Smaller is Better?

Antimicrobial Stewardship in the Neonatal Intensive Care Unit

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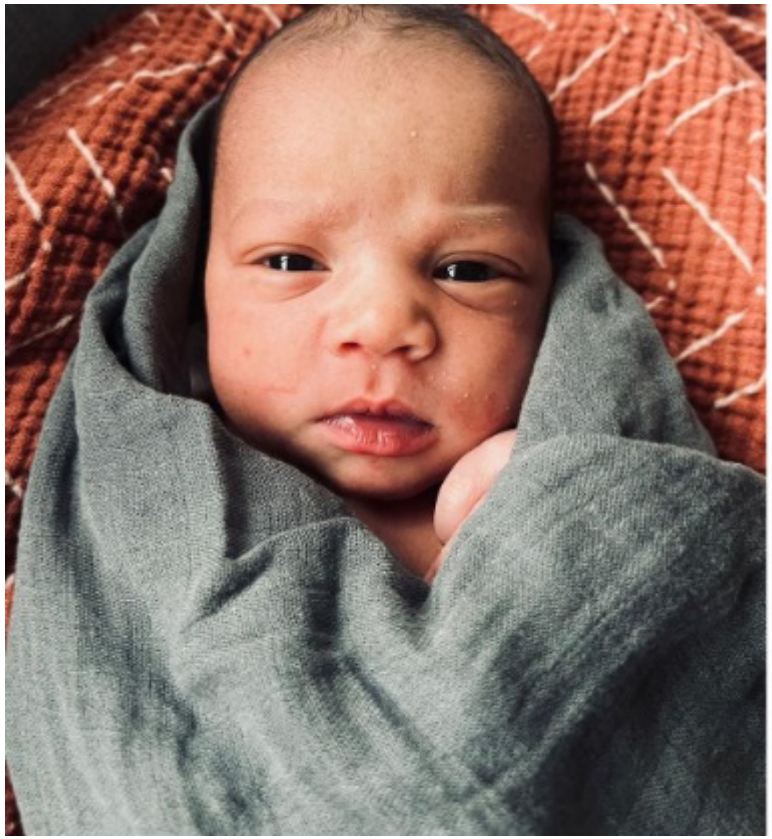
MEMORIAL HERMANN

Disclosures

No financial relationships to disclose

First newborns of 2024!

Griffin Beck Golemon



Teleio James Carter

Photo credit: KHOU

-Getty Images

Neonatal ICU (NICU) Definitions

Low birth weight (LBW) less then 2500 grams

- Very low birth weight <1500 grams
- Extremely low birth weight <1000 grams

Preterm birth before 37 weeks completed weeks of gestation

- Moderate or late preterm 32 to <37 weeks
- Very preterm 28 to <32 weeks
- Extremely preterm <28 weeks

https://www.who.int/publications/i/item/WHO-NMH-NHD-14.5
https://www.who.int/news-room/fact-sheets/detail/preterm-birth

