**Combination Pulmonary Hypertension Drug Exposure in Critically Ill Infants**

**Supplementary Material**

 Supplementary Figure S1

Supplementary Table S1

 Supplementary Table S2

Supplementary Figure S2

 Supplementary Table S3

 Supplementary Table S4

 Supplementary Table S5

**Supplementary Figure S1.** Flow diagram of infants included in the study



Abbreviations: PH, pulmonary hypertension

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| **Supplementary Table S1. Therapy or Support At or Before First PH Medication Exposure** |
| **Therapy or Support** | **Monotherapy** | **Combination Therapy** | **p-Value** |
| (n = 7017) | (n = 664) |
| Postnatal steroids | 982 (14) | 221 (33) | <0.001 |
| Diuretics | 1003 (14) | 250 (38) | <0.001 |
| Inotropes | 1779 (25) | 231 (35) | <0.001 |
| Highest level of respiratory support |   |   |   |
|  Non-Invasive | 3272 (47) | 217 (33) | <0.001 |
|  Mechanical Ventilation | 3745 (53) | 447 (67) |
| Days on ventilator | 1 (0, 3) | 3 (0, 30) | <0.001 |
| FiO2 (%) | 75 (40, 100) | 70 (38, 100) | 0.09 |
| Days with FiO2 > 21% | 1 (0, 3) | 3 (0, 45) | <0.001 |
| Tracheostomy | 23 (0) | 15 (2) | <0.001 |
| ECMO | 13 (0) | 6 (1) | <0.001 |
| *Continuous and categorical variables presented as median (25th, 75th percentile) and frequency (%), respectively* |
| *ECMO, extracorporeal membrane oxygenation; FiO2, fraction of inspired oxygen; PH, pulmonary hypertension* |

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| **Supplementary Table S2. Combination Pulmonary Hypertension Medication Use** |
| **PH Medication Combination** | **N** | **Gestational Age** | **PNA at First Exposure** | **PMA at First Exposure** | **Duration of Use** | **Frequency of Use** |
| **iNO** | **Sildenafil** | **Epoprostenol** | **Bosentan** | **(Weeks)** | **(Days)** | **(Weeks)** | **(Days)** | **At Discharge** | **At Death** |
| ✓ | — | — | — | 7104 | 31 (26, 37) | 1 (0, 4) | 33 (27, 38) | 6 (4, 9) | 0 (0) | 957 (13) |
| — | ✓ | — | — | 968 | 27 (24, 36) | 73 (20, 117) | 40 (37, 43) | 25 (10, 54) | 437 (45) | 119 (12) |
| — | — | ✓ | — | 18 | 38 (35, 39) | 10 (3, 29) | 38 (36, 42) | 4 (2, 7) | 0 (0) | 4 (22) |
| — | — | — | ✓ | 6 | 32 (25, 39) | 108 (28, 141) | 44 (43, 46) | 16 (6, 34) | 0 (0) | 3 (50) |
| ✓ | ✓ | — | — | 599 | 28 (25, 36) | 45 (11, 107) | 39 (35, 42) | 11 (5, 26) | 0 (0) | 115 (48) |
| ✓ | — | ✓ | — | 45 | 37 (32, 38) | 2 (1, 11) | 38 (35, 39) | 6 (4, 10) | 0 (0) | 6 (33) |
| ✓ | — | — | ✓ | 5 | 30 (25, 34) | 132 (91, 172) | 43 (43, 47) | 11 (9, 26) | 0 (0) | 1 (33) |
| — | ✓ | ✓ | — | 13 | 38 (37, 38) | 15 (2, 29) | 40 (38, 42) | 9 (7, 19) | 0 (0) | 1 (17) |
| — | ✓ | — | ✓ | 33 | 28 (24, 36) | 161 (78, 198) | 48 (45, 53) | 55 (10, 84) | 17 (52) | 4 (44) |
| — | — | ✓ | ✓ | 0 | N/A | N/A | N/A | N/A | N/A | N/A |
| ✓ | ✓ | ✓ | — | 38 | 32 (26, 38) | 24 (2, 114) | 40 (36, 42) | 8 (6, 20) | 0 (0) | 10 (42) |
| ✓ | ✓ | — | ✓ | 49 | 26 (24, 30) | 135 (105, 177) | 45 (42, 50) | 14 (7, 33) | 0 (0) | 14 (48) |
| ✓ | — | ✓ | ✓ | 1 | 28 (28, 28) | 204 (204, 204) | 57 (57, 57) | 78 (78, 78) | 0 (0) | 0 (0) |
| — | ✓ | ✓ | ✓ | 2 | 38 (37, 39) | 33 (29, 37) | 42 (42, 43) | 26 (3, 48) | 0 (0) | 0 (0) |
| ✓ | ✓ | ✓ | ✓ | 7 | 28 (26, 38) | 94 (53, 173) | 46 (39, 50) | 131 (44, 286) | 0 (0) | 1 (14) |
| *Continuous and categorical variables presented as median (25th, 75th percentile) and frequency (%), respectively* |
| *iNO, inhaled nitric oxide; PH, pulmonary hypertension; PNA, postnatal age; PMA, postmenstrual age* |

**Supplementary Figure S2.** Alluvial flow diagram illustrating the dynamic changes in pulmonary hypertension medication combinations from initial to final exposure among all infants in our study. Each flow stream in the diagram represents a singular sequence and demonstrates the complex transitions of medication combinations over time. The height of a flow stream represents the number of unique sequences and not the frequency of occurrences for each sequence.



