received a large volume of crystalloids (weak recommendation, moderate quality of evidence)
- Hydroxyethyl starch (HES) administration is not recommended (strong recommendation, high quality of evidence)
- Gelatin administration is not recommended (weak recommendation, moderate quality of evidence)
- Response to fluid administration should be evaluated by dynamic heamodynamic parameters whenever possible (weak recommendation, very low quality of evidence)
- In patients with septic shock under vasopressors the target Mean Arterial Pressure is ≥65 mmHg (strong recommendation, moderate quality of evidence)
- It is recommended to repeat blood lactate measurement and/or use the time to capillary refill to guide resuscitation of tissue oxygenation (weak recommendation, low quality of evidence)

[1]Evans L, et al. *Crit Care Med* 2021; 49: e1063-e1143

## RECOMMENDATIONS ON THE TYPE OF VAPRESSORS[1]

- Noerepinephrine is the vasopressor of choice (strong recommendation, moderate quality of evidence)
- If the target of Mean Arterial Pressure is not achieved with norepinephrine administration, the addition of vasopressin is recommended (weak recommendation, low quality of evidence)
- If the target of Mean Arterial Pressure is not achieved with norepinephrine and vasopressin administration, the addition of epinephrine is recommended (weak recommendation, low quality of evidence)
- Administartion of vasopressors should be initiated from a peripheral vein until central venous catheter acess is available (weak recommendation, very low quality of evidence)
- In case of cardiac dysfunction with persistent hypoperfusion despite intravascular volume expansion and arterial pressure restoration, the addition of dobutamine to norepinephrine or the administration of epinephrine alone is recommended (weak recommendation, low quality of evidence)

[1]Evans L, et al. *Crit Care Med* 2021; 49: e1063-e1143

## PRINCIPLES OF INFECTION CONTROL[1,2]

- Search/diagnosis of the site of the infection (best clinical practice)
- Control/eradication of the infection site as soon as possible (best clinical practice)
- Minimally invasive procedures are preferred, e.g. percutaneous versus surgical drainage, where possible
- Timely removal of endovascular catheters when there is high suspicion of central catheter infections when another vascular access is ensured (best clinical practice). The tip of the catheter should be cultured.

[1]Evans L, et al. *Crit Care Med* 2021; 49: e1063-e1143

## SEPSIS AND CARDIOVASCULAR DISEASE

- Patient with sepsis and coexisting cardiovascular disease are at increased risk for unfavorable outcome
- Individualized management is required and a careful and target-directed resuscitation under close monitoring is recommended

There are no randomized studies on the administration of intravenous fluids and vasopressors in patients with sepsis and known cardiovascular disease. Most recommendations are empirical and they are based on observational studies and/or expert opinion. The following points are the basic principles of the management of these patients:

- Immediate start of resuscitation under continuous monitoring
- Assessment of cardiac function using ultrasound (the most important variables are left ventricular ejection fraction, presence of congestion, pulmonary artery pressure and the diameter of the inferior vena cava)
- Careful fluid administration is recommended, up to 2-3 liters/24 hours when cardiac dysfunction is present (left ventricular ejection fraction < 50%), with or without pulmonary congestion.
- Fluid resuscitation is a dynamic process and it should be guided by clinical, laboratory and sonographic reassessment and modified accordingly. In selected cases, pulmonary artery catheterization is also recommended.
- Laboratory assessment using biomarkers. Measurement of high-sensitivity troponin and natriuretic peptides is recommended for risk stratification and exclusion of acute coronary syndrome. A differential diagnosis should be done between type 1 and type 2 myocardial infarction. Type 2 infarction is induced by increased metabolic demands and the inflammatory process, without coronary occlusion.
- Norepinephrine is the first-line vasopressor. In refractory cases, the addition of vasopressin is recommended.

- Vasopressor support with dobutamine in combination with norepinephrine is recommended for coexisting cardiac dysfunction[1,2].
- In coexisting tachyarrhythmia with cardiac dysfunction and/or hypotension, administration of the selective β-blocker landiolol is recommended to control the heart rate, since this has a neutral hemodynamic effect. The administration of amiodarone is also recommended. In cases without hemodynamic instability and/or cardiac dysfunction, diltiazem or esmolol can be administered as an alternative. In these patients, the initiation of anticoagulation therapy is indicated[2,3].
- All patients with sepsis and cardiovascular disease should receive prophylactic antithrombotic therapy with low molecular weight heparin or fondaparinux[4].


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3. Bezati S, et al. *Eur Heart J* 2022; 24 Suppl D: D22-D33
4. Evans L, et al. *Crit Care Med* 2021; 49: e1063-e1143

**Antimicrobials should start within the FIRST HOUR from the onset of sepsis or septic shock (strong recommendation, low quality of evidence)[1]**

**In patients with possible sepsis without shock, rapid search for the site of infection and initiation of antimicrobials within the first 3 hours is recommended (weak recommendation, very low quality of evidence)**

In a retrospective analysis of the clinical data of 2731 patients with septic shock, final survival was associated with the time interval between the presence of hypotension and the start of appropriate antimicrobial therapy. Final survival was 79.9% for patients who started the appropriate antimicrobial therapy within the first hour. The probability of survival decreased by 7.6% for every hour of delay of start of antimicrobials[2].

ATTENTION

- The early empiric administration of antimicrobials is required within the first hour of admission to the Emergency Department. This is done after culture samplings. The cultures sampled are blood from a peripheral vein and from a central catheter (if applicable), urine and other biological fluids depending on the type of infection (sputum, bronchial secretions, pus, etc.)
- Antimicrobials which are administered bolus should start before those which are administered as slow intravenous infusion.

**REFERENCES**
1. Evans L, et al. *Crit Care Med* 2021; 49: e1063-e1143
2. Kumar A, et al. *Crit Care Med* 2006; 34: 1589-1596

**ADMINISTERED ANTIMICROBIALS SHOULD[1]:**

- Be active against all possible pathogens (strong recommendation, moderate quality of evidence)
- Achieve the optimal pharmacodynamic effect, e.g. continuous infusion or shorter infusion intervals for β-lactams
- Be administered initially at the maximum dose regardless of the renal function and then be modified according to the renal function (see Appendix 2)
- Be active against methicillin-resistant *Staphylococcus aureus* (MRSA) if the patient is at high risk for MRSA infection (best clinial practice)
- Be modified according to the results of the microbiology cultures (best clinial practice)

**It is necessary** to know the common pathogens of the department where the patient is admitted, as well as their resistance profiles[1]

Evans L, et al. *Crit Care Med* 2021; 49: e1063-e1143

## DE-ESCLATION/MODIFICATION OF ANTIMICROBIAL TRATMENT

Patients should be assessed daily for de-escalation/modification of antimicrobial therapy (best clinical practice)[1]. This strategy includes:

- The replacement of the administered antimicrobial by another with a more narrow antimicrobial spectrum, provided it is active against the isolated pathogen
- Discontinuation of empirically prescribed anti-staphylococcal or antifungal antibiotics as long as the suscpected pathogens are not isolated
- The de-escalation strategy should be applied to both non-ICU and ICU patients with sepsis
- It has been shown in Greek patients that de-escalation did not adversely affect outcome[2,3].

