**Supplemental Digital Content 2. Patient-Level Details of Pathophysiologic Processes and Therapeutic Advances**

Theses tables include pathophysiologic processes contributing to morbidity or mortality in critically ill children (eTables 1-12), chronic conditions (eTable 13), and needed therapeutic advances to prevent or reduce morbidity and mortality (eTables 14-28).

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eTable 7. Pathophysiologic Process: Toxicities

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eTable 28. Therapeutic Advances: Other Therapies

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| **eTable 1. Pathophysiologic Process: Impaired Substrate Delivery** |
| **Impaired Substrate Delivery (N=158)** |
| **Type of impaired substrate delivery** | **N (%)** |
| **Ischemia** | 43 (27) |
| Global | 35 (22) |
|  Low cardiac output | 24 (15) |
|  Distributive shock | 7 (4) |
|  Sepsis | 5 (3) |
|  Cytokine release syndrome | 2 (1) |
|  Hemorrhage | 4 (3) |
| Trauma | 2 (1) |
|  Procedural complication | 2 (1) |
| Regional | 8 (5) |
|  Decreased cerebral perfusion | 8 (5) |
|  |  |
| **Hypoxia (all global)** | 25 (16) |
| Cardiac | 7 (4) |
|  Cyanotic heart disease | 4 (3) |
|  Shunt occlusion | 2 (1) |
|  Pulmonary over circulation | 1 (1) |
| Airway (central) | 5 (3) |
| ARDS | 5 (3) |
| Bronchiolitis obliterans | 2 (1) |
| Infection (lung) | 2 (1) |
| Other  | 4 (3) |
|  |  |
| **Hypoxia and Ischemia** | 90 (57) |
| Global | 79 (50) |
|  Cardiac arrest | 44 (28) |
|  Cardiac (non-arrest) | 20 (13) |
|  Congenital heart disease related | 19 (12) |
|  Cardiomyopathy related | 1 (1) |
|  Sepsis/MODS/±ARDS | 13 (8) |
|  Other  | 2 (1) |
| Regional | 11 (7) |
|  Decreased cerebral perfusion and hypoxemia | 11 (7) |
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Abbreviations: ARDS is acute respiratory distress syndrome; MODS is multiple organ dysfunction syndrome

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| **eTable 2. Pathophysiologic Process: Inflammation** |
| **Inflammation (N=104)*a*** |
|  | **N (%)** |
| **Infection-related** | 81 (78) |
|  Unspecified organism | 27 (26) |
|  Viral | 27 (26) |
|  Gram (+) bacteria | 12 (12) |
|  Gram (-) bacteria | 12 (12) |
|  Fungal | 8 (8) |
|  Other | 2 (2) |
| **Clinical manifestation (infection-related)** |  |
|  Sepsis | 30 (29) |
|  Respiratory failure (not ARDS) | 27 (26) |
|  MODS | 15 (14) |
|  ARDS | 10 (10) |
|  Meningoencephalitis/ventriculitis/brain abscess | 9 (9) |
|  AKI | 7 (7) |
|  Osteomyelitis  | 2 (2) |
|  Myocarditis | 2 (2) |
|  Mastoiditis | 2 (2) |
|  Other | 12 (12) |
|  |  |
| **Oxidative injury or other inflammation (non-infectious)** | 29 (28)  |
| **Clinical manifestation (non-infectious)** |  |
|  Reperfusion injury/cardiopulmonary bypass-related | 5 (5) |
|  MODS | 4 (4) |
|  ARDS | 4 (4) |
|  Aspiration pneumonia (not ARDS) | 4 (4) |
|  Respiratory failure (not ARDS or aspiration) | 4 (4) |
|  Inflammatory bowel disease | 3 (3) |
|  Other | 8 (8) |
| *a* Subjects can have more than one type of inflammation, type of organism, or clinical manifestation of the inflammatory process.Abbreviations: ARDS is acute respiratory distress syndrome; MODS is multiple organ dysfunction syndrome; AKI is acute kidney injury |