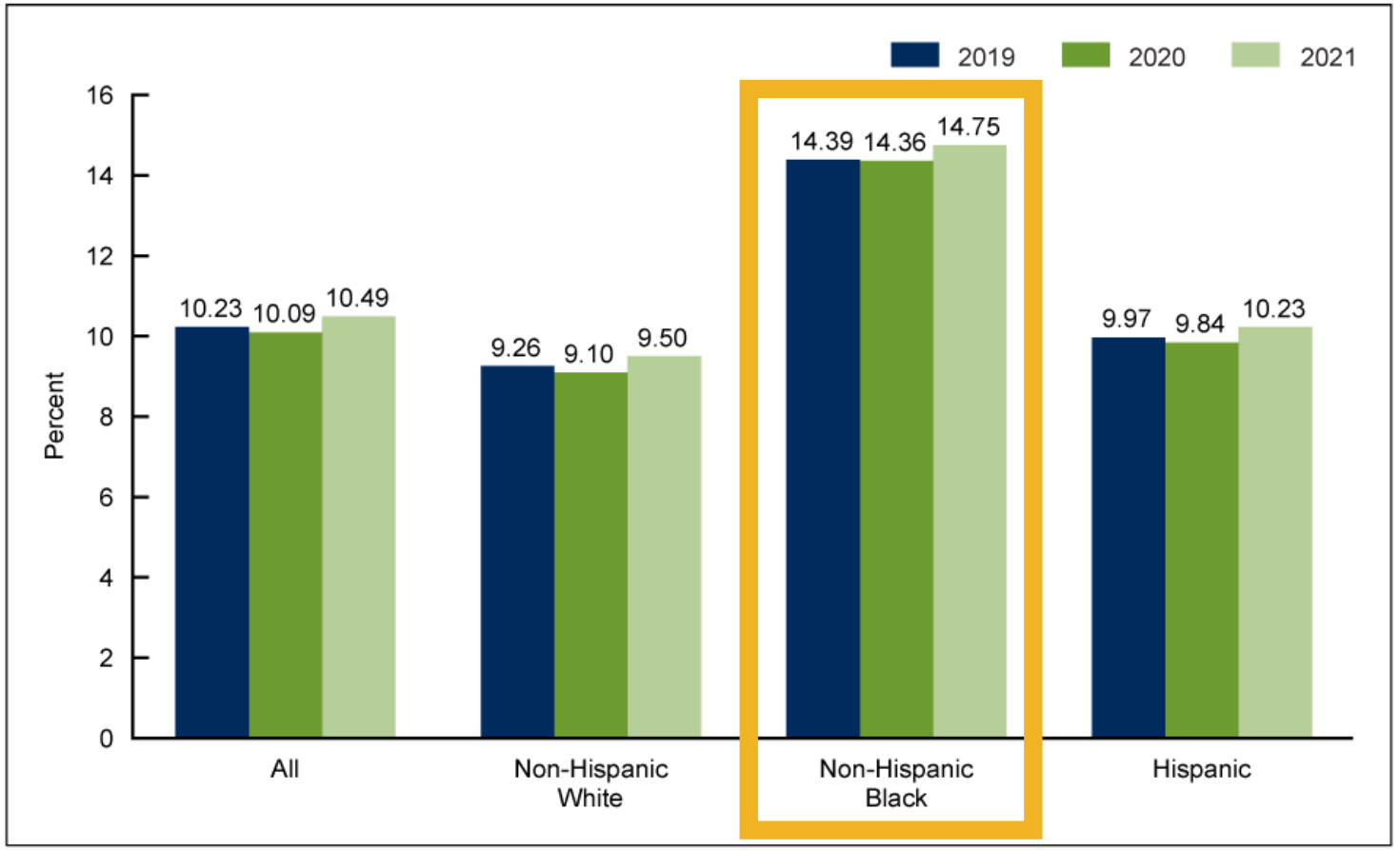
NICU – Burden & Volume

3.6 million live births in the United States 2020

9-13% of infants require neonatal intensive care (324K to 468,000)

- Disproportionate effect on non-Hispanic Black mothers

Figure 4. Percentage of preterm births, by race and Hispanic origin of mother: United States, 2019–2021



NOTES: Significant declines from 2019 to 2020 for all groups except non-Hispanic Black ($p < 0.05$). Significant increases for all groups from 2020 to 2021 ($p < 0.05$). Significant difference between all race and Hispanic-origin groups for all years ($p < 0.05$). Preterm is less than 37 completed weeks of gestation. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db442_tables.pdf#4.
SOURCE: National Center for Health Statistics, National Vital Statistics System, Natality.

Risk for infection – Preterm infants

Preterm infants have **immature and dysregulated**:

- Skin and mucosal barriers (microbiome, breast milk bioactive molecules)
- innate inflammatory response
- cellular innate immunity
- adaptive immunity
- B cells / immunoglobulins (class switching, polysaccharide responses)

Collins A et al. *Why are preterm newborns at increased risk of infection?* Archives of Disease in Childhood - Fetal and Neonatal Edition 2018;103:F391-F394.

Risk for infection – Preterm infants

Preterm infants are more likely:

To have bacteremia / bloodstream infection

Increased mortality from bacterial sepsis

Melanie C. Marsh et al; Preterm and Term Infants Evaluated for Sepsis: Differences in Management and Clinical Outcomes. *Hosp Pediatr* June 2023; 13 (6): 544–554. https://doi.org/10.1542/hpeds.2022-007050

Agyeman PKA et al. Swiss Pediatric Sepsis Study. Epidemiology of blood culture-proven bacterial sepsis in children in Switzerland: a population-based cohort study. *Lancet Child Adolesc Health*. 2017 Oct;1(2):124-133. doi: 10.1016/S2352-4642(17)30010-X.

Neonatal Sepsis

No consensus definition for neonatal sepsis

- Neonatal bacteremia, pneumonia, meningitis, other focal serious bacterial infections

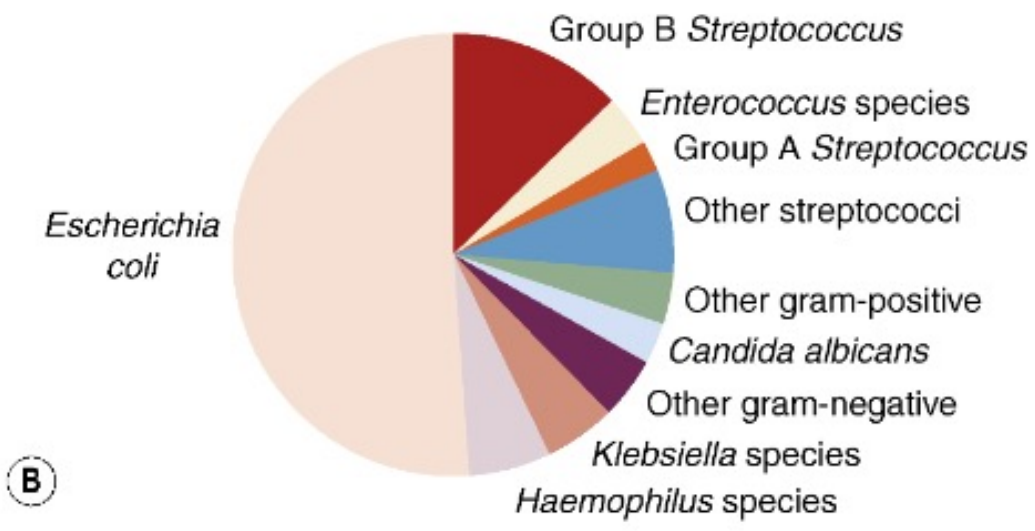
Early onset sepsis <72 hours (0.3-1.0 per 1000 neonates)

Late onset sepsis >72 hours (2.2 per 1000)

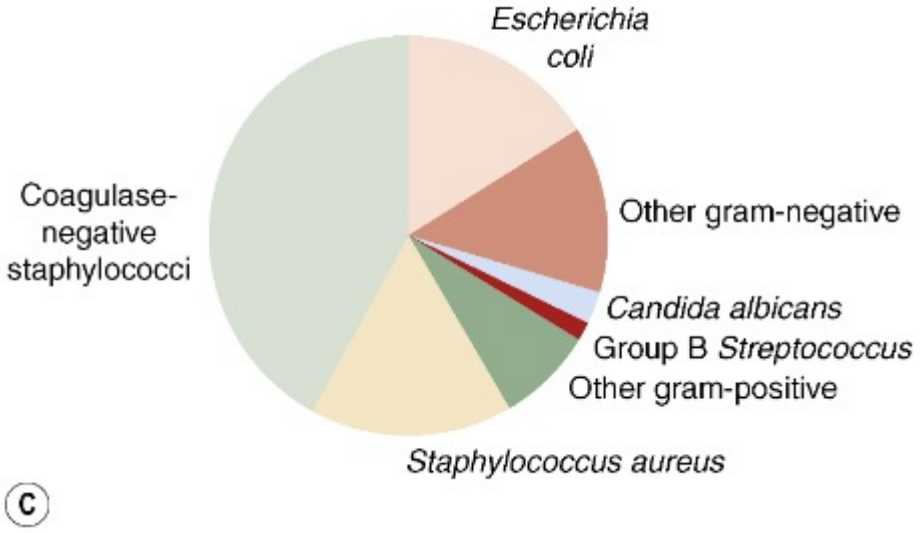
Benitez WE, Clinical Approach to the Neonate with Suspected Infection. Principles and Practice of Pediatric Infectious Diseases 6th Ed, 90, 561-564.e1