[1]Evans L, et al. *Crit Care Med* 2021; 49: e1063-e1143
[2]Koupetori M, et al. *BMC Infect Dis* 2014 ; 14: 272
[3]Routsi C, et al. *J Antimicrob Chemother* 2020; 75: 3665-3674

**PREDISPOSING FACTORS FOR INFECTIONS BY MULTIDRUG RESISTANT PATHOGENS:**

- Administration of broad-spectrum antimicrobials[1] the last three months
- Hospitalization for ≥2 days the last three months
- Current hospitalization ≥5 days
- Staying in a nursing home or long-term health care facility
- Contact with health care facility[2]
- Stage IV chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis
- Regular hemodialysis (patients started for at least a month)
- Immunosupression[3]

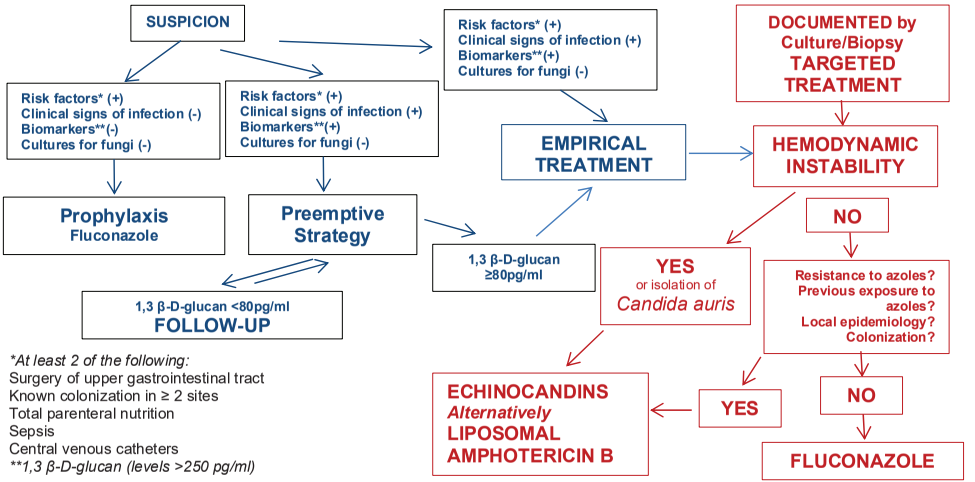
**PREDISPOSING FACTORS FOR INFECTIONS BY METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA)[1]:**

- Recent infection or colonization by MRSA
- Recurrent skin infections or chronic ulcers
- Presence of endovascular catheters
- Regular hemodialysis

[1] 3rd or 4th generation cephalosporins, aztreonam, quinolones, piperacillin/tazobactam, carbapenems
[2] eg intravenous Outpatient antibiotic therapy (OPAT)
[3] hematologic malignancies, solid tumors, neutropenia, neoplams under chemotherapy/irradiation, transplantation, corticosteroid intake (>10 mg of prednisone equivalent/day x 21 days or >700 mg in total), intake of immunosuppressive drugs

# ALGORITHM FOR FUNGAL INFECTION MANAGEMENT IN THE ICU

(Modified from Dimopoulos G, et al. *J Crit Care* 2013; 28: 717-727 and Bailly S et al. *Intensive Care Med* 2015; 41:1931)




*At least 2 of the following:*
Surgery of upper gastrointestinal tract
Known colonization in ≥ 2 sites
Total parenteral nutrition
Sepsis
Central venous catheters
***1,3 β-D-glucan (levels >250 pg/ml)*

## ANALYSIS OF THE HELLENIC REGISTRY OF PATIENTS WITH SEPSIS

In the analysis, patients are divided into those who developed an episode of sepsis outside the Intensive Care Unit (ICU) and into those who developed the first episode of sepsis after admission to the ICU. Patients registered before February 2016 were reclassified according to the new Sepsis-3 definitions. Starting March 2016 onwards, the new Sepsis-3 definitions are used. The analysis is divided into two parts. The first part lists the most frequent pathogens and their rate of antimicrobial resistance for the time periods 2014-2017 and 2018-2023. The second part describes the antimicrobial combinations which are statistically associated with optimal survival after Cox multivariate analysis. The analysis was done considering the following variables:

- the comorbidities as expressed by the Charlson index
- the presence of risk factors for infection by multidrug resistant pathogens
- the total number of patients registered since 2006, and
- the most commonly prescribed combinations of antimicrobials

The analysis does not have the design of a randomized trial, and the results should be interpreted with caution considering that antimicrobials were chosen by the attending physicians based on the site of infection and the patient's history. For patients with non-ICU sepsis and a total SOFA score of less than 8 the most frequently prescribed antibiotics were:

- β-lactams/β-lactamase inhibitors
- 3rd generation cephalosporins/ceftaroline
- Macrolides

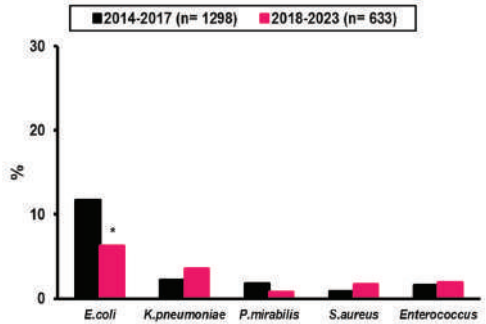
For patients with non-ICU sepsis and total SOFA score 8 or more the most frequently prescribed antibiotics were:

- Piperacillin/tazobactam
- Carbapenems
- Colistin
- Glycopeptides/linezolid

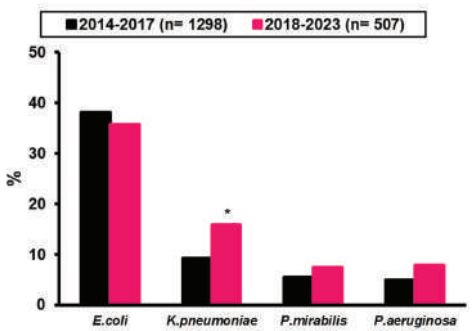
For patients with sepsis presenting after ICU admission and total SOFA score 8 or more the most frequently prescribed combinations of antibiotics were:

- Carbapenems + tigecycline + colistin
- Carbapenems + colistin + glycopeptides/linezolid
- Carbapenems + tigecycline + colistin + glycopeptides/linezolid

## PATHOGENS (%) FROM BLOOD CULTURES OF NON-ICU SEPSIS PATIENTS

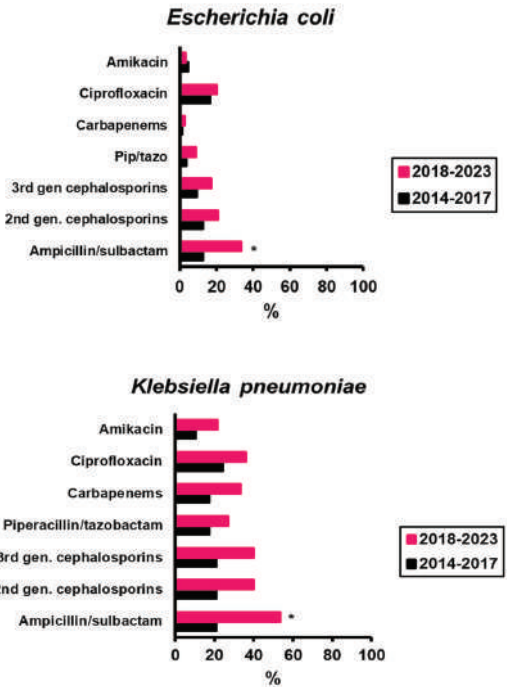



## PATHOGENS (%) FROM URINE CULTURES OF NON-ICU SEPSIS PATIENTS



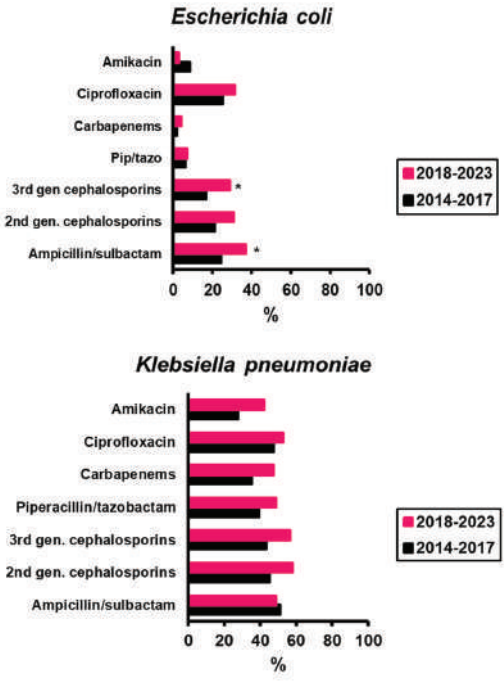

*Statistically significant difference between the two time periods

## RESISTANCE (%) OF COMMON PATHOGENS FROM BLOOD CULTURES OF NON-ICU SEPSIS PATIENTS



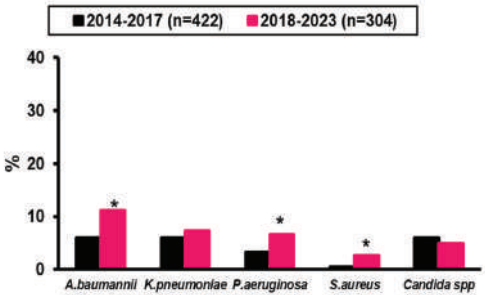

*Statistically significant difference between the two time periods

## RESISTANCE (%) OF COMMON PATHOGENS FROM URINE CULTURES OF NON-ICU SEPSIS PATIENTS



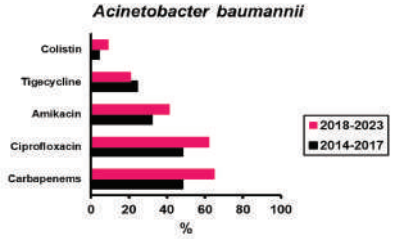

*Statistically significant difference between the two time periods

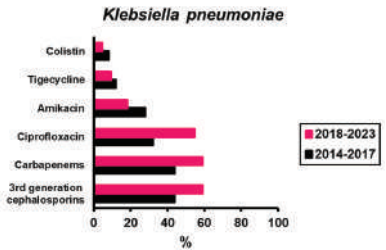
## PATHOGENS (%) FROM BLOOD CULTURES OF ICU SEPSIS PATIENTS

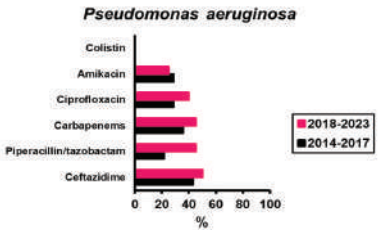



*Statistically significant difference between the two time periods

## RESISTANCE (%) OF COMMON PATHOGENS FROM BLOOD CULTURES OF ICU PATIENTS




No statistically significant differences were recorded between the two time periods

# SUGGESTIONS FOR EMPIRICAL ANTIMICROBIALAS FR SEPSIS OUTSIDE THE ICU IN PATIENTS WITH SOFA SCORE ≤7

## EXPERT OPINION

- In the absence of risk factors for infection by multidrug-resistant pathogens = 3rd generation cephalosporin. We suggest adding a macrolide for community-acquired pneumonia and metronidazole for anaerobic infections[1, 2].
- In the absence of risk factors for infection by multidrug-resistant pathogens (and prior exposure to 3rd generation cephalosporin) = Piperacillin/ tazobactam. We suggest adding a macrolide for community-acquired pneumonia[1,2].
- In the presence of risk factors for infection by extended spectrum β- lactamase (ESBL)-producing Gram (-) pathogens = carbapenem or ceftolozane/tazobactam[2]
- In the presence of risk factors for infection by carbapenem-resistant Gram (-) pathogens = newer β- lactam/ carbapenemase inhibitors combination + colistin[2]

## BASIC PRINCIPLES OF MANAGEMENT

- We recommend the daily clinical assessment and de-escalation of antimicrobial treatment based on culture results, since it is demonstrated that this strategy is not asssociated with worse outcomes.
- 3rd generation cephalosporins and meropenem are preferably administered as a 3-hour infusion and piperacillin/tazobactam as a 4-hour infusion.
- The choice of the newer β- lactam/ carbapenemase inhibitor combination is driven by antimicrobial susceptibility testing.

- Metronidazole should be added if β- lactam/ carbapenemase inhibitors are prescribed for intra-abdominal infections.