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| **eTable 3. Pathophysiologic Process: Tissue Injury (Direct)** |
| **Tissue Injury (Direct) (N=64)** |
| **Type of tissue injury** | **N (%)** |
| **Trauma** | 37 (58) |
|  Accidental | 21 (33) |
|  With brain and/or spinal cord injury | 18 (28) |
|  Without brain and/or spinal cord injury | 3 (5) |
|  Non-Accidental | 12 (19) |
|  With brain and/or spinal cord injury | 10 (16) |
|  Without brain and/or spinal cord injury | 2 (3) |
|  Accidental/non-accidental unknown | 4 (6) |
|  With brain and/or spinal cord injury | 4 (6) |
|  Without brain and/or spinal cord injury | 0 |
|  |  |
| **Surgical/device injury** | 11 (17) |
| With brain and/or spinal cord injury | 3 (5) |
| Without brain and/or spinal cord injury | 8 (12) |
|  |  |
| **Ventilator associated lung injury** | 7 (11) |
|  |  |
| **Burns** | 3 (5) |
|  With inhalation injury | 2 (3) |
|  Without inhalation injury | 1 (1) |
|  |  |
| **Other/unknown** | 6 (9) |
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| **eTable 4. Pathophysiologic Process: Electrical Signaling Dysfunction** |
| **Electrical Signaling Dysfunction (N=52)** |
| **Type of electrical signaling dysfunction** | **N (%)** |
| **Neurologic** | 36 (69) |
|  Seizures | 19 (37) |
|  Brain/brainstem tumor | 3 (6) |
|  Spinal muscle atrophy  | 3 (6) |
|  Dysautonomia | 2 (4) |
|  Spinal cord injury | 2 (4) |
|  Infantile botulism | 2 (4) |
|  Other | 5 (10) |
|  |  |
| **Cardiac** | 15 (29) |
|  Dysrhythmia | 15 (29) |
|  |  |
| **Neurologic and cardiac** | 1 (2) |
|  Seizures and dysrhythmia | 1 (2) |

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| **eTable 5. Pathophysiologic Process: Abnormal Growth/Abnormal Cell Cycle** |
| **Abnormal Growth/Abnormal Cell Cycle (N=52)** |
| **Type of abnormal growth/abnormal cell cycle** |  **N (%)** |
| **Malignancy** | 33 (63) |
|  Leukemia | 13 (25) |
|  ALL | 10 (19) |
|  AML | 3 (6) |
|  Medulloblastoma | 4 (8) |
|  Neuroblastoma | 3 (6) |
|  Pontine glioma | 2 (4) |
|  Hepatoblastoma | 2 (4) |
|  Histiocytosis | 2 (4) |
|  Other | 7 (13) |
|  |  |
| **Congenital malformations** | 19 (37) |
|  Cardiac | 12 (23) |
|  Brain | 3 (6) |
|  Septo optic dysplasia | 1 (2) |
|  Pineal cyst | 1 (2) |
|  Arteriovenous malformation | 1 (2) |
|  Airway | 2 (4) |
|  Complete tracheal rings | 1 (2) |
|  Laryngomalacia | 1 (2) |
|  Gastrointestinal (jejunal atresia) | 1 (2) |
|  Multiple congenital anomalies | 1 (2) |
| Abbreviations: ALL is acute lymphoblastic leukemia; AML is acute myelocytic leukemia |
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| **eTable 6. Pathophysiologic Process: Capillary/Vascular Dysfunction** |
| **Capillary/Vascular Dysfunction (N=52)** |
| **Type of capillary/vascular dysfunction** | **N (%)** |
| Anasarca | 18 (35) |
|  Related to sepsis/MODS/±ARDS | 13 (25) |
|  Related to cardiac failure | 5 (10) |
| Pulmonary hypertension | 12 (23) |
| Cerebral edema | 10 (19) |
| Arteriovenous malformation | 4 (8) |
| Lymphatic malformation/disruption | 4 (8) |
| Airway edema | 2 (4) |
| Other | 2 (4) |
| Abbreviations: ARDS is acute respiratory distress syndrome; MODS is multiple organ dysfunction syndrome |
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| **eTable 7. Pathophysiologic Process: Toxicities** |
| **Toxicities (N= 51)** |
| **Type of toxicity** | **N (%)** |
| **Drug** *a* | 36 (71) |
|  Sedation *b* | 23 (45) |
|  Chemotherapy *c* | 8 (16) |
|  Antiepileptic *d* | 4 (8) |
|  Antifungal *e* | 1 (2) |
|  Anticoagulation/thrombolytic *f* | 1 (2) |
|  Prostaglandin *g* | 1 (2) |
|  Ingestion (unknown drugs) *h* | 2 (4) |
|  |  |
| **Electrolyte** | 6 (12) |
|  Hyperkalemia | 2 (4) |
|  Other | 4 (8) |
|  |  |
| **Endogenous substance** | 6 (12) |
|  Genetic/metabolic disorder | 3 (6) |
| Hepatic failure | 3 (6) |
|  |  |
| **Other** | 3 (6) |
|  Botulinum toxin | 2 (4) |
|  TPN | 1 (2) |