Neonatal Sepsis - Etiologies

Early onset sepsis in preterm infants



Hospital-acquired late onset sepsis



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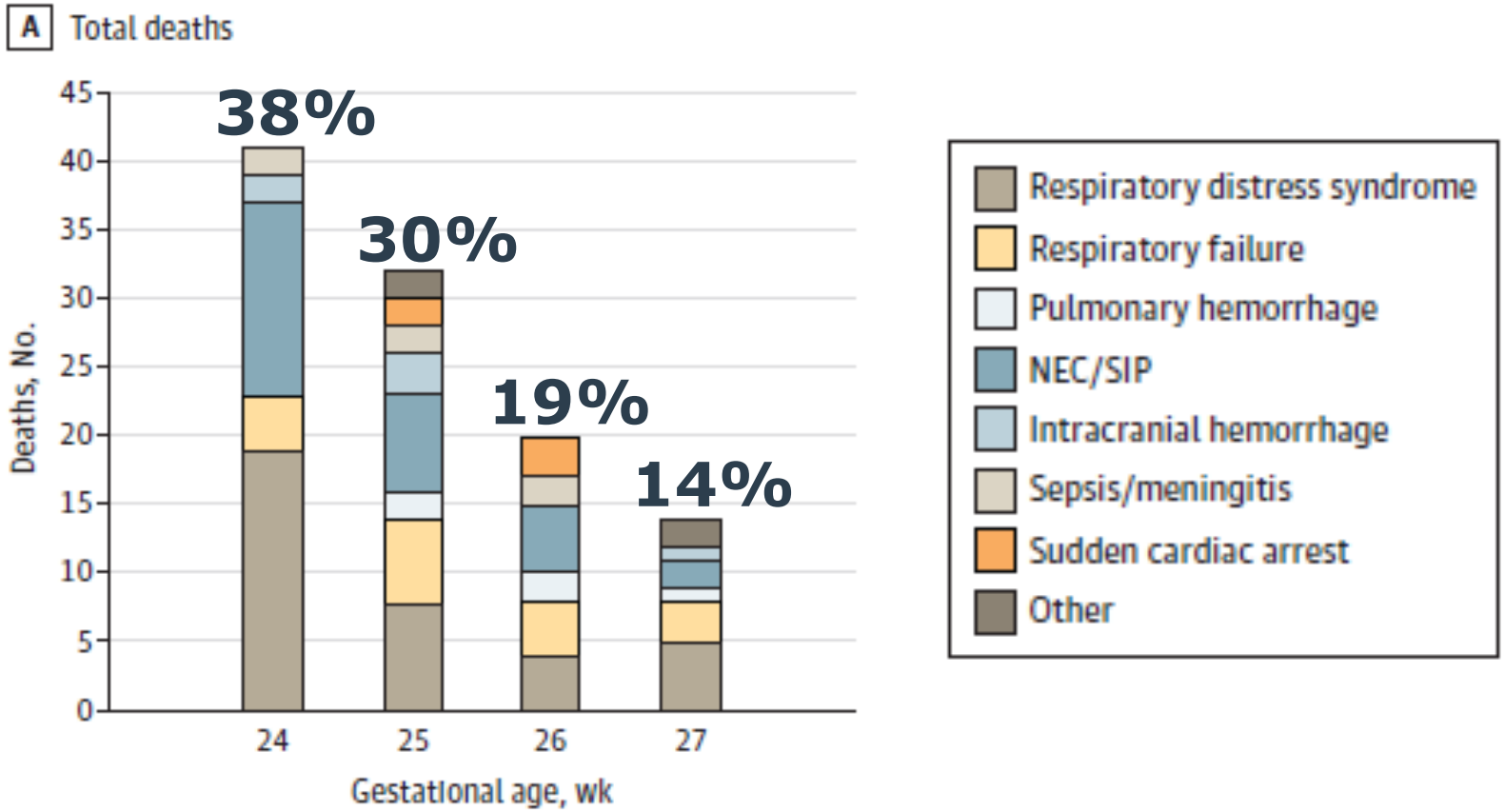
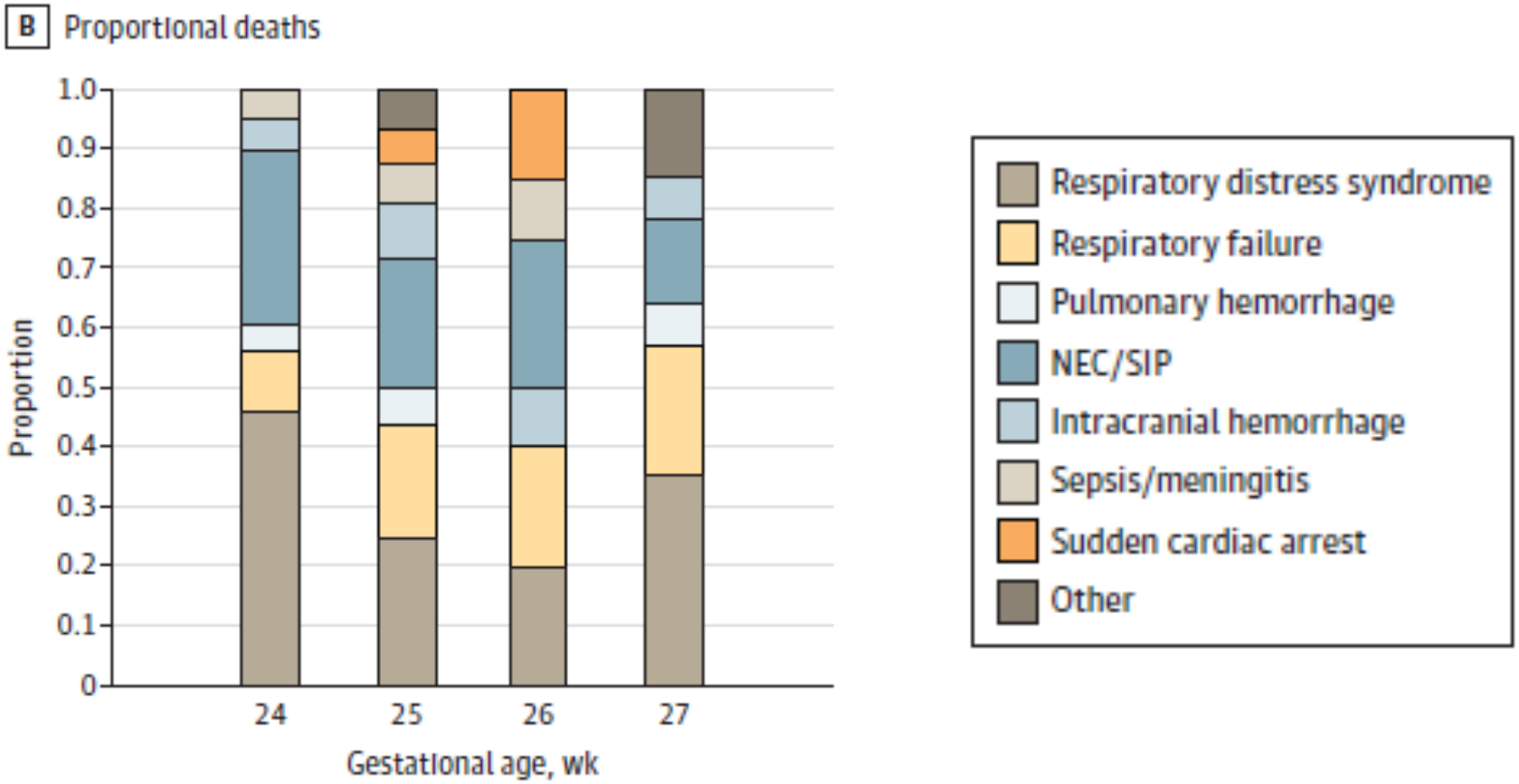
NICU Mortality



