**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).

eTable 1. Pathophysiologic Process: Impaired Substrate Delivery

eTable 2. Pathophysiologic Process: Inflammation

eTable 3. Pathophysiologic Process: Tissue Injury (direct)

eTable 4. Pathophysiologic Process: Electrical Signaling Dysfunction

eTable 5. Pathophysiologic Process: Abnormal Growth/Abnormal Cell Cycle

eTable 6. Pathophysiologic Process: Capillary/Vascular Dysfunction

eTable 7. Pathophysiologic Process: Toxicities

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eTable 27. Therapeutic Advances: Suspended Animation

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) |