a Subjects can have more than one type of drug toxicity.

*b* Sedation: toxic effects are deconditioning, and withdrawal.

*c* Chemotherapy: toxic effects are cytokine release syndrome, cardiomyopathy, esophagitis/enteritis, pericardial effusion, and seizures

*d* Antiepileptic: toxic effects are sedation/deconditioning, and pancreatitis

*e* Antifungal: toxic effect is prolonged QT

*f* Anticoagulation/thrombolytic: toxic effect is intracranial hemorrhage

*g* Prostaglandin: toxic effect is apnea

*h* Ingestion: toxic effect is hypoxic-ischemic encephalopathy and death

Abbreviations: TPN is total parenteral nutrition.

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| **eTable 8. Pathophysiologic Process: Immune Dysfunction**  |
| **Immune Dysfunction (N=49)** |
| **Type of immune dysfunction** | **N (%)** |
|  Decreased function | 20 (41) |
|  Increased function | 10 (20) |
|  Decreased and increased function | 8 (16) |
|  Other | 11 (22) |
|  |  |
| **Specific immune disorder or condition*a*** |  |
|  Immune suppressing drugs (e.g., chemotherapy) | 19 (39) |
|  Malignancy | 16 (33) |
|  BMT  | 10 (20) |
|  Transplant (not BMT) | 7 (14) |
|  Transplant rejection | 6 (12) |
|  GVHD | 6 (12) |
|  HLH | 4 (8) |
|  Presumed due to secondary/recurrent infection or multiple organisms  | 4 (8) |
|  Autoimmune encephalitis/transverse myelitis | 3 (6) |
|  PTLD | 2 (4) |
|  CAR-T | 2 (4) |
|  DiGeorge syndrome | 2 (4) |
|  SCID | 1 (2) |
|  ADEM | 1 (2) |
|  Histiocytosis X | 1 (2) |
|  Autoimmune movement disorder | 1 (2) |
|  Autoimmune lung disease (scleroderma and fibrosis) | 1 (2) |
|  Engraftment syndrome | 1 (2) |
|  Post-trauma immune dysfunction | 1 (2) |
|  Congenital immune deficiency (unspecified) | 1 (2) |
|  Idiopathic angioedema | 1 (2) |
|  CNS vasculitis | 1 (2) |
|  Lung inflammation | 1 (2) |
|  Myocarditis | 1 (2) |
| *a* Subjects can have more than one specific disorder or condition. |

Abbreviations: BMT is bone marrow transplant; GVHD is graft-versus-host disease; HLH is hemophagocytic lymphohistiocytosis; PTLD is post-transplant lymphoproliferative disorder; CAR-T is chimeric antigen receptor T cell therapy; SCID is severe combined immune deficiency; ADEM is acute disseminated encephalomyelitis; CNS is central nervous system

