**Supplemental data**

**HEPARIN BINDING PROTEIN FOR THE EARLY DIAGNOSIS AND PROGNOSIS OF SEPSIS IN THE EMERGENCY DEPARTMENT: THE PROMPT MULTICENTER STUDY**

**Running heading: Heparin binding protein in sepsis**

**Konstantinos Katsaros1\*, Georgios Renieris2\*, Asimina Safarika2,**

**Evangelia-Maria Adami2, Theologia Gkavogianni2, George Giannikopoulos3,**

**Nicky Solomonidi2, Stamatios Halvatzis2, Ioannis M. Koutelidakis4,**

**Nikolaos Tsokos5, Maroula Tritzali3,** **Pantelis Koutoukas6, Cristina Avgoustou2, Anil Vasishta7, Evangelos J. Giamarellos-Bourboulis2**

**\*equal contribution**

**1Department of Surgery, Nafplion General Hospital, 211 00 Nafplion, Greece;**

**24th Department of Internal Medicine, National and Kapodistrian University of Athens, Medical School, 124 62 Athens, Greece;**

**3Department of Internal Medicine, Siros General Hospital, 841 00 Ermoupolis, Syros, Greece;**

**42nd Department of Surgery, Aristotle University of Thessaloniki, 546 35 Thessaloniki, Greece;**

**5Department of Internal Medicine, Chalkida General Hospital, 341 00 Chalkida, Greece;**

**6Department of Internal Medicine, Sparti General Hospital, 231 00 Sparti, Greece**

# Definitions of sepsis and infections for study inclusion

Sepsis

Presence of sequential organ failure assessment (SOFA) score of ≥2 points for emergency admission patients or of a ≥2-point increase on the admission SOFA score for hospitalized patients.1

Community-acquired pneumonia (CAP)

New or evolving infiltrate on chest X-ray with presence of at least two of the following:

* new onset or worsening of cough;
* dyspnea;
* auscultatory findings consistent with pulmonary consolidation AND presence of at least one of the following:
  + PCT ≥0.25 μg/liter;
  + hypoxemia pO2 ≤60mm Hg or oxygen saturation ≤90% in room air;
  + respiratory rate ≥20 breaths/min.3

Acute bronchitis

* Acute cough
* Exclusion of conditions associated with acute cough (pneumonia, influenza, COPD, asthma, pertussis)
  + Normal chest X- ray
  + Absence of abnormality in vital signs
  + Absence of abnormalities of pulmonary function
  + Negative PCR for influenza/ pertussis2

Aspiration pneumonia

* characteristic clinical history (witnessed macroaspiration),
* compatible findings on chest radiography (infiltrates in gravity-dependent lung segments (superior lower-lobe or posterior upper-lobe segments, if the patient is in a supine position during the event, or basal segments of the lower lobe, if the patient is upright during the event)
* quantitative lung-lavage cultures2

Acute pyelonephritis

Presence of ≥10 leukocytes/high-power field in urine sediments with positive leukocyte esterase in urine and presence of at least two of the following:

* fever (tympanic or oral temperature ≥380C; rectal temperature ≥38.3oC);
* dysuria, increased urinary frequency or urgency;
* flank pain or lumbar pain at palpation;
* consistent ultrasound findings.4,5

Acute cystitis

Upper urinary tract infection (kidney, ureter, bladder, urethra, or tissue surrounding the retroperitoneal or perinephric space)

Must meet one of the following criteria:

* Organism isolated from culture of fluid (other than urine) or tissue from the affected site;
* an abscess or other evidence of infection seen on direct examination, during surgery, or by histopathologic examination

or two of the following:

* Fever (38°C)
* Urgency
* localized pain or tenderness at involved site

and any of the following

* purulent drainage from the affected site
* pyuria
* hematuria
* organism isolated from culture, positive Gram stain
* radiographic evidence of infection (e.g., ultrasound, computed tomography, magnetic resonance imaging, radiolabeled scan) 2

Bacteremia

* At least 1 positive blood culture yielding a pathogen that is not a skin commensal (e.g. coagulase-negative *Staplylococcus* spp).
* Failure to identify a primary infection site despite thorough clinical and radiology investigation2

Acute biliary tract infection

* Pain at the right upper quadrant
* Fever (tympanic or oral temperature ≥380C, rectal ≥38.30C)
* Isolation of pathogenic microorganisms obtained via percutaneous or direct surgical collection of samples in the lumen of the gall bladder or the biliary tract or the blood. 2

Intraabdominal abscess

Clinical, radiographic, and direct surgical confirmation of an inflammatory collection within the peritoneal space or surrounding structures with isolation of one or multiple microbial pathogens from the fluid collection. 2

Acute gastroenteritis

abrupt onset 3 or more loose or liquid stools above baseline in a 24-h period to meet the criteria of acute diarrhea associated with other clinical features suggest- ing enteric involvement including nausea, vomiting, abdominal pain and cramps, bloating, flatulence, fever, passage of bloody stools, tenesmus, and fecal urgency 6

Skin and soft tissue infection

* Surgical site infections

Infection that arises within 30 days of an operative procedure and at the site of surgical intervention.