Juul SE et al. Deaths in a Modern Cohort of Extremely Preterm Infants From the Preterm Erythropoietin Neuroprotection Trial. *JAMA Netw Open*. 2022;5(2):e2146404. doi:10.1001/jamanetworkopen.2021.46404

NICU Mortality



Juul SE et al. Deaths in a Modern Cohort of Extremely Preterm Infants From the Preterm Erythropoietin Neuroprotection Trial. *JAMA Netw Open*. 2022;5(2):e2146404. doi:10.1001/jamanetworkopen.2021.46404

Diagnostic Difficulty

Table 90.1

Minor and Major Signs of Illness in the First Several Hours After Birth

Adapted, with permission, from Berardi A *et al* : Serial clinical observation for management of newborns at risk of early-onset sepsis . *Curr Opin Pediatr* 2020;32:245.

Minor	Major
Tachypnea (>60/minute) without increased respiratory effort Tachycardia >160/minute Metabolic acidosis (BE ≤–10 mmol/L) Temperature <36.0°C or 37.5°–38.8°C	Moderate/severe respiratory distress (requiring respiratory support), tachypnea with increased respiratory effort Hypoxemia, reduced O_2 saturation Reduced skin perfusion, capillary refill time >3 seconds, signs of shock Temperature >38.8°C Worsening of general well-being, apnea, lethargy, irritability, convulsions Grey, pale, or mottled skin color

Benitez WE, Clinical Approach to the Neonate with Suspected Infection. Principles and Practice of Pediatric Infectious Diseases 6th Ed, 90, 561-564.e1

Diagnostic Difficulty

Lack of localizing symptoms for focal infections

Blood cultures improperly obtained?