**RISK FACTORS FOR INFECTION BY EXTENDED SPECTRUM B- LACTAMASE (ESBL)-PRODUCING Gram (-) PATHOGENS[3]:**

- Hospital stay ≥48 hours the last 90 days
- Broad spectrum antimicrobial administration the last 90 days
- Regular renal replacement therapy
- Residency in long term care facilities
- Recurrent urinary tract infection
- Presence of inravascular catheters or urinary catheters
- Known colonization by ESBL-producing pathogens

**RISK FACTORS FOR INFECTION BY CARBAPENEM-RESISTANT Gram (-) PATHOGENS (CRE)[4]:**

- History of recent infection by carbapenem-resistant pathogens
- Known colonization by carbapenem-resistant pathogens
- Prolonged or recent admission in the Intensive Care Unit
- Severe immunosupression

[1]this recomendation is based on survival data analysis. This analysis was not performed separately per site of infection. Suggested combinations are not recommendations of empirical treatment for all patients.
[2]accoring to the expert opinion of the panel
[3]epidemiological data available from Koupetori M, et al. *BMC Infect Dis* 2014 ; 14: 272
[4]Galera SP, et al. *EClinicalMedicine* 2023; 57:101871

## SUGGESTIONS FOR EMPIRICAL ANTIMICROBIALS FOR SEPSIS OUTSIDE THE ICU IN PATIENTS WITH SOFA SCORE ≥8

### EXPERT OPINION

- In the absence of risk factors for infection by multidrug-resistant pathogens = piperacillin/ tazobactam. We suggest adding a macrolide for community-acquired pneumonia[1, 2].
- In the presence of risk factors for infection by extended spectrum β- lactamase (ESBL)-producing Gram (-) pathogens= carbapenem or ceftolozane/tazobactam +/- colistin + glycopeptides/linezolid[1, 2]
- In the presence of risk factors for infection by carbapenem-resistant Gram (-) pathogens (CRE)= newer β- lactam/ carbapenemase inhibitors combination (+ metronidazole in case of intra-abdominal infection) + colistin + glycopeptides/linezolid[2]

### BASIC PRINCIPLES OF MANAGEMENT

- We recommend the daily clinical assessment and de-escalation of antimicrobial treatment based on available cultures, since it is demonstrated that this strategy is not asssociated with worse outcomes.
- Meropenem is preferably administered as a 3-hour infusion
- The choice of the newer β- lactam/ carbapenemase inhibitor combination is driven by antimicrobial susceptibility testing.
- We suggest adding glycopeptides for patients at high risk of infection by Gram-positive cocci (e.g. presence of intravascular catheters, neurosurgical patients, immunosuppression, presence of intra-vascular, orthopedic or any other implant)

**RISK FACTORS FOR INFECTION BY EXTENDED SPECTRUM B- LACTAMASE (ESBL)-PRODUCING Gram (-) PATHOGENS[3]:**

- Hospital stay ≥48 hours the last 90 days
- Broad spectrum antimicrobial administration the last 90 days
- Regular renal replacement therapy
- Residency in long term care facilities
- Recurrent urinary tract infection
- Presence of inravascular catheters or urinary catheters
- Known colonization by ESBL-producing pathogens

**RISK FACTORS FOR INFECTION BY CARBAPENEM-RESISTANT Gram (-) PATHOGENS (CRE)[4]:**

- History of recent infection by carbapenem-resistant pathogens
- Known colonization by carbapenem-resistant pathogens
- Prolonged or recent admission in the Intensive Care Unit
- Severe immunosupression

[1]this recomendation is based on survival data analysis. This analysis was not performed separately by site of infection. Suggested combinations are not recommendations of empirical treatment for all patients.

[2]accoring to the expert opinion of the panel

[3]epidemiological data available from Koupetori M, et al. *BMC Infect Dis* 2014; 14: 272

[4]Galera SP, et al. *EClinicalMedicine* 2023; 57:101871

## PATIENTS WITH SEPSIS IN THE ICU

### EPIDEMIOLOGY DATA

- The final outcome is mainly driven by the presence of comorbidities and infection by multidrug-resistant pathogens[1]
- Empirical antimicrobial treatment should be guided by local epidemiology and healthcare facility[2].
- Monotherapy with carbapenems should be avoided[1, 2].
- We suggest adding glycopeptides in case of possible infection due to Gram (+) cocci, as well as in the presence of central venous catheter and/or septic shock[2].
- In the most severe patients with septic shock or total SOFA score ≥ 8 we suggest combination treatment for broad Gram (-) coverage and additional administration of glycopeptides[1,2].
- In the presence of risk factors for infection due to carbapenem-resistant Gram (-) pathogens (CRE) we suggest newer β- lactam/ carbapenemase inhibitors combination[2]
- In documented infection by carbapenem-resistant enterobacterales (CRE)= selection of newer β- lactam/ carbapenemase inhibitor combination, based on antimicrobial susceptibility testing[2]

[1]this recomendation is based on survival data analysis. This analysis was not performed separately by site of infection. Suggested combinations are not recommendations of empirical treatment for all patients.

[2]accoring to the expert opinion of the panel

## PROCALCITONIN AND ANTIMICROBIAL TREATMENT MONITORING

In patients with sepsis or septic shock and adequate source control, we suggest using procalcitonin TO SUPPORT clinical evaluation and decide when to discontinue antimicrobial treatment (weak recommendation, low quality of evidence)[1]

In a randomized controlled interventional trial, antibiotics were discontinued according to usual practice for 785 critically ill patients; this was compared to procalcitonin - guided discontinuation of antibiotics in 761 patients. Results demonstrated a significant decrease of both 28-day mortality (20% vs 25% in usual care group) and 1-year mortality (36% vs 43% in usual care group)[2]. Results were further supported by the Hellenic multi-center PROGRESS study in 256 patients with sepsis. The study showed significant decrease of 28-day mortality (15.2% vs 28.2% in usual care group). Survival benefit was mainly associated with reduction in the incidence of adverse events due to long-term antimicrobial treatment and of secondary infections by multidrug-resistant pathogens and *Clostridioides difficile*[3].