* Nonsurgical site infections
  + Cellulitis: acute spreading infection of the skin and underlying soft tissue suggested by the presence of a rapidly expanding erythema, local tenderness, pain, swelling, lymphangitis, and lymphadenopathy, which is frequently accompanied by systemic signs and symptoms including malaise, fever (temperature >38.0°C), and chills.
  + Necrotizing cellulitis and fasciitis are defined as acute, rapidly progressing, and life-threatening destructive (i.e., necrotizing) infections of the subcutaneous tissues dissecting along tissue planes.
* Typical symptoms
* wound erythema and blanching,
* tenderness
* pain
* purulent discharge
* fever (temperature > 38.0°C) 2

**Supplementary Table 1** Comparative baseline demographics of patients who died early after ED admission (the first 72 hours) and of those who did not die early after ED admission.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **72-hour non-survivors (n=10)** | **72-hour survivors (n=361)** | **Difference**  **(95% CIs)** |
| Male gender (%) | 5 (50.0) | 175 (48.5) | 1.5 (-25.3; 28.4) |
| Age (years, mean ± SD) | 88.6 ± 5.8 | 61.7 ± 21.8 | 26.9 (13.2; 40.6) |
| Number of SIRS criteria (mean ± SD) | 2.20 ± 1.03 | 1.76 ± 1.01 | 0.49 (-0.16; 1.14) |
| qSOFA score (mean ± SD) | 1.80 ± 1.22 | 0.57 ± 0.67 | 1.23 (0.77; 1.69) |
| Charlson’s comorbidity index (mean ± SD) | 5.00 ± 2.05 | 2.98 ± 3.03 | 2.02 (0.09; 3.94) |
| SOFA score (mean ± SD) | 7.22 ± 3.67 | 1.51 ± 1.71 | 5.71 (4.50; 6.91) |
| APACHE II score (mean ± SD) | 23.11 ± 5.60 | 8.29 ± 5.42 | 14.8 (11.3; 18.4) |
| White blood cells (/mm3, mean ± SD) | 11,484.0 ± 5097.0 | 11,539.4 ± 5900.9 | 55.4  (-3715.2; 3826.1) |
| Platelets (/mm3, mean ± SD) | 204,333.3 ± 42255.2 | 242,293.1 ± 84988.9 | -37959.8  (-91534.9; 15611.5) |
| PCT (ng/ml, median, IQR) | 0.27 (3.17) | 0.12 (0.38) | 0.15 (2.79) |
| CRP (mg/l, median, IQR) | 55.6 (153.9) | 35.2 (92.9) | 20.3 (61.0) |
| HBP (ng/ml, median, IQR) | 35.7 (98.5) | 29.2 (62.4) | 6.5 (36.1) |
| Final infection diagnosis (n, %) |  |  |  |
| Upper respiratory tract infections | 0 (0) | 64 (17.7) | -17.7 (-22.0; 10.3) |
| Community-acquired pneumonia | 0 (0) | 61 (16.9) | -16.9 (-21.3; 17.8) |
| Acute bronchitis | 1 (10.0) | 49 (13.6) | -3.6 (-27.0; 12.7) |
| Aspiration pneumonia | 4 (40.0) | 19 (5.3) | 34.8 (11.4; 63.5) |
| Acute pyelonephritis | 2 (20.0) | 55 (15.2) | 4.8 (-10.1; 35.9) |
| Acute cystitis | 0 (0) | 9 (2.5) | -2.5 (-25.3; 4.7) |
| Primary bloodstream infection | 0 (0) | 6 (1.7) | -1.7 (-26.1; 3.6) |
| Acute biliary tract infection | 1 (10.0) | 20 (5.5) | 4.5 (-4.2; 34.9) |
| Intrabdominal abscess | 0 (0) | 9 (2.5) | -2.5 (-25.7; 4.7) |
| Acute gastroenteritis | 1 (10.0) | 13 (3.6) | 6.4 (-2.2; 36.9) |
| Skin and soft tissue infection | 0 (0) | 13 (3.6) | -3.6 (-24.2; 6.1) |
| Co-morbidities (n, %) |  |  |  |
| Type 2 diabetes mellitus | 2 (20.0) | 64 (17.7) | 2.3 (-12.7; 33.5) |
| Chronic heart failure | 1 (10.0) | 33 (9.1) | 0.9 (-8.0; 31.4) |
| Coronary heart disease | 0 (0) | 40 (11.1) | -11.1 (-16.8; 14.7) |
| Chronic obstructive pulmonary disease | 3 (30.0) | 45 (12.5) | 17.5 (-2.1; 48.0) |
| Chronic renal disease | 0 (0) | 23 (6.4) | -6.4 (-21.9; 9.4) |
| Corticosteroid intake | 0 (0) | 13 (3.6) | -3.6 (-24.2; 6.1) |
| Chemotherapy | 0 (0) | 18 (5.0) | -5.0 (-22.8; 7.7) |
| Non-metastatic solid tumor | 0 (0) | 15 (4.2) | -4.2 (-23.7; 6.7) |
| Metastatic solid tumor | 0 (0) | 19 (5.3) | -5.3 (-22.6; 8.1) |
| Ischemic stroke | 1 (10.0) | 21 (5.8) | 4.2 (-4.5; 34.7) |
| Atrial fibrillation | 1 (10.0) | 37 (10.2) | -0.2 (-30.3; 9.2) |
| Dementia | 3 (30.0) | 43 (11.9) | 18.1 (-1.5; 48.6) |
| Parkinson disease | 0 (0) | 10 (2.8) | -2.8 (-25.0; 5.0) |
| Nephrolithiasis | 0 (0) | 10 (2.8) | -2.8 (-25.0; 5.0) |
| Gallstones | 1 (10.0) | 23 (6.4) | 3.6 (-5.1; 34.1) |
| Depression | 0 (0) | 32 (8.9) | -8.9 (-19.0; 12.3) |