Non-culture based biomarkers lack sensitivity and/or specificity


-Getty Images

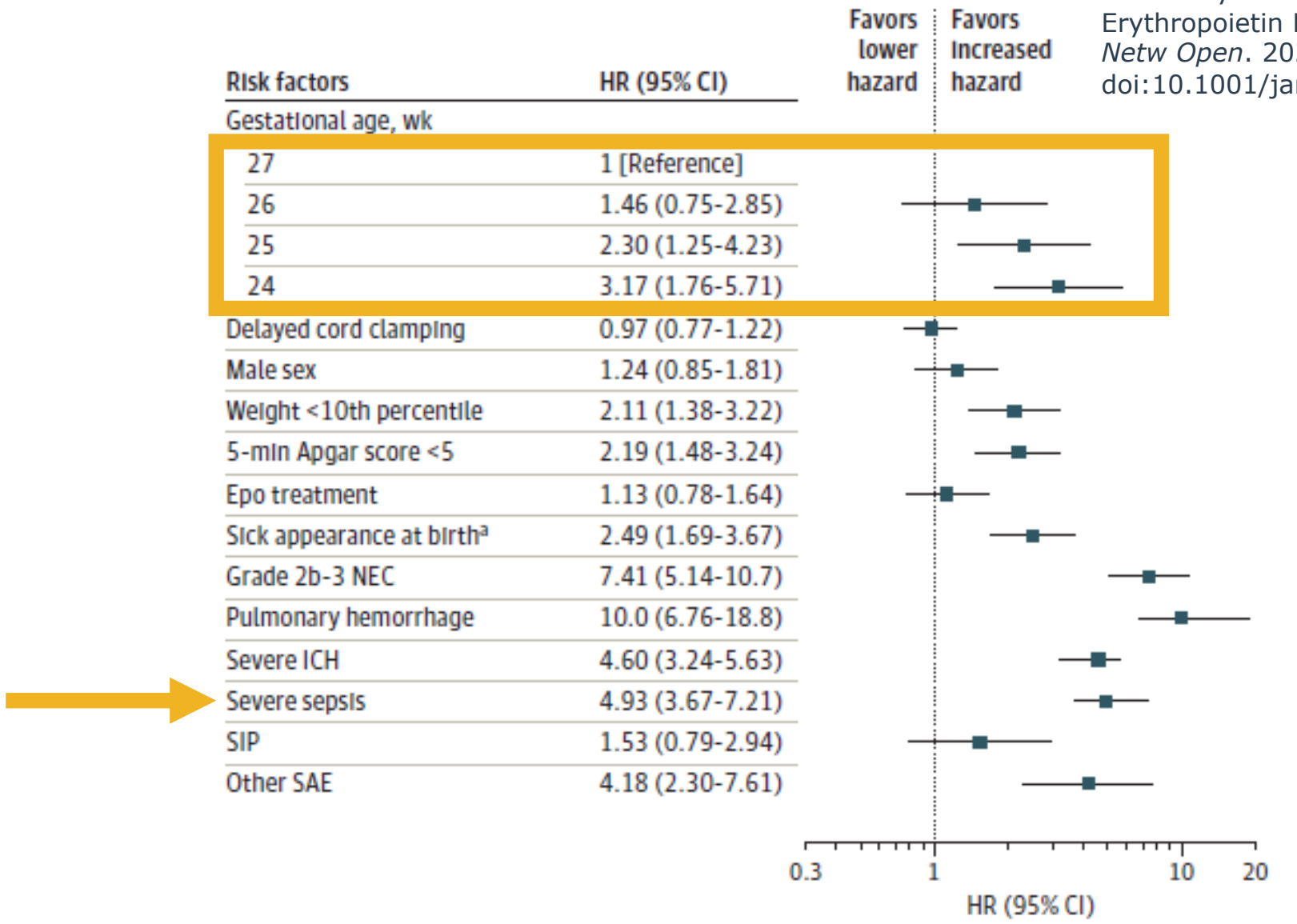
Camacho-Gonzalez A et al. Neonatal infectious diseases: evaluation of neonatal sepsis. Pediatr Clin North Am. 2013 Apr;60(2):367-89. doi: 10.1016/j.pcl.2012.12.003.

Joseph B. Cantey, John H. Lee, Biomarkers for the Diagnosis of Neonatal Sepsis, *Clinics in Perinatology*, Volume 48, Issue 2, 2021, Pages 215-227

Woodford, E.C. et al. Neonatal blood culture inoculant volume: feasibility and challenges. *Pediatr Res* **90**, 1086–1092 (2021). https://doi.org/10.1038/s41390-021-01484-9

NICU Acuity

Juul SE et al. Deaths in a Modern Cohort of Extremely Preterm Infants From the Preterm Erythropoietin Neuroprotection Trial. *JAMA Netw Open*. 2022;5(2):e2146404. doi:10.1001/jamanetworkopen.2021.46404



MEMORIAL HERMANN

NHSN NICU acuity level

- Level I Well Newborn-Nursery
  - Hospital area for evaluation and postnatal care of healthy newborns. May include neonatal resuscitation and stabilization of ill newborns until transfer to a facility at which specialty neonatal care is provided.
- Level II Special Care Nursery
  - Provide care for infants born ≥32 wks. gestation and weighing ≥1500 g who have physiologic immaturity or who are moderately ill with problems that are expected to resolve rapidly and are not anticipated to need subspecialty services on an urgent basis
  - Provide care for infants convalescing after intensive care
  - Provide mechanical ventilation for brief duration (<24 h) or continuous positive airway pressure or both
  - Stabilize infants born before 32 wks. gestation and weighing less than 1500 g until transfer to a neonatal intensive care facility

https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf

NHSN NICU acuity level

- Level III Neonatal Critical Care
  - Provide sustained life support
  - Provide comprehensive care for infants born <32 wks. gestation and weighing <1500 g and infants born at all gestational ages and birth weights with critical illness
  - Provide prompt and readily available access to a full range of pediatric medical subspecialists, pediatric surgical specialists, pediatric anesthesiologists, and pediatric ophthalmologists
  - Provide a full range of respiratory support that may include conventional and/or high-frequency ventilation and inhaled nitric oxide
  - Perform advanced imaging, with interpretation on an urgent basis, including computed tomography, MRI, and echocardiography

https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf

NHSN NICU acuity level

- Level IV Neonatal Critical Care supervised by neonatologist
  - Located within an institution with the capability to provide surgical repair of complex congenital or acquired conditions
  - Maintain a full range of pediatric medical subspecialists, pediatric surgical subspecialists, and pediatric subspecialists at the site
  - Facilitate transport and provide outreach education