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| **eTable 9. Pathophysiologic Process: Coagulation Dysfunction** |
| **Coagulation Dysfunction (N=39)** |
| **Type of coagulation dysfunction** | **N (%)** |
| **Bleeding (acquired)** | 24 (62) |
| **Cause of bleeding *a***  |  |
|  DIC  | 7 (18) |
|  DIC due to sepsis/MODS  | 6 (15) |
|  DIC due to circulatory shock  | 1 (3) |
|  Trauma | 6 (15) |
|  Trauma – surgical  | 4 (10) |
|  Trauma – non-surgical  | 2 (5) |
|  ECMO-related | 3 (8) |
|  Thrombocytopenia secondary to leukemia | 3 (8) |
|  Liver failure | 2 (5) |
|  Ruptured aneurism | 1 (3) |
|  GVHD | 1 (3) |
|  Unknown | 3 (8) |
| **Site of bleeding**  |  |
|  Intracranial | 6 (15) |
|  Intra-abdominal | 4 (10) |
|  Pulmonary | 2 (5) |
|  Intrathoracic (extra-pulmonary) | 1 (3) |
|  Gastrointestinal | 1 (3) |
|  Generalized or unknown | 10 (26) |
|  |  |
| **Thrombosis (acquired)** | 11 (28) |
| **Cause of thrombosis** |  |
|  Infection - related | 2 (5) |
|  ECMO - related | 1 (3) |
|  Unknown  | 8 (21) |
| **Site of thrombosis *b*** |  |
|  Stroke (thromboembolic) | 6 (15) |
|  Blalock Tausig shunt thrombus | 3 (8) |
|  Deep venous thrombosis | 2 (5) |
|  Pulmonary embolism | 1 (3) |
|  |  |
| **Bleeding (acquired) & Thrombosis (acquired)** | 3 (8) |
| **Cause of bleeding/thrombosis** |  |
|  ECMO-related | 2 (5) |
|  Tissue plasminogen activator administration | 1 (3) |
| **Site of bleeding** |  |
|  Intracranial | 1 (3) |
|  Pulmonary | 1 (3) |
|  Intrathoracic (extra-pulmonary) | 1 (3) |
| **Site of thrombosis** |  |
|  Blalock Tausig shunt thrombus | 1 (3) |
|  Deep venous thrombosis | 1 (3) |
|  Intrathoracic thrombus | 1 (3) |
|  |  |
| **Thrombosis (congenital) & Thrombosis (acquired)** | 1 (3) |
| **Cause of thrombosis** |  |
|  Unknown | 1 (3) |
| **Site of thrombosis *b*** |  |
|  Left atrial thrombus  | 1 (3) |
|  Stroke (thromboembolic) | 1 (3) |

*a* Subjects can have more than one cause of bleeding.

*b* Subjects can have more than one site of thrombosis

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| **eTable 10. Pathophysiologic Process: Malnutrition**  |
| **Malnutrition (N=36)** |
| **Type of malnutrition** | **N (%)** |
| General malnutrition | 35 (97) |
| Specific nutrient deficiency (Vitamin D deficiency) | 1 (3) |
|  |  |
| **Duration/course of malnutrition** |  |
| Acute on chronic malnutrition | 17 (47) |
|  Chronic congenital heart disease with acute poor feeding ability/tolerance post-op  | 7 (19) |
|  Chronic malignancy with acute gastrointestinal condition | 4 (11) |
|  Chronic malignancy with acute sepsis | 2 (6) |
|  Chronic gastrointestinal condition with acute gastrointestinal hemorrhage | 2 (6) |
|  Chronic congenital heart disease with acute necrotizing enterocolitis | 1 (3) |
|  Chronic congenital heart disease with acute deterioration in cardiac function | 1 (3) |
|  |  |
| Chronic malnutrition | 13 (36) |
|  Congenital heart disease  | 5 (14) |
|  Neurologic condition | 3 (8) |
|  Respiratory condition | 1 (3) |
|  Gastrointestinal condition | 1 (3) |
|  Skeletal condition | 1 (3) |
|  Genetic disorder  | 1 (3) |
|  Vitamin D deficiency | 1 (3) |
|  |  |
| Acute malnutrition | 6 (17) |
|  Acute gastrointestinal conditions | 2 (6) |
|  Acute respiratory distress syndrome  | 2 (6) |
|  Acute sepsis event | 1 (3) |
|  Acute post-op chylothorax | 1 (3) |
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Abbreviations: DIC is disseminated intravascular coagulation; ECMO is extracorporeal membrane oxygenation; GVHD is Graft versus host disease; MODS is multiple organ dysfunction syndrome

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| **eTable 11. Pathophysiologic Process: Mitochondrial Dysfunction** |
| **Mitochondrial Dysfunction (N=5)** |
| **Type of mitochondrial dysfunction** | **N (%)** |
| Congenital myopathy or metabolic disorder | 3 (60) |
|  Congenital myopathy (undiagnosed) | 2 (40) |
|  Beta ketothiolase deficiency | 1 (20) |
| Lactic Acidosis associated with MODS | 2 (40) |