*We suggest antimicrobial treatment discontinuation after favorable clinical response AND decrease of serum PCT by ≥ 80% of the baseline value OR when blood PCT is lower than 0.5 ng/ml.*

**REFERENCES**
1. Evans L, et al. *Crit Care Med* 2021; 49: e1063-e1143
2. De Jong E, et al. *Lancet Infect Dis* 2016 ; 16: 819-827
3. Kyriazopoulou E, et al. *Am J Respir Crit Care Med* 2021 ; 203: 202-210

# NEWER ANTIMICROBIALS

## TEDIZOLID PHOSPHATE

- Active against *Enterococcus spp*, *Streptococcus spp*, methicillin-resistant *Staphylococcus aureus* (MRSA) with minimum inhibitory concentration (MIC) of vancomycin ≥1µg/ml and/or non-susceptibility to daptomycin
- **Indication**: acute bacterial skin and skin structure infections (ABSSSI)
- Clinical response 78-85% within the first 72 hours[1,2]
- Lower incidence of low platelet count (4.9% vs 10.8%) and gastrointestinal side effects (10.3% vs 15.4%) compared to linezolid[3]


1. Promocimer P, et al. *JAMA* 2013; 309: 559-569
2. Moran GJ, et al. *Lancet Infect Dis* 2014 ; 14: 696-705
3. Shorr AF, et al. *Antimicrob Agents Chemother* 2015; 59: 864-871


## DALBAVANCIN

- Active against *Streptococcus spp*, methicillin-resistant *Staphylococcus aureus* (MRSA) with MIC of vancomycin ≥1µg/ml and/or non-susceptibility to daptomycin
- **Indication**: acute bacterial skin and skin structure infections (ABSSSI) with likelihood for early hospital discharge
- Clinical response 79.7% within the first 72 hours and 94.9% in patients with systemic inflammatory response syndrome and possible concomittant decrease of length of hospital stay[1,2]


1. Boucher HW, et al. *N Engl J Med* 2014, 370: 2169-2179
2. Dunne MW, et al. *Clin Infect Dis* 2016, 62: 545-551

## CEFTAROLINE

- Active against Gram (+) cocci (including methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae*) and Gram (-) enterobacterales non-producing extended spectrum lactamase (ESBL)[1,2]
- **Indications**: ABSSSI, community-acquired pneumonia and secondary bacteremia due to the above-mentionned pathogens.
- Clinical response 82.1% vs 77.2% of ceftriaxone in patients with community-acquired pneumonia[3]


1. Saravolatz LD, et al. *Clin Infect Dis* 2011 ; 52: 1156-1163
2. Leventogiannis K, et al. *Curr Opin Infect Dis* 2023; 36: 89-94
3. Low D, et al. J. Antim Chemother 2011; 66 suppl 3 33-4


## CEFTOLOZANE/ TAZOBACTAM

- Active against Gram (-) enterobacterales (including ESBL-producing), *Pseudomonas aeruginosa* and *Haemophilus influenzae* producing β-lactamase[1]
- No activity against AmpC-, OXA-, carbapenemase- and metallo-β-lactamase-producing strains[1]
- **Indications**: complicated urinary tract infections including acute pyelonephritis, complicated intra-abdominal infections, and hospital-acquired pneumonia including ventilator-associated pneumonia
- Non-inferiority versus the clinical response of patients with hospital-acquired pneumonia treated with meropenem (54% vs 53%)[2]


1. Zhanel G., et al. *Drugs* 2014;, 74: 31-51
2. Kollef MH, et al. *Lancet Infect Dis* 2019 ; 19:1299-1311

## CEFTAZIDIME/AVIBACTAM

- Active against Gram (-) enterobacterales producing extended-spectrum β- lactamase (ESBL), KPC and OXA-48 carbapenemase and carbapanem-susceptible *Pseudomonas aeruginosa*[1,2]
- Lack of activity against strains producing metallo-β-lactamase[3]
- **Indications**: complicated urinary tract infections including acute pyelonephritis, complicated intra-abdominal infections in combination with metronidazole, and hospital-aquired pneumonia including ventilator-associated pneumonia
- Significant decrease of mortality in patients with bacteremia by *Klebsiella pneumoniae* producing KPC (36.5% versus 55.8% of best available treatment)[4]


1. Sharma R, et al. *Clin Ther* 2016; 38: 431-444
2. Zasowski EJ, et al. *Pharmacotherapy* 2015; 35: 755-770
3. Paul M, et al. *Clin Infect Dis* 2022 ; 28: 521-547
4. Tumbarello M A, et al. *Clin Infect Dis* 2019 ; 68: 355-364


## MEROPENEM/VABORBACTAM

- Active against Gram (-) enterobacterales producing extended-spectrum β- lactamase (ESBL) and KPC carbapenemase and carbapenem-susceptible *Pseudomonas aeruginosa*.
- Lack of activity against strains producing OXA β-lactamase or metallo-β- lactamase[1]
- **Indications**: complicated urinary tract infections including acute pyelonephritis, complicated intra-abdominal infections, and hospital-aquired pneumonia including ventilator-associated pneumonia
- Cinical superiority as monotherapy for documented infections by KPC-producing enterobacterales with concomitant decrease of mortality and nephrotoxicity (18.8% versus 60% with best available treatment)[2]


1. Mouktaroudi M, et al. *Expert Rev Anti-infect Ther* 2022; 20: 809-818
2. Wunderink R, et al. *Infect Dis Ther* 2018, 7: 439-455

## IMIPENEM/CILASTATIN/RELEBACTAM

- Highly active against Gram (-) strains producing extended-spectrum β-lactamases (ESBL), AmpC β-lactamase- and KPC carbapenemase- producing enterobacterales and against *Pseudomonas aeruginosa* [1]
- Lack of activity against enterobacterales producing OXA- or metallo- β- lactamase[1]
- **Indications**: hospital-aquired and ventilator-associated pneumonia, bacteremia secondary to hospital-aquired pneumonia, and anaerobic infections with limited other available therapeutic choices
- Clinical response in 71% of infections by pathogens resistant to imipenem[2]
- Mortality 15.9% verus 21.3% compared to piperacillin/tazobactam treatment in hospital-aquired pneumonia[3]
- Clinical benefit against infections by resistant *Pseudomonas aeruginosa* is reported in small-scale case-series[4]


1. Karlowsky J, et al. *J Antim Chemother* 2018; 73: 1872-1879
2. Mothsch J, et al. *Clin infect Dis* 2020 ; 70: 1799-1808
3. Titov I, et al. *Clin Infect Dis* 2021; 73: e4539-e4548
4. Rebold N, et al. *Open Forum Infect Dis* 2021; 8: ofab554

## INTRAVENOUS ITRACONAZOLE[1]

One study assessed the in vitro activity of itraconazole against *Candida* spp strains isolated from Greek patients participating in the Hellenic Registry. Results showed:

- Similar activity to other azoles and echinocandins against *C. albicans* strains
- Higher activity than the other azoles and echinocandins against *C. parapsilosis* strains

Empirical intravenous itraconazole decreased the risk of secondary candidemia by *C.parapsilosis* compared to intravenous echinocandins. Benefit is observed in patients not responding after 7 days of empirical antifungal treatment and having at leat two of the following risk factors:

- Abdominal surgery
- Acute pancreatitis
- Colonization of skin, oropharynx, rectum or bronchial secretions
- Administration of total parenteral nutrition
- Type 2 diabetes mellitus
- Regular hemodialysis
- Solid tumor or lymphoma

[1]Giamarellos-Bourboulis EJ, et al. *Int J Antimicrob Agents* 2019; 54: 471-477

## ANTIMICROBIAL STEWARDSHIP AND DIAGNOSTIC TESTS

**Surveillance signifies the ordering of appropriate diagnostic tests in order to avoid overconsumption of antimicrobials**

As part of the antimicrobial stewardship policy, diagnostic test surveillance policy must also be implemented. Ordering of appropriate diagnostic tests is crucial (e.g. cultures of blood, bronchial secretions and urine, diagnostic tests for *Clostridioides difficile* and other special tests, PCR) in order to avoid overtesting which leads to incorrect diagnosis e.g. of colonization as infection (diagnostic error) and consequently to the administration of unnecessary antibiotics. A typical example is to avoid ordering of diagnostic tests for *C. difficile* in a patient with diarrhea under laxatives. The appropriate-rationale choice of tests (diagnostic stewardship, best pretest probability of disease) corrects the diagnostic error (sepsis, urinary tract infections, *C. difficile* infections) which leads to overconsumption of unnecessary antimicrobials and delays appropriate treatment (disorientation of diagnosis)[1,2].

**REFERENCES**
1. Morgan DJ, et al. *JAMA* 2017; 318: 607-608
2. Fabre V, et al. *Infect Control Hosp Epidemiol* 2023; 44: 178-185

# GUIDELINES ON IMMUNOTHERAPY

**Immunotherapy aims to restore the dysregulated host immune response to an infection**

Despite advances in antimicrobial therapy, the mortality of patients with sepsis remains high. Immunotherapy aims to restore the imbalance of the immune response, to promote efficient phagocytosis and to limit organ dysfunction. In the current Booklet, the following strategies of immunotherapy are discussed:

- Hydrocortisone administration
- Blood glucose control
- Nutrition
- Probiotics
- Macrolides/Intravenous clarithromycin
- Immunoglobulins
- Anakinra
- Tocilizumab
- Precision immunotherapy

For every strategy, the respective grade of recommendation is given according to the Surviving Sepsis Campaign 2021 Guidelines (Appendix 1). Recommendations of other scientific societies are also provided, if applicable. Focusing on data reported in Greek studies is also done.

## CORTICOSTEROIDS

In patients with septic shock under vasopressors, intravenous administration of hydrocortisone is recommended (weak recommendation, moderate quality of evidence)[1]

In the APROCHSS clinical trial which was conducted in France, patients with septic shock were randomized to receive either a combination of intravenous hydrocortisone and oral fludrocortisone or placebo as adjunctive to standard-of-care treatment. 90-day all-cause mortality was significantly decreased in the intervention arm compared to placebo (43% vs 49.1%). Patients receiving combination treatment experrienced also faster weaning from vasopressors and mechanical ventilation[2]. However, in the ADRENAL randomised controlled trial conducted in Australia and New Zealand results were controversial. In the ADRENAL study, fludrocortisone was not administered, but patients allocated to intervention were discharged earlier from the ICU[3]. A retrospective analysis from the Hellenic Sepsis Study Group in 170 patients showed that administration of hydrocortisone within the first 9 hours from start of vasopressors was associated with lower mortality. Hydrocortisone was also found to possess and anti-inflammatory effect on peripheral blood mononuclear cells[4]. In a recent clinical study of hospitalized patients in an ICU due to severe community-acquired pneumonia, hydrocortisone administration was associated with lower all-cause mortality compared to placebo (6.2% vs 11.9)[5].
*The dose of hydrocortisone is either 200mg per day over a 24hour-continuous intravenous infusion or 50mg every 6 hours. Treatment should be initiated at least 4 hours after the start of vasopressors and lasts for 7 days.*


**REFERENCES**
1. Evans L, et al. *Crit Care Med* 2021; 49: e1063-e1143
2. Annane D, et al. *N Engl J Med* 2018; 378: 809-819
3. Venkatesh B, et al. *N Engl J Med* 2018; 378: 797-808
4. Katsenos C, et al. *Crit Care Med* 2014; 42: 1651-1657
5. Dequin PF, et al. *N Engl J Med* 2023; 25: 388: 1931-1941

# BLOOD GLUCOSE CONTROL

In sepsis:

- Per-patient monitoring of blood glucose levels with insulin administration is recommended when blood glucose levels are > 180mg/dl on two serial measurements.
- Blood glucose target levels are between 144-180 mg/dl (strong recommendation, moderate quality of evidence[1])

Both hyperglycemia and the wide diaily variations of blood glucose levels are risk factors for mortality in the critically ill patients. The main risk when trying to maintain normoglycemia with insulin administration is hypoglycemia. In the multicenter, randomized clinical trial, NICE-SUGAR (n=6104), tight glucose control at the range of 80-110mg/dl was associated with severe episodes of hypoglycemia in 6-29% of patients and increased mortality[2]. In a meta-analysis of 35 randomized clinical trials, it was also found that blood glucose levels ≤ 144 mg/dl achieved by insulin administration were associated with higher mortality[3].


**REFERENCES**

1. Evans L, et al. *Crit Care Med* 2021; 49: e1063-e1143
2. Finfer S, et al. *N Engl J Med* 2012; 367: 1108-1118
3. Yatabe T, et al. *Intensive Care Med* 2017; 43: 16-28

## NUTRITION

- Whenever possible, enteral feeding is recommended in patients with sepsis/septic shock (weak recommendation, very low quality of evidence[1])
- Administration of vitamin C is not recommended (weak recommendation, low quality of evidence[1])

The early start of enteral feeding is associated with maintenance of the integrity of enteric mucosa, decrease of inflammation and decrease of insulin resistance. In a recent, multicenter, randomized clinical trial conducted in 44 ICUs in France, 2410 patients (62% with sepsis) under mechanical ventilation were randomized to receive either early (within the first 72hrs) enteral or parenteral nutrition. No difference of survival was found[2].

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## PROBIOTICS

- Meta-analyses of randomized controlled trials showed benefit from the administration of probiotics for the prevention of ventilator-associated pneumonia (VAP).
- There is no clear recommendation for the administration of probiotics.