https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf

Children’s Memorial Hermann Hospital

~1000 admissions per year to the Children’s Memorial Hermann Hospital NICU

All beds are Level IV beds

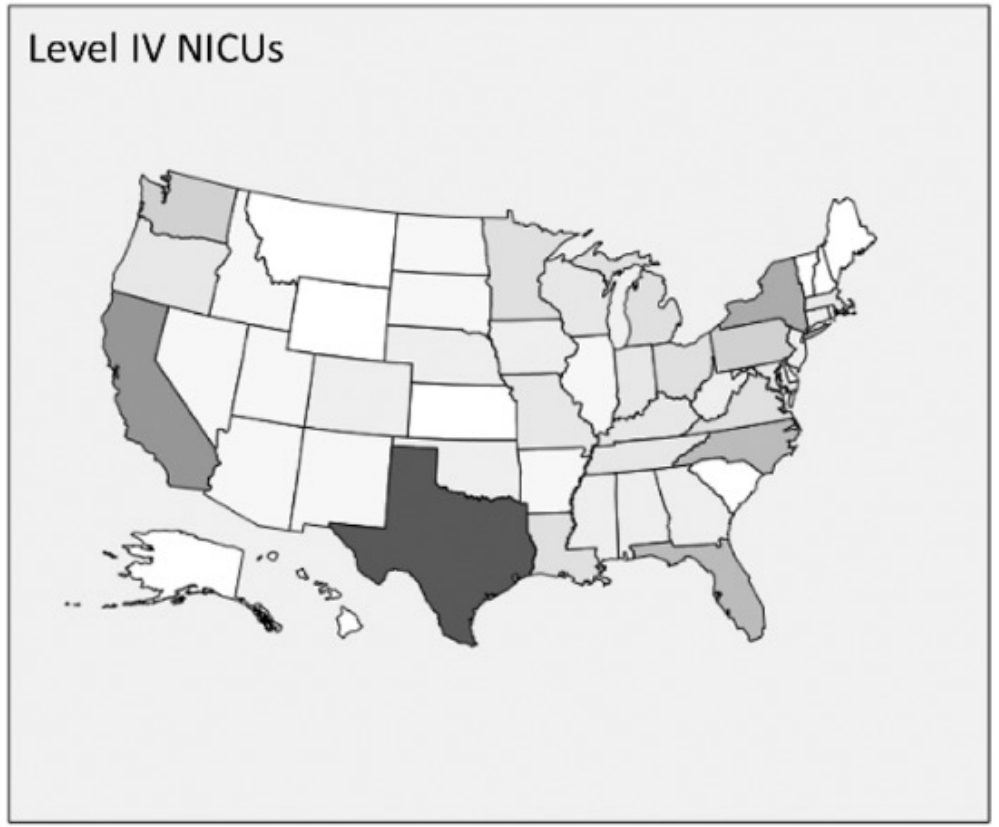
85% preterm (<37 weeks)

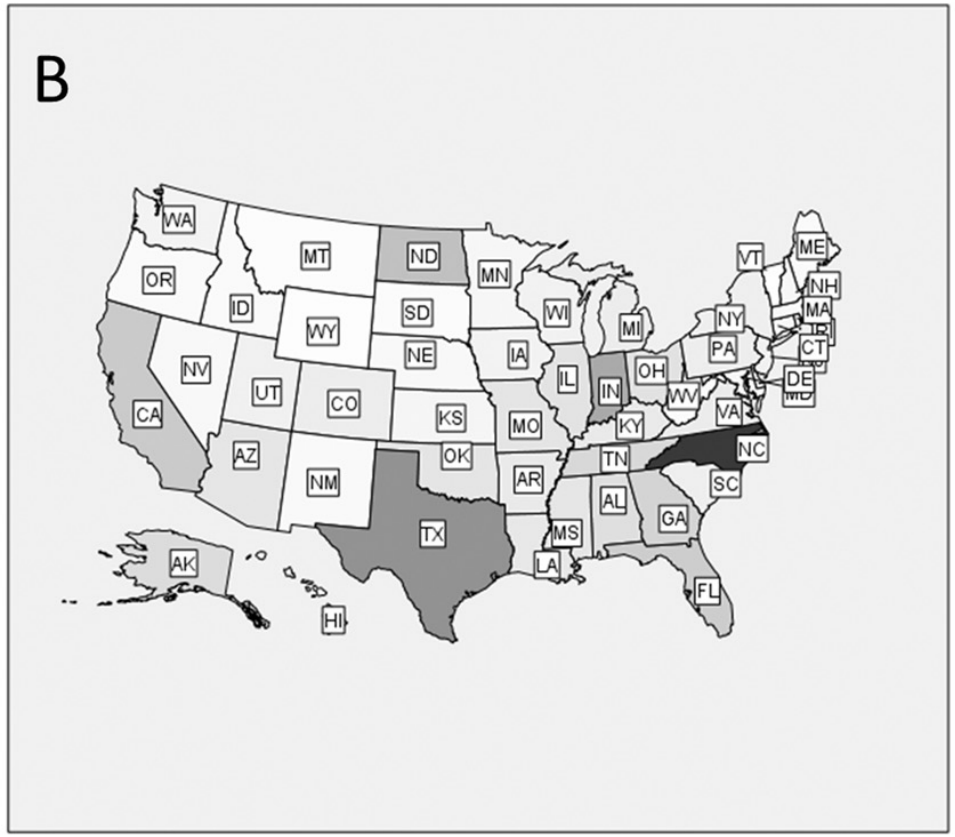
50% very preterm (<32 weeks)

34% extremely preterm (<28 weeks)

80% survival at 28 weeks
50% survival at 25 weeks (12% of CMHH NICU population)

National Healthcare Safety Network (NHSN) NICU acuity level





11% of NICU beds across the country are Level IV beds

Pineda, R., Kati Knudsen, Breault, C.C. *et al.* NICUs in the US: levels of acuity, number of beds, and relationships to population factors. *J Perinatol* **43**, 796–805 (2023). https://doi.org/10.1038/s41372-023-01693-6

CMHH NICU Antibiotic Utilization

PSL Specific Code - Title	Total Patient Days	Cases Rec'd Antibiotics	DOT/1,000 pt days	% of Total DOT/1,000 pt days
106 - Neonates w/ECMO or Major Px	10,779	182	573.15	18.20%
901 - Infectious Disease - Medical	4,237	458	1,305.88	16.30%
103 - Neonates w/Major Anomaly/Resp Condition - Medical	14,034	352	179.56	7.42%
401 - Respiratory - Medical	4,042	382	598.22	7.12%
302 - Cardiothoracic - Surgical	2,661	164	869.22	6.81%
702 - Gastroenterology - Surgical	1,849	249	839.91	4.57%
102 - Neonates w/Extreme Immaturity - Medical	5,707	68	232.00	3.90%