Abbreviation: MODS is multiple organ dysfunction syndrome

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| **eTable 12. Pathophysiologic Process: Other** |
| **Pathophysiologic Process: Other (N=19)** |
| **Type of other pathophysiologic process** | **N (%)** |
| Deconditioning syndrome | 3 (16) |
| Acute renal failure | 2 (11) |
| Psychiatric disorder | 2 (11) |
| Genetic metabolic disease | 2 (11) |
| Other (single cases) | 10 (53) |

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| **eTable 13. Chronic Conditions** |
| **Chronic Condition (N=156)** |
| **Type of chronic condition** | **N (%)** |
| **Cardiac** | 64 (41) |
|  Hypoplastic left heart syndrome | 21 (13) |
|  Tetralogy of Fallot | 7 (4) |
|  Atrioventricular canal defect | 5 (3) |
|  Transposition of the great arteries | 5 (3) |
|  Truncus arteriosus | 5 (3) |
|  Cardiac transplant | 4 (3) |
|  Aortic stenosis | 2 (1) |
|  Other  | 15 (10) |
| **Neuromuscular** | 24 (15) |
|  Seizure disorder | 5 (3) |
|  Spinal muscle atrophy | 4 (3) |
|  Static encephalopathy (±seizures) | 3 (2) |
|  Muscular disease | 3 (2) |
|  Hydrocephalus | 3 (2) |
|  Other  | 6 (4) |
| **Malignancy** | 19 (12) |
|  ALL | 7 (4) |
|  Brain tumor | 4 (3) |
|  AML | 3 (2) |
|  Wilms tumor | 2 (1) |
|  Other  | 3 (2) |
| **Chromosomal anomalies** | 14 (9) |
| **Respiratory conditions** | 13 (8) |
|  Upper airway obstruction | 5 (3) |
|  Asthma | 2 (1) |
|  Bronchopulmonary dysplasia | 2 (1) |
|  Other  | 4 (3) |
| **Gastrointestinal conditions** | 11 (7) |
|  Congenital malformations | 7 (4) |
|  Other  | 4 (3) |
| **Hematologic** | 3 (2) |
|  Sickle cell disease | 2 (1) |
|  Other  | 1 (1) |
| **Congenital immune deficiencies** | 2 (1) |
| **Other multiple congenital malformations** | 3 (2) |
| **Miscellaneous** | 3 (2) |
| Abbreviations: ALL is acute lymphoblastic leukemia; AML is acute myelocytic leukemia |
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| **eTable 14. Therapeutic Advances: Drugs** |
| **Drugs (N=149)** |
| **Type of drug *a*** | **N (%)** |
| Chemotherapy | 30 (20) |
| Inotropes | 26 (17) |
| Vasoactive agents | 24 (16) |
| Sedatives | 20 (13) |
| Antiviral | 20 (13) |
| Anticonvulsants | 17 (11) |
| Antibacterial | 15 (10) |
| Anticoagulation | 10 (7) |
| Other |  |
|  Pulmonary vasodilators | 7 (5) |
|  Anti-fungal | 6 (4) |
|  Anti-inflammatory | 6 (4) |
|  Immune modulator | 5 (3) |
|  Anti-dysrhythmic | 4 (3) |
|  Neuroprotection | 4 (3) |
|  Other  | 14 (9) |

*a* Subjects can be in need of more than one type of drug advance or addition.

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| **eTable 15. Therapeutic Advances: Cell Regeneration** |
| **Cell Regeneration (N=115)** |
| **Type of cell regeneration *a*** | **N (%)** |
|  Neuronal | 80 (70) |
|  Cardiovascular | 13 (11) |
|  Lung | 5 (4) |
|  Blood/Bone marrow | 2 (2) |
|  Bowel | 2 (2) |
|  Liver | 1 (1) |
|  Pancreas | 1 (1) |
|  Bone | 1 (1) |
|  Muscle | 1 (1) |
|  Lymphatics | 1 (1) |
|  Skin | 1 (1) |
| General/unspecified | 8 (7) |

*a* Subjects can be in need of more than one type of cellular regeneration.