Ventilator-associated pneumonia (VAP) is the result of the interaction between immune system and lung microbiota[1]. Many randomized controlled clinical trias have evaluated the role of probiotics for the prevention of VAP in patients under mechanical ventilation. The two largest meta-analyses of 23 and 31 clinical trials with 5574 and 8339 patients respectively, reported a relative risk reduction in VAP incidence by 33%[2] and 25%[3] respectively. Meta-analyses are subject to statistical error due to high heterogeneity in the administered probiotic preparations regarding the type and number of microorganisms. The double-blind, randomized, controlled trial, pro-VAP in Greek patients showed that a 15-day treatment with *Saccharomyces boulardii*, *Bifidobacterium lactis* BB-12, *Lactobacillus acidophilus* LA-5 και *Lactobacillus plantarum* was associated with risk reduction in VAP development from 28.3% to 11.9%. Enrolled patients were multi-injured, under mechanical ventilation, without active infection and had at least one organ dysfunction along with head injury[4]. In a randomized clinical trial of 2653 patients, there was no benefit from *Lactobacillus rhamnosus* GG administration for the prevention of VAP. However, the vast majority of these patients, had already one severe infection at enrollment[5].


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# MACROLIDES AND INTRAVENOUS CLARITHROMYCIN

- Co-administration of a macrolide with β-lactams in severe community-acquired pneumonia (CAP) regardless of the causative microorganism is associated with significant reduction of the risk for death[1].
- Intravenous clarithromycin reduces mortality in patients with ventilator-associated pneumonia and attenuates the risk of sepsis relapse[1,2].

In a recent analysis from 1174 Greek patients with sepsis due to CAP, it was found that co-administration of clarithromycin with β-lactams was associated with a two-fold reduction in mortality compared to all the other available treatment regimens (β-lactam monotherapy, respiratory fluoroquinolones, or combination treatment of β-lactams plus azithromycin)[3]. *Post-hoc* analysis of a randomized clinical trial in patients with VAP showed a significant risk reduction of 90-day mortality following intravenous administration of adjunctive clarithromycin[1]. In the randomized controlled clinical trial INCLASS, adjunctive intravenous clarithromycin was administered in 110 patients with multi-organ failure secondary to Gram negative infections. Although no difference in all-cause mortality was shown, treatment with intravenous clarithromycin was associated with significant risk reduction of the incidence of new sepsis episodes (30.4% versus 67.9% of patients treated with placebo)[2]. The updated European guidelines for severe CAP recommend the co-administration of macrolides with β-lactams over monotherapy with either β-lactam or respiratory fluoroquinolone[4].

*The dose of intravenous clarithromycin is 1gr per day over a 1-hour continuous intravenous infusion for 4 consecutive days.*


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## INTRAVENOUS IMMUNOGLOBULINS

- In patients with sepsis/septic shock, administration of intravenous immunoglobulins is not recommended (weak recommendation, low quality of evidence)[1].
- A retrospective analysis showed that administration of intravenous immunoglobulins enriched with IgM was associated with significant risk reduction of all-cause mortality in patients with septic shock and infections by multidrug-resistant Gram-negative bacteria[2].

Available preparations of immunoglobulins for intravenous administration are divided into those which contain only IgG immunoglobulins and those which are enriched with IgM immunoglobulins (IgGAM). A large trial with 624 patients failed to show any benefit from IgG administration. Meta-analyses of available clinical trials reported a mortality risk reduction from administration of IgGAM preparations, but the recommendation based on these trials is considered moderate[1].

The Hellenic Sepsis Study Group analyzed 100 patients with infections, of which 86% with septic shock due to infections by multidrug-resistant Gram-negative bacteria. These patients were treated with adjunctive IgGAM and they were compared with 100 patients who did not receive adjunctive treatment. The two study groups were totally comparable regarding sepsis severity, causative pathogens, administered antibiotics and comorbidities. 28-day mortality was significantly lower among patients treated with IgGAM than the comparators (39% vs 58%)[2].

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## ANAKINRA

Anakinra is licenced by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for the treatment of patients with COVID-19 pneumonia who need supplementary oxygen and have blood suPAR levels 6ng/ml or more[1,2].

Anakinra is the recombinant preparation of the interleukin (IL)-1 receptor antagonist. In patients with severe COVID-19 pneumonia, blood levels of the biomarker suPAR (soluble urokinase plasminogen activator receptor) ≥ 6ng/ml indicate an increased risk for severe respiratory failure. The results from phase II SAVE and phase III SAVE-MORE clinical trials with 1000 and 594 patients respectively, showed overall 64% risk reduction for unfavorable outcome after 28 days (odds ratio 0.36 with confidence intervals 0.26-0.50) with similar benefit on risk reduction for death, development of severe respiratory failure and mechanical ventilation as well towards infection cure[3,4]. The efficacy remains the same regardless of the time interval between onset of symptoms and start of treatment[5]. The FDA has also set a score of eight 8 clinical variables and laboratory findings for the early detection of patients who should be treated[2]. No severe adverse events were reported from anakinra treatment.

*Anakinra is administered subcutaneously at a dose of 100mg per day for 7-10 days.*


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## TOCILIZUMAB

- In patients with COVID-19-associated sepsis, the combination of tocilizumab with corticosteroids is recommended (moderate recommendation, moderate quality of evidence)[1].
- In patients with sepsis or septic shock due to any other infection rather than COVID-19 disease, there are no sufficient data to support tocilizumab administration.

Tocilizumab is the recombinant antagonist of interleukin (IL)-6 receptor. In a meta-analysis with 10,930 hospitalized patients with severe COVID-19 pneumonia, it was found that the combination of tocilizumab with corticosteroids was associated with reduced 28-day mortality (odds ratio 0.77, 95% confidence intervals 0.68-0.87). The most of benefit was observed for patients with C-reactive protein (CRP) 75mg/l or more. In the same meta-analysis it is reported that the number of available patients was not large enough to draw safe conclusions for groups under mechanical ventilation or need for vasopressors[2]. In a multicenter clinical trial of 537 patients, there was no association between tocilizumab administration and secondary infections or bacteremias[3].

*The suggested dose is 8mg/kg once, over one-hour intravenous infusion at a maximum dose of 800mg. If there is no clinical improvement after 24hours, the administration should be repeated.*

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## PRECISION IMMUNOTHERAPY

Aims to classify patients into different endotypes based on pathophysiologic patterns and to administer precision treatment per endotype to achieve immunological homeostasis.

