**Supplement**

**Sepsis subclasses: a framework for development**

**and interpretation**

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eTable 1. Proposed sepsis subclasses…………………………………………………………………………..2

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**eTable 1.** Proposed sepsis subclasses

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| **ID** | **Author** | **Year** | **Journal** | **Type of phenotype** | **Primary modeling strategy** | **Data source** | **No. of patients** | **Type of patients** | **No.** | **Location** | **Prognostic of outcomes** | **Predictive of treatment** |
| (1) | Wong | 2009 | *BMC Medicine* | Genomic | Consensus k means clustering | Cohort | 98 | Pediatric septic shock | 3 | ICU | Yes  1. Mortality | No |
| (2) | Wong | 2011 | *Crit Care Med* | Genomic | Computer-assisted image analysis and microarray based reference mosaics | Cohort | 82 | Pediatric septic shock | 3 | ICU | Yes  1. Maximal organ failure  2. ICU-free days | No |
| (3) | Maslove | 2012 | *Critical Care* | Genomic | Partitioning around medoids clustering based on Euclidean distance | Cohort | 126 | Sepsis | 2 | ICU | Yes  1. Mortality  2. Length of stay. | No |
| (4) | Calfee | 2014 | *Lancet Respir Med* | Clinical and biological | Latent class analysis | Two RCTs  (ARMA and ALVEOLI) | Derived:  ARMA: 473  ALVEOLI: 549 | Adult ARDS | 2 | ICU | Yes 1. Ventilator free days 2. Organ failure free days 3. Mortality | Yes Positive Higher PEEP vs Low PEEP |
| (5) | Knox | 2015 | *Intensive Care Med* | Clinical | Kohonen self-organizing maps | Cohort data from 3 hospitals | 2533 | Adult severe sepsis and septic shock | 4 | ICU | Yes 1. 30 day mortality 2. ICU-free days at 30 days | No |
| (6) | Wong | 2015 | *Am J Respir Crit Care Med* | Genomic | Computer-assisted image analysis and microarray based reference mosaics | Cohort data | Derived: 168 Validated: 132 | Pediatric septic shock | 2 | PICU | Yes 1. 28 day mortality 2. Complicated course | Yes corticosteroids (positive) |
| (7) | Davenport | 2016 | *Lancet Respir Med* | Genomic | Transcriptomic analysis | Cohort data | Derived: 265 Validated: 106 | Sepsis due to community - acquired pneumonia (adult) | 2 | ICU | Yes 1. 14 day mortality | No |
| (8) | Shakoory | 2016 | *Crit Care Med* | Clinical |  | RCT | 763 | Severe sepsis and septic shock | 2 | ICU | Yes 1. 28 day mortality | Yes Interleukin-1 receptor blockade (positive) |
| (9) | Wong | 2017 | *Crit Care Med* | Genomic | Gene Expression Dynamics Inspector | Cohort data | 549 | Adults with sepsis | 4 | ICU | Yes 1. Mortality | No |
| (10) | Famous | 2017 | *Am J Respir Crit Care Med* | Clinical and biological | Latent class analysis | RCTs | Derived:  FACTT: 1000 Validated:  FACTT:1000  ARMA: 473  ALVEOLI: 549 | Adult ARDS | 2 | ICU | Yes 1. 60 day mortality 2. 90 day mortality 3. Ventilator free days | Yes 1. Subphenotype and fluid management strategy for mortality (positive); 2. Subphenotype and fluid management strategy for ventilator - free days (negative); 3. Subphenotype and cathetertype for mortality or forventilator-free days (negative) |
| (11) | Scicluna | 2017 | *Lancet Respir Med* | Genomic | Unsupervised consensus clustering method | Cohort data | Derived: 306 First validation: 216 Second validation: 265 | Adult sepsis | 4 | ICU | Yes 1. 28 day mortality | No |
| (12) | Burnham | 2017 | *Am J Respir Crit Care Med* | Genomic | Genome-wide gene expression profiling | Cohort data | Fecal peritonitis: 117  Pneumonia: 126 | Adult sepsis due to fecal peritonitis or community-acquired pneumonia | 2 | ICU | Yes  1. 14 day mortality | No |
| (13) | Gardlund | 2018 | *J Crit Care* | Clinical | Latent class analysis | RCT | 1696 | Adult septic shock | 6 | ICU | Yes 1. 90 day mortality 2. 28 day mortality 3. Ventilator free days (from 28 days) 4. Vasopressor free days (from 28 days) 5. CRRT free days (from 28 days) | Yes  1. Subphenotypes and rhAPC treatment for 28 day and 90 day survival (negative) |