NHSN AUR Module

Risk-adjusted inter- and intra-facility antimicrobial use benchmarking

Evaluate antimicrobial use trends over time at the facility and national levels

Primary metric

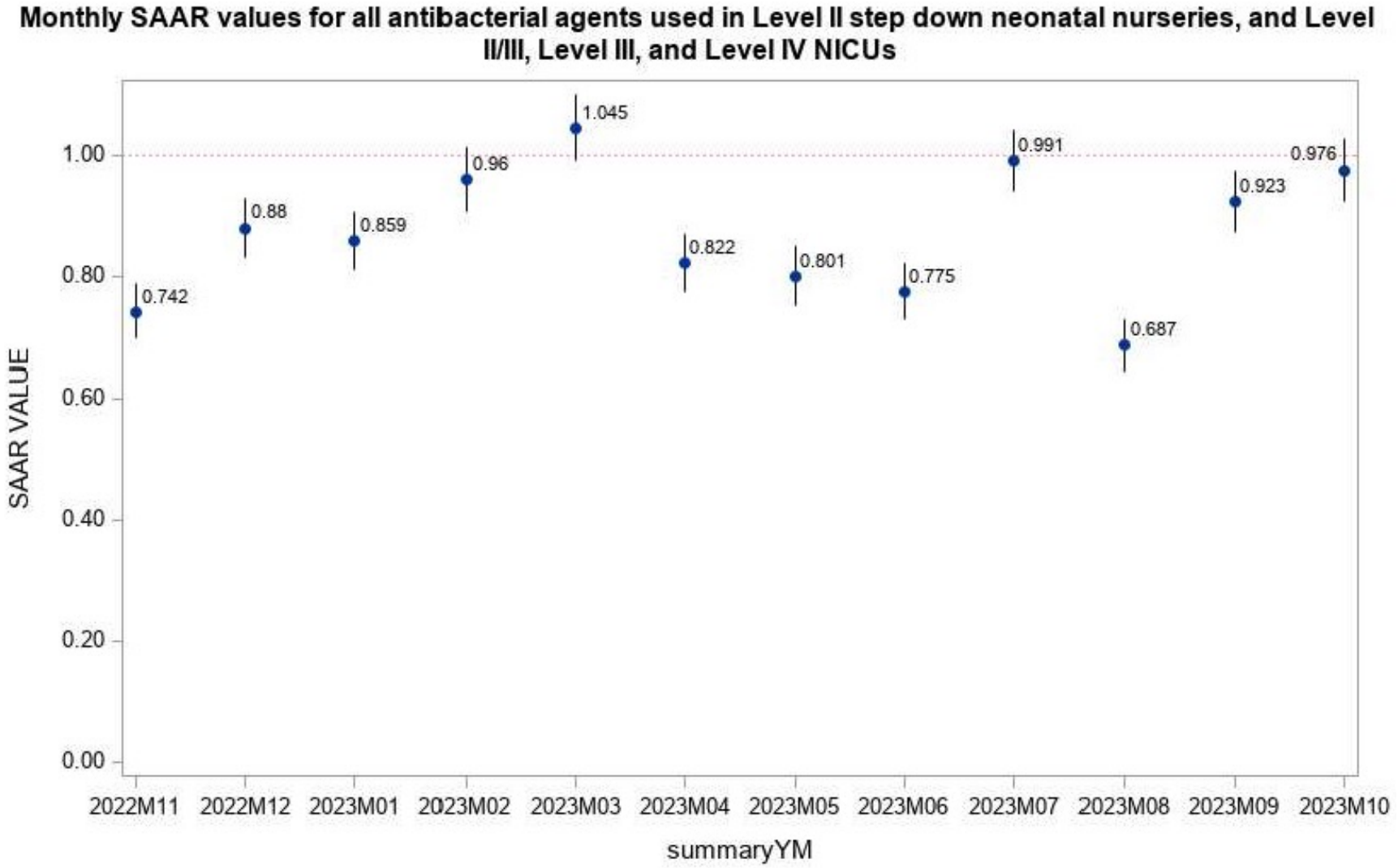
Antimicrobial days per 1,000 days present

NHSN AUR Module

Location type	Neonatal locations
Special Care Nurseries	56
Level II/III intensive care units	152
Level III (Or IV) intensive care units	116
Total	324

$$SAAR = \frac{Observed\ Antimicrobial\ Use}{Predicted\ Antimicrobial\ Use}$$

NHSN AU SAAR – CMHH NICU



Preterm infants are broadly exposed to antibiotics

Ampicillin and gentamicin are the most frequently prescribed medications in the NICU