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| **eTable 16. Therapeutic Advances: Immune and Inflammatory Modulation** |
| **Immune and Inflammatory Modulation (N=79)** |
| **Type of immune/inflammatory modulation**  | **N (%)**  |
|  Immune suppression only | 32 (41) |
|  Immune suppression and enhancement | 13 (16) |
|  Immune enhancement only | 9 (11) |
|  Other/unspecified | 25 (32) |
|  |  |
| **Advances or additions to address the following conditions *a*** |  |
|  Systemic inflammatory response syndrome | 17 (22) |
|  Central nervous system inflammation | 13 (16) |
|  Lung inflammation (not ARDS) | 8 (10) |
| Prevent/treat infection | 8 (10) |
|  Transplant rejection | 7 (9) |
|  GVHD | 5 (6) |
|  ARDS | 3 (4) |
|  MODS | 3 (4) |
|  Inflammatory bowel disease | 3 (4) |
|  Hemophagocytic lymphohistiocytosis | 3 (4) |
|  Pancreatitis | 2 (3) |
|  Asthma | 2 (3) |
|  Chemotherapy-related immune dysfunction | 2 (3) |
|  Other  | 12 (15) |

*a* Subjects can be in need of immune and inflammatory modulation for more than one condition.

Abbreviations: ARDS is acute respiratory distress syndrome; GVHD is graft-versus-host disease; MODS is multiple organ dysfunction syndrome.

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| **eTable 17. Therapeutic Advances: Extracorporeal Support and Artificial Organs** |
| **Extracorporeal Support or Artificial Organs (N=47)** |
| **Type of support** | **N (%)** |
|  Extracorporeal circulatory support only | 29 (62) |
|  Extracorporeal circulatory support and oxygenation | 11 (23) |
|  Extracorporeal oxygenation only | 5 (11) |
|  Other | 2 (4) |
|  |  |
| **Needed advances or additions in extracorporeal support *a*** |  |
|  Faster and more accessible extracorporeal support (ECPR) | 7 (15) |
|  Improved extracorporeal support for long-term use | 6 (13) |
|  Improved extracorporeal support as bridge to cardiac transplant | 6 (13) |
|  Improved anticoagulation | 5 (11) |
|  Improved extracorporeal support as bridge until medical therapies have time to work | 3 (6) |
|  Extracorporeal support with less activation of inflammatory cascade | 2 (4) |
|  Less invasive extracorporeal support | 2 (4) |
|  Improvement in cannula placement  | 2 (4) |
|  Improved extracorporeal support for single ventricle | 2 (4) |
|  Extracorporeal support with less deconditioning | 1 (2) |
|  Improved neuroprotection during extracorporeal support | 1 (2) |
|  Improved sepsis prevention during extracorporeal support | 1 (2) |
|  Improved extracorporeal support for trauma | 1 (2) |
|  Artificial liver | 1 (2) |
|  Artificial lung  | 1 (2) |
|  Unspecified | 7 (15) |

*a* Subjects can be in need of more than one extracorporeal advance or addition.

Abbreviation: ECPR is extracorporeal cardiopulmonary resuscitation

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| **eTable 18. Therapeutic Advances: Organ Transplant** |
| **Organ Transplant (N=47)** |
| **Type of organ transplant**  | **N (%)** |
|  Heart | 25 (53) |
|  Bone marrow/stem cell | 8 (17) |
|  Lung | 4 (9) |
|  Liver | 3 (6) |
|  Small bowel | 2 (4) |
|  Multi-organ |  |
|  Heart and lung | 3 (6) |
|  Liver and small bowel | 2 (4) |
|  |  |
| **Needed advances or additions for organ transplantation** |  |
|  Ability to provide earlier organ transplant | 14 (30) |
|  Increased availability of organs | 4 (9) |
|  Better evaluation and criteria for listing for transplant | 2 (4) |
|  Prevention and treatment of complications of organ transplant |  |
|  Rejection | 5 (11) |
|  Graft-versus-host disease | 2 (4) |
|  Post-transplant lymphoproliferative disorder | 1 (2) |
|  Other  | 2 (4) |
|  Improved pre-transplant chemotherapy | 2 (4) |
|  Unspecified | 15 (32) |