Abbreviations APACHE acute physiology and chronic health evaluation; CI: confidence interval; CRP: C-reactive protein; HBP: heparin binding protein; IQR: interquartile range; PCT: procalcitonin; SIRS: systemic inflammatory response syndrome; SOFA: sequential organ failure assessment

**Supplementary Table 2** Comparative baseline demographics of patients who died within 28 days ED admission and of those who survived.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **28- day non- survivors (n=29)** | **28-day survivors (n=342)** | **p** |
| Male gender (%) | 17 (58.6) | 174 (50.9) | 7.7 (-10.9; 24.5) |
| Age (years, mean ± SD) | 83.1 ± 7.9 | 60.7 ± 21.2 | 22.4 (14.6; 30.2) |
| Number of SIRS criteria (mean ± SD) | 2.07 ± 0.96 | 1.75 ± 1.02 | 0.32 (0.0; 0.70) |
| qSOFA score (mean ± SD) | 1.48 ± 1.02 | 0.53 ± 0.64 | 0.95 (0.69; 1.21) |
| Charlson’s comorbidity index (mean ± SD) | 5.72 ± 2.96 | 2.81 ± 2.93 | 2.91 (1.79; 4.03) |
| SOFA score (mean ± SD) | 4.68 ± 3.33 | 1.46 ± 1.59 | 3.22 (2.54; 3.89) |
| APACHE II score (mean ± SD) | 17.46 ± 7.62 | 7.91 ± 5.09 | 9.55 (7.52; 11.58) |
| White blood cells (/mm3, mean ± SD) | 10575.2 ± 6174.4 | 11621.5 ± 5849.5 | 1046.5  (-1188.0; 3280.6) |
| Platelets (/mm3, mean ± SD) | 227777.8 ± 76387.3 | 242451.7 ± 84986.0 | -14673.9  (-43727.5; 17379.7) |
| PCT (ng/ml, median, IQR) | 0.26 (1.77) | 0.12 (0.34) | 0.14 (1.43) |
| CRP (mg/l, median, IQR) | 82.1 (133.7) | 32.9 (90.5) | 49.2 (43.2) |
| HBP (ng/ml, median, IQR) | 34.6 (60.2) | 28.6 (62.2) | 6.0 (-2.0) |
| Final infection diagnosis (n, %) |  |  |  |
| Upper respiratory tract infections | 0 (0) | 64 (18.7) | -18.7 (-23.2; -6.4) |
| Community-acquired pneumonia | 5 (17.2) | 56 (16.4) | 0.8 (-9.7; 18.5) |
| Acute bronchitis | 4 (13.8) | 46 (13.5) | 0.3 (-8.9; 17.4) |
| Aspiration pneumonia | 11 (37.9) | 12 (3.5) | 34.4 (18.9; 52.6) |
| Acute pyelonephritis | 4 (13.8) | 53 (15.5) | -1.7 (-15.4; 11.0) |
| Acute cystitis | 0 (0) | 9 (2.6) | -2.6 (-9.1; 4.9) |
| Primary bloodstream infection | 0 (0) | 6 (1.8) | -1.8 (-9.9; 3.8) |
| Acute biliary tract infection | 1 (3.4) | 20 (5.8) | -2.4 (-11.5; 6.5) |
| Intrabdominal abscess | 0 (0) | 9 (2.5) | -2.6 (-15.4; 11.0) |
| Acute gastroenteritis | 1 (3.4) | 13 (3.6) | -0.3 (-13.5; 4.0) |
| Skin and soft tissue infection | 1 (3.4) | 12 (3.5) | -0.1 (-13.8; 4.3) |