| (14) | Sweeney | 2018 | *Crit Care Med* | Genomic | COmbined Mapping of Multiple clUsteriNg ALgorithms (COMMUNAL) | Cohort data | Derived: 700 Validated: 600 | Bacterial sepsis | 3 | Inhospital | Yes 1. 30 day mortality | No |
| (15) | Sinha | 2018 | *Intensive Care Med* | Clinical and biological | Latent class analysis | RCT | 745 | Adult sepsis-associated ARDS | 2 | ICU | Yes 1. 60 day mortality 2. 90 day mortality 3. Ventilator free days | Yes Subphenotype and rosuvastatin for 60 day, 90 day mortality or for ventilator-free days (negative) |
| (16) | Calfee | 2018 | *Lancet Respir Med* | Clinical and biological | Latent class analysis | RCT | 540 | Adult ARDS | 2 | ICU | Yes 1. 28 day mortality 2. 90 day mortality 3. Ventilator free days | Yes Subphenotype and simvastatin for 28 day, 90 day mortality or for ventilator-free days (positive) |
| (17) | Zhang | 2018 | *Critical care* | Clinical | Latent profile analysis | Cohort data from MIMIC-III | 14993 | Sepsis | 4 | ICU | Yes 1. Hospital mortality 2. Length of ICU stay  3. Length of hospital stay 3. 90 - day mortality | Yes Positive Fluid input (more fluid inputs were associated with improved outcome in profile 3) |
| (18) | Wong | 2018 | *Crit Care Med* | Genomic | Gene expression score | Cohort data | 375 | Pediatric septic shock | 4 | PICU | Yes 1. Mortality | Yes corticosteroids (positive) |
| (19) | Seymour | 2019 | *JAMA* | Clinical | Consensus k means clustering | Cohort data | Derived: 20,189 Validated: 43,086  GenIMS:  583  ACCESS: 1,706  PROWESS: 1,690  ProCESS: 1,341 | Sepsis | 4 | Hospital | Yes  1. 28 day mortality  2. Hospital mortality  3. 365 day mortality  4. Mechanical ventilation time  5. Administration of a vasopressor time  6. Admitted to intensive care unite | Yes  1. ACCESS: Eritoran (positive);  2. PROWESS: Drotrecogin alfa (positive);  3. ProCESS: EGDT therapy (positive). |
| (20) | Santhakumaran | 2019 | *Critical Care* | Clinical | Risk based models using APACHE II score | RCT | VANISH: 409  LeoPARDS: 515  HARP-2: 539 | Sepsis  ARDS | 2 | ICU | No | Yes  1. VANISH: vasopressin (negative), hydrocortisone (negative);  2. LeoPARDS: levosimendan (negative);  3. HARP-2: simvastatin (positive) |
| (21) | Antcliffe | 2019 | *Am J Respir Crit Care Med* | Genomic | Generalized linear model | RCT | 176 | Sepsis | 2 | ICU | Yes  1. 28 day mortality;  2. Kidney failure–free days up to Day 28;  3. ICU mortality;  4. Hospital mortality;  5. Rates of kidney failure;  6. Weaning from vasopressors for greater than 24 hours;  7. Time to shock reversal;  8. Duration of mechanical ventilation | Yes  1. Hydrocortisone (positive). |

*Abbreviations*: ACCESS, A Controlled Comparison of Eritoran Tetrasodium and Placebo in Patients With Severe Sepsis; APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; ARDS, Acute Respiratory Distress Syndrome; ARMA, Acute Respiratory Distress Syndrome Network trial; ALVEOLI, Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury; FACTT, Fluids and Catheters Treatment Trial; GenIMS, Genetic and Inflammatory Markers of Sepsis; HARP-2, Hydroxymethylglutaryl-CoA Reductase Inhibition with Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction–2; ICU, Intensive care unit; LeoPARDS, Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis; MIMIC-III, Medical Information Mart for Intensive Care; PEEP, Positive end-expiratory pressure; PICU, Pediatric intensive care unit; ProCESS, Protocolized Care for Early Septic Shock; PROWESS,  Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis; RCT, Randomized controlled trial; VANISH, Vasopressin vs Norepinephrine as Initial Therapy in Septic Shock

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