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| **eTable 19. Therapeutic Advances: Mechanical Respiratory Support** |
| **Mechanical Respiratory Support (N=41)** |
| **Needed advances or additions in mechanical respiratory support**  | **N (%)** |
| Better support for specific conditions | 12 (29) |
|  ARDS | 5 (12) |
|  Pulmonary hypertension | 2 (5) |
|  Bronchiolitis | 1 (2) |
| Pneumonia | 1 (2) |
|  Pulmonary hemorrhage | 1 (2) |
|  Restrictive lung disease | 1 (2) |
|  Neuromuscular weakness | 1 (2) |
| Ventilation that reduces ventilator-induced lung injury | 7 (17) |
| Better non-invasive mechanical ventilation | 5 (12) |
| Ventilation that requires less sedation  | 3 (7) |
| Better home ventilators | 2 (5) |
| Negative pressure ventilation | 2 (5) |
| Liquid ventilation | 1 (2) |
| Better ventilation during foreign body removal | 1 (2) |
| Direct diaphragm support | 1 (2) |
| General/unspecified improvement | 7 (17) |

Abbreviation: ARDS is acute respiratory distress syndrome

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| **eTable 20. Therapeutic Advances: Nutritional Support** |
| **Nutritional Support (N=39)** |
| **Needed advances or additions in nutritional support** | **N (%)** |
|  Better tolerated enteral formulas *a* | 10 (26) |
|  Improved nutrition for congenital heart disease | 8 (21) |
|  Improved nutritional monitoring *b* | 4 (10) |
|  Improved therapies to enhance infant nippling skills | 3 (8) |
|  Alternative to TPN or TPN without hepatic dysfunction | 3 (8) |
|  Improved nutrition for short gut syndrome | 2 (5) |
|  Improved nutrition for long-term chronic illness | 2 (5) |
|  Improved nutrition for acute critical illness | 1 (3) |
|  Vitamin D deficiency | 1 (3) |
|  Improved nutrition for chylothorax | 1 (3) |
|  Prevention of aspiration of enteral feeds | 1 (3) |
|  Prevention of Clostridium difficile | 1 (3) |
|  Unspecified | 2 (5) |

*a* Better tolerated enteral formulas includes tolerating high calorie formulas, and tolerating enteral formula in face of various conditions such as GVHD of gut or Crohn’s disease.

*b* Monitoring includes energy expenditure, nutritional immunity, and long-term home monitoring of nutritional intake.

Abbreviation: TPN is total parenteral nutrition

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| **eTable 21. Therapeutic Advances: Therapeutic Devices** |
| **Therapeutic devices (N=28)** |
| **Type of therapeutic devices** | **N (%)** |
| Stents | 7 (25) |
|  Intracardiac or intravascular stent | 5 (18) |
|  Airway stent | 1 (4) |
|  Stent to drain cholecystitis | 1 (4) |
| Cardiovascular shunts | 6 (21) |
| Vascular access device | 2 (7) |
| Nerve Stimulator | 1 (4) |
| Other | 12 (43) |
|  Drainage device | 2 (7) |
|  Cardiac catheterization devices (balloons, wires, etc.) | 2 (7) |
|  Nutritional delivery devices | 2 (7) |
|  Catheter-directed device for embolization | 1 (4) |
|  Physical therapy devices | 1 (4) |
|  Radiation therapy | 1 (4) |
|  Cardiac valves | 1 (4) |
|  Emergency tracheostomy device | 1 (4) |
|  Ventriculoperitoneal shunt | 1 (4) |
|  |  |
| **Needed advances or additions in therapeutic devices** |  |
| Availability for use in pediatrics or adjustable size | 9 (32) |
| Less thrombogenic | 5 (18) |
| Less invasive/easier to place | 3 (11) |
| Improved materials (e.g., durability) | 2 (7) |
| Resistance to infection | 2 (7) |
| Less potential for displacement | 1 (4) |
| Earlier use of device | 1 (4) |
| Unspecified | 5 (18) |