The phase IIa PROVIDE clinical trial, which took place in Greek Intensive Care Units (ICUs) succeeded to distinguish two main immunological endotypes of sepsis. The first endotype is the macrophage activation-like syndrome (MALS) and the second endotype is sepsis-induced immunoparalysis (SII). MALS is found approximately in 5-10% of patients and is diagnosed when blood ferritin levels are greater than 4420 ng/ml. SII is found in 40% of patients and it is diagnosed when the number of HLA-DR receptors on the cellular membrane of peripheral monocytes are less than 5000 per cell[1]. The first ever, worldwide, randomized precision clinical trial is currently being conducted since 2021, with a main target to evaluate the effectiveness of precision immunotherapy in septic patients. This trial is called ImmunoSep. By utilizing the diagnostic tools of ferritin levels and the number of HLA-DR receptors, patients with MALS are treated with anakinra and patients with SII are treated with recombinant human interferon-gamma (rhIFNγ). The efficacy is compared to placebo treatment. The clinical trial is conducted in 26 ICUs from Greece, in 2 ICUs from the Netherlands, and in 1 ICU from Germany, Switzerland, Italy and Romania respectively[2]. The Hellenic Institute for the Study of Sepsis (HISS) acts as the study sponsor.

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## APPENDIX 1

In the grading system of a therapeutic intervention, which was used in the recent Surving Sepsis Campaign guidelines, the degree of recommendation is defined by the level of recommendation and by the quality of evidence.

The factors which define the quality of evidence are:

- High: randomized clinical trials without methodological problems and restrictions
- Modarate: randomized clinical trials with methodological problems and restrictions or well-designed observational studies
- Low: observational studies
- Very low: bad quality-controlled studies or expert opinions or other recommendations

Strong level of recommendation is supported by:

- Very high benefit (immediate recommendation, odds ratio > 2 without possible confounding factors)
- Very high benefit with odds ratio > 5 without reliability risks (at least two levels)
- Dose-dependent correlation

Moderate level of recommendation is supported by:

- Methodological problems of randomized trials that indicate high likelihood of error
- Discrepancy of results and problems in subgroup analysis
- Inaccurate results
- High probability of reporting errors

In the recent Surviving Sepsis Campaign guidelines, the best clinical practice is introduced and defined by the following criteria:

- Proposal's clarity and applicability
- Proposal's necessity
- Probability of benefit over risk
- Difficulty in collecting the required indication
- Analysis of proposal's rationale
- Possibility the GRADE system to be included

Before the initiation of each Consensus Conference for subjects related to a therapeutic intervention, the evaluation criteria are predetermined not only for the available clinical

trials, but also for the clinical significance of results for most of patients. Finally, the benefit/risk ratio for a therapeutic intervention is also considered. With all the above mentioned, the committee of participating experts in Consensus Conference determines the degree of recommendation for a certain practice or therapeutic approach, as summarized in the appendix.


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| **FACTORS WHICH DETERMINE THE RECOMMENDATION OF THERAPEUTIC INTERVENTIONS** | |
|---|---|
| moderate or high indication | High quality of indication makes the strong recommendation more likely |
| Certainty of benefit/risk ratio | • Big difference in benefit/risk ratio makes the strong recommendation more likely<br>• Small difference in benefit/risk ratio makes the weak recommendation more likely |
| Certainty in result values | Strong certainty or values similarities makes the strong recommendation more likely |
| Association with financial resources | The small cost of intervention makes the strong recommendation more likely |

| | RENAL CLEARANCE DOSE ADJUSTMENTS OF ANTIMICROBIALS (ml/min) | | | | |
|---|---|---|---|---|---|
| **Antimicrobial agent** | **Normal** | **50-<90** | **30-<50** | **10-<30** | **ESRD or CVVHF** |
| 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 |
| Ceftaroline | 600 mg x 2 | 600 mg x 2 | 400 mg x 2 | No data | |
| Piperacillin/tzaobactam | 4.5g x 4 | 4.5g x 4 | 2.25g x 4 | 2.25g x 3 | 2.25g x 3 |
| Ceftolozane/tazobactam | 1.5g x 3 | 1.5g x 3 | 750 mg x 3 | 375 mg x 3 | 750mg loading dose and 150mg x3 |
| Ceftazidime/avibactam | 2.5 γg x 3 | 2.5 g x 3 | 1.25 g x 3 | 0.94 g x 1 | 0.94 g per 48 h |
| IImipenem | 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 |
| Imipenem/cilastatin/relebactam | 1.25g x 4 | 1.25g x 4 | 0.75 x 4 | 0.5 x 4 | No data |
| Meropenem/vaborbactam | 4g x 3 | 4g x 3 | 2g x 3 | 2g x 2 | No data |
| Tigecycline | 50mg x 2 (100mg loading dose)* | 50mg x 2 (100mg loading dose)* | 50mg x 2 (100mg loading dose)* | 50mg x 2 (100mg loading dose* | 50mg x 2 (100 mg loading dose |

ESRD= endstage renal disease, CVVHF= Continuous veno-venous hemofiltration, *100mg x 2 (200mg load dose) if MIC >0.25µg/ml

| | RENAL CLEARANCE DOSE ADJUSTMENTS OF ANTIMICROBIALS (ml/min) | | | | |
|---|---|---|---|---|---|
| **Antimicrobial agent** | **Normal** | **50-<90** | **30-<50** | **10-<30** | **ESRD or CVVHF** |
| Colistin (mU) | 10.9* | 80-<90: 10.3<br>70-<80: 9<br>60-<70: 8.35<br>50-<60: 7.40* | 40-<50: 6.56<br>30-<40: 5.90 | 20-<30: 5.30<br>10-<20: 4.85 | 4.40* |
| Vancomycin | 1g x 2 | 1g x 1 | 1g/24-96 ώρες | 1 g/4-7 days | 0.5 g/24-48 hours |
| Teikoplanin | 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 |
| Tedizolid | 200 mg x 1 | 200 mg x 1 | 200 mg x 1 | 200 mg x 1 | 200 mg x 1 |
| Fosfomycin (intravenous)** | 8 gr x 3 | 8 gr x 3 | 8gr x 2<br>40-<50: 16 gr/ day<br>30-<40: 14 gr/ ημέρα | 20-<30: 8 gr x 2<br>10-<20: 4 gr x 2 | ESRD 2 gr x 1 after dialysis<br>CVVHF: 8 gr x 3 |
| Daptomycin (check CPK weekly) | 8-10 mg/kg x 1 | 8-10 mg/kg x 1 | 8-10 mg/kg/<br>48 hours | 8-10 mg/kg/<br>48 hours | 8-10 mg/kg /<br>48 hours |
| Dalbavancin | 1.5 g once or 1 g and 500 mg after 7 days | 1.5g once or1g and 500 mg after 7 days | 1.5 g once or 1 g and 500 mg after 7 days | 100mg once | 100mg once |
| 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 |

ESRD= endstage renal disease, CVVHF= Continuous veno-venous hemofiltration, *loading dose 9 mU and continuing after 12 hours, ** https://www.ema.europa.eu/en/documents/referral/fosfomycin-article-31-referral-annex-iii_en.pdf

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