| Co-morbidities (n, %) |  |  |  |
| Type 2 diabetes mellitus | 8 (27.6) | 58 (17.0) | 10.9 (-2.6; 29.4) |
| Chronic heart failure | 6 (20.7) | 28 (8.2) | 12.5 (1.1; 30.4) |
| Coronary heart disease | 5 (17.2) | 35 (10.2) | 7.0 (-3.3; 24.5) |
| Chronic obstructive pulmonary disease | 9 (31.0) | 39 (11.4) | 19.6 (5.4; 38.1) |
| Chronic renal disease | 2 (6.9) | 21 (6.1) | 0.8 (-5.1; 15.9) |
| Corticosteroid intake for | 1 (3.4) | 12 (3.5) | -0.1 (-13.8; 4.3) |
| Chemotherapy | 4 (13.8) | 14 (4.1) | 9.7 (0.9; 26.6) |
| Non-metastatic solid tumor | 2 (6.9) | 13 (3.8) | 3.1 (-2.5; 18.2) |
| Metastatic solid tumor | 2 (6.9) | 17 (5.0) | 1.9 (-3.8; 17.1) |
| Ischemic stroke | 5 (17.2) | 17 (5.0) | 12.3 (2.2; 29.7) |
| Atrial fibrillation | 4 (13.8) | 34 (9.9) | 3.9 (-5.2; 20.8) |
| Dementia | 8 (27.6) | 38 (11.1) | 16.4 (3.1; 34.8) |
| Parkinson disease | 1 (3.4) | 9 (2.6) | 0.8 (-2.8; 14.6) |
| Nephrolithiasis | 0 (0) | 10 (2.8) | 2.9 (-8.8; 5.3) |
| Gallstones | 2 (6.9) | 22 (6.4) | 0.5 (-5.4; 15.7) |
| Depression | 2 (6.9) | 30 (8.8) | -1.9 (-15.7; 8.6) |

Abbreviations APACHE acute physiology and chronic health evaluation; CI: confidence interval; CRP: C-reactive protein; HBP: heparin binding protein; IQR: interquartile range; PCT: procalcitonin; SIRS: systemic inflammatory response syndrome; SOFA: sequential organ failure assessment

**References**

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315: 801–10.
2. Calandra T, Cohen J. [The international sepsis forum consensus conference on definitions of infection in the intensive care unit.](https://www.ncbi.nlm.nih.gov/pubmed/16003060) *Crit Care Med* 2005; 33: 1538-1548
3. Müller B, Harbarth S, Stolz D, Bingisser R, Mueller C, Leuppi J, et al. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. *BMC Infect Dis* 2007; 7: 10.
4. Mitterberger M, Pinggera GM, Colleselli D, Bartsch G, Strasser H, Steppan I, et al. Acute pyelonephritis: comparison of diagnosis with computed tomography and contrast-enhanced ultrasonography. *BJU Int* 2008; 101: 341.
5. Pinson AG, Philbrick JT, Lindbeck GH, Schorling JB. Fever in the clinical diagnosis of acute pyelonephritis. *Am J Emerg Med* 1997; 15: 148.
6. Riddle MS, DuPont HL, Connor BA. ACG Clinical Guideline: Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults. Am J Gastroenterol. 2016 May;111(5):602-22.