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| **eTable 22. Therapeutic Advances: Monitoring Devices** |
| **Monitoring Devices (N=28)** |
| **Type of monitoring device *a*** | **N (%)** |
| Cardiac Output | 9 (32) |
| Regional Blood Flow | 9 (32) |
|  Brain | 4 (14) |
|  Bowel | 2 (7) |
|  Coronaries | 1 (4) |
|  Pulmonary-to-systemic blood flow (Qp:Qs) | 1 (4) |
|  Unspecified | 1 (4) |
| Brain oxygenation | 8 (28) |
| Intracranial pressure | 2 (7) |
| Substrate utilization | 2 (7) |
| EEG | 1 (4) |
| Other | 7 (25) |
|  Intra-operative neurologic activity  | 2 (7) |
|  Anticoagulation | 1 (4) |
|  Continuous hemoglobin concentration | 1 (4) |
|  Continuous endotracheal tube position | 1 (4) |
|  Detection of varices | 1 (4) |
|  Non-invasive work of breathing  | 1 (4) |

 *a* Subjects can be in need of more than one monitoring device advance or addition.

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| **eTable 23. Therapeutic Advances: Blood and Blood Products** |
| **Blood and Blood Products (N=9)** |
| **Needed advances or additions in blood and blood products** | **N (%)** |
| To treat bleeding | 8 (89) |
|  Coagulopathy (DIC, liver-related, improved clotting factors) | 5 (56) |
|  Hemorrhagic shock | 2 (22) |
|  Local bleeding | 1 (11) |
| To provide granulocyte transfusion (with less side effects) | 1 (11) |

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| **eTable 24. Therapeutic Advances: Renal Replacement and Plasmapheresis** |
| **Renal Replacement and Plasmapheresis (N=8)** |
| **Type of renal support** | **N (%)** |
|  Vascular  | 8 (100) |
|  Peritoneal  | 0 |
|  |  |
| **Needed advances or additions in renal replacement therapy** |  |
|  Improved fluid removal with low cardiac output and massive capillary leak | 3 (38) |
|  Renal replacement therapy via peripheral vascular access | 1 (12) |
|  Improved knowledge of drug pharmacokinetics | 1 (12) |
|  Unspecified  | 3 (38) |

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| **eTable 25. Therapeutic Advances: Mitochondrial Support** |
| **Mitochondrial Support (N=6)** |
| **Type of mitochondrial disorder *a*** | **N (%)** |
| Genetic mitochondrial disorder | 3 (50) |
| Mitochondrial dysfunction associated with sepsis and MODS  | 2 (33) |
| Myocardial mitochondrial dysfunction after cardiopulmonary by-pass | 1 (17) |

*a* Support for these conditions included diagnostics and therapies.

Abbreviation: MODS is multiple organ dysfunction syndrome

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| **eTable 26. Therapeutic Advances: Inhaled Respiratory Support** |
| **Inhaled Respiratory Support (N=5)** |
| **Type of inhaled respiratory support** | **N (%)** |
| To treat pulmonary hypertension | 2 (40) |
| To improve mucociliary clearance | 1 (20) |
| To prevent asthma attack | 1 (20) |
| To decrease cardiopulmonary work | 1 (20) |

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| **eTable 27. Therapeutic Advances: Suspended Animation** |
| **Suspended Animation (N=2)** |
| **Advances or additions to address the following situations** | **N (%)** |
| During cardiac arrest - to prevent mismatch between cellular energy supply and demand | 1 (50) |
| During hyperkalemia - to give time to resolve hyperkalemia and prevent cardiac arrest | 1 (50) |

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| **eTable 28. Therapeutic Advances: Other Therapies** |
| **Other therapies (N=92)** |
| **Other types of therapies** | **N (%)** |
| Treatment for hypoxic-ischemic encephalopathy | 14 (15) |
| Trauma prevention | 12 (13) |
| Gene therapy | 11 (12) |
| Better surgery for congenital heart disease (non-HLHS) | 10 (11) |
| Better surgery for hypoplastic left heart syndrome (HLHS) | 8 (9) |
| Better neurosurgical resection (e.g., tumor, cyst, seizure focus) | 6 (7) |
| Better treatment for cerebral edema | 6 (7) |
| Diagnosis and treatment for rare genetic disorders | 5 (5) |
| Prevention of deconditioning | 5 (5) |
| Diagnosis and treatment of psychiatric disorders | 2 (2) |
| Other (single cases) | 9 (10) |
| Unspecified | 4 (4) |