Abbreviations: B, bosentan; E, epoprostenol; I, inhaled nitrc oxide; S, sildenafil

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| **Supplementary Table S3. Any Pulmonary Hypertension Medication Use in Infants with BPD** |
| **Characteristic** | **iNO** | **Sildenafil** | **Epoprostenol** | **Bosentan** |
| (n = 2576) | (n = 883) | (n = 48) | (n = 74) |
| Gestational age (weeks) | 26 (24, 30) | 26 (24, 31) | 33 (26, 38) | 26 (24, 32) |
| PNA at first exposure (days) | 4 (0, 24) | 87 (35, 119) | 24 (2, 121) | 134 (91, 175) |
| PMA at first exposure (weeks) | 29 (26, 35) | 39 (36, 43) | 40 (36, 43) | 46 (42, 50) |
| Duration of use (days) | 8 (5, 19) | 40 (17, 78) | 12 (7, 40) | 32 (10, 85) |
| Frequency of use |   |   |   |   |
|  Any single use | 2455 (95) | 749 (85) | 8 (17) | 5 (7) |
|  Any combination use | 468 (18) | 460 (52) | 0 (0) | 72 (97) |
| At discharge | 0 (0) | 375 (42) | 0 (0) | 16 (22) |
|  In isolation | 0 (0) | 359 (96) | 0 (0) | 0 (0) |
|  In combination | 0 (0) | 16 (4) | 0 (0) | 16 (100) |
| At death | 180 (7) | 202 (23) | 15 (31) | 26 (35) |
|  In isolation | 76 (42) | 97 (48) | 15 (100) | 3 (12) |
|  In combination | 104 (58) | 105 (52) | 0 (0) | 23 (88) |
| *Continuous and categorical variables presented as median (25th, 75th percentile) and frequency (%), respectively* |
| *BPD, bronchopulmonary dysplasia; iNO, inhaled nitric oxide; PNA, postnatal age; PMA, postmenstrual age* |

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| **Supplementary Table S4. Any Pulmonary Hypertension Medication Use in Infants with CHD** |
| **Characteristic** | **iNO** | **Sildenafil** | **Epoprostenol** | **Bosentan** |
| (n = 1032) | (n = 297) | (n = 18) | (n = 15) |
| Gestational age (weeks) | 32 (26, 37) | 30 (25, 37) | 33 (26, 38) | 29 (25, 35) |
| PNA at first exposure (days) | 1 (0, 9) | 54 (15, 104) | 20 (4, 138) | 94 (69, 133) |
| PMA at first exposure (weeks) | 34 (28, 38) | 39 (36, 42) | 38 (36, 42) | 44 (42, 45) |
| Duration of use (days) | 6 (4, 12) | 27 (12, 54) | 12 (7, 39) | 25 (10, 62) |
| Frequency of use |   |   |   |   |
|  Any single use | 995 (96) | 249 (84) | 3 (17) | 1 (7) |
|  Any combination use | 155 (15) | 153 (52) | 17 (94) | 0 (0) |
| At discharge | 0 (0) | 120 (40) | 0 (0) | 3 (20) |
|  In isolation | 0 (0) | 117 (98) | 0 (0) | 0 (0) |
|  In combination | 0 (0) | 3 (2) | 0 (0) | 3 (100) |
| At death | 189 (18) | 64 (22) | 6 (33) | 4 (27) |
|  In isolation | 153 (81) | 27 (42) | 1 (17) | 4 (100) |
|  In combination | 36 (19) | 37 (58) | 5 (83) | 0 (0) |
| *Continuous and categorical variables presented as median (25th, 75th percentile) and frequency (%), respectively* |
| *CHD, congenital heart disease; iNO, inhaled nitric oxide; PNA, postnatal age; PMA, postmenstrual age* |

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| **Supplementary Table S5. Any Pulmonary Hypertension Medication Use in Infants with CDH** |
| **Characteristic** | **iNO** | **Sildenafil** | **Epoprostenol** | **Bosentan** |
| (n = 276) | (n = 97) | (n = 21) | (n = 14) |
| Gestational age (weeks) | 38 (37, 39) | 38 (37, 39) | 38 (36, 39) | 37 (37, 39) |
| PNA at first exposure (days) | 0 (0, 1) | 15 (7, 26) | 3 (1, 21) | 34 (28, 54) |
| PMA at first exposure (weeks) | 38 (37, 39) | 40 (38, 41) | 39 (37, 40) | 43 (42, 46) |
| Duration of use (days) | 10 (6, 20) | 39 (17, 60) | 10 (6, 19) | 38 (11, 82) |
| Frequency of use |   |   |   |   |
|  Any single use | 258 (93) | 72 (74) | 6 (29) | 1 (7) |
|  Any combination use | 75 (27) | 72 (74) | 18 (86) | 13 (93) |
| At discharge | 0 (0) | 36 (37) | 0 (0) | 4 (29) |
|  In isolation | 0 (0) | 32 (89) | 0 (0) | 0 (0) |
|  In combination | 0 (0) | 4 (11) | 0 (0) | 4 (100) |
| At death | 59 (21) | 20 (21) | 5 (24) | 1 (7) |
|  In isolation | 43 (73) | 5 (25) | 2 (40) | 1 (100) |
|  In combination | 16 (27) | 15 (75) | 3 (60) | 0 (0) |
| *Continuous and categorical variables presented as median (25th, 75th percentile) and frequency (%), respectively* |
| *CDH, congenital diaphragmatic hernia; iNO, inhaled nitric oxide; PNA, postnatal age; PMA, postmenstrual age* |