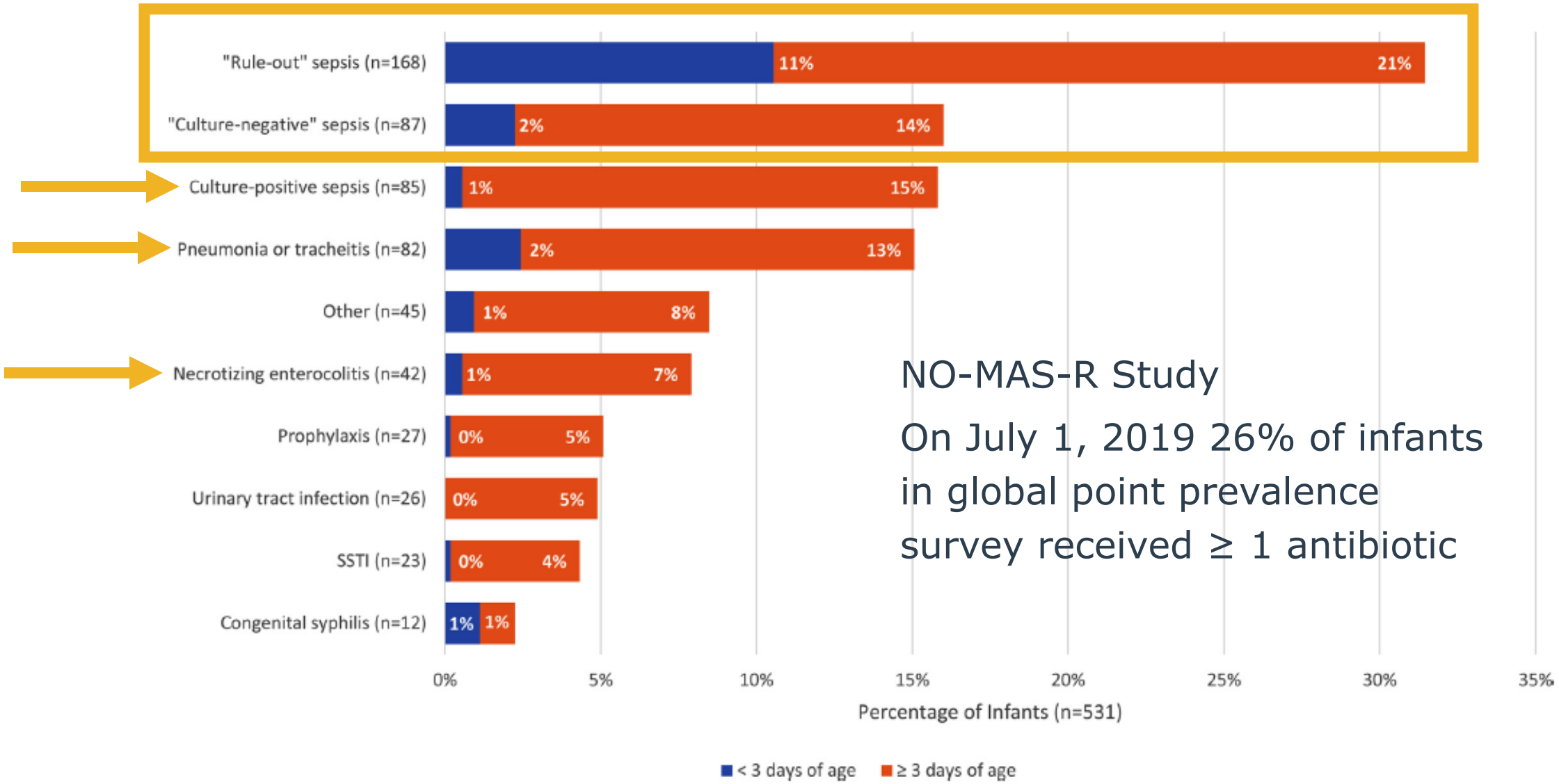
~ 60% of all NICU infants receive antibiotics during their hospitalization

79% of antimicrobials administered in the NICU is off-label or unlicensed

Reese H. Clark et al; Reported Medication Use in the Neonatal Intensive Care Unit: Data From a Large National Data Set. *Pediatrics* June 2006; 117 (6): 1979–1987. 10.1542/peds.2005-1707

Boverman G et al. Neonatal ICU antibiotic use trends within an integrated delivery network. *Antimicrob Resist Infect Control*. 2022 Jan 31;11(1):21. doi: 10.1186/s13756-022-01057-3

Costa HTML et al. Use of off-label and unlicensed medicines in neonatal intensive care. PLoS One. 2018 Sep 25;13(9):e0204427. doi: 10.1371/journal.pone.0204427



NO-MAS-R Study

On July 1, 2019 26% of infants in global point prevalence survey received ≥ 1 antibiotic

Prusakov P et al. Global NEO-ASP Study Group. A global point prevalence survey of antimicrobial use in neonatal intensive care units: The no-more-antibiotics and resistance (NO-MAS-R) study. *EClinicalMedicine*. 2021 Jan 29;32:100727. doi: 10.1016/j.eclinm.2021.100727

Harms of antibiotic administration in neonates

C. Michael Cotton et al, for the NICHD Neonatal Research Network; Prolonged Duration of Initial Empirical Antibiotic Treatment Is Associated With Increased Rates of Necrotizing Enterocolitis and Death for Extremely Low Birth Weight Infants. Pediatrics January 2009; 123 (1): 58–66. 10.1542/peds.2007-3423

TABLE 2 Duration of Initial Empirical Antibiotic Treatment and Frequency of Prolonged Initial Empirical Antibiotic Treatment According to Network Center ($N = 4039$)

Center	Duration of Initial Empirical Antibiotic Treatment, Median (Range), d	Prolonged Initial Empirical Antibiotic Course (≥5 d), %[a]
1	6 (2–21)	55
2	4 (2–11)	49
3	8 (1–33)	73
4	5 (1–33)	56
5	7 (1–36)	73
6	7 (3–29)	68
7	4 (2–17)	38
8	6 (1–26)	55
9	4 (2–26)	47
10	6 (1–15)	55
11	3 (2–26)	29
12	4 (2–19)	49
13	4 (2–22)	43
14	4.5 (2–23)	50
15	5 (2–32)	54
16	9.5 (2–17)	85
17	4 (2–33)	27
18	4.5 (2–15)	50
19	7 (3–21)	72
Total	5 (1–36)	53 ($N = 2147$)

[a] Proportion of infants included in the study cohort ($P < .001$ for center differences).

Harms of antibiotic administration in neonates

TABLE 5 Multivariate Logistic Regression Analysis of Antibiotic Duration and NEC or Death

Outcome	Duration of Initial Empirical Antibiotic Treatment (Odds per Day)		Prolonged Initial Empirical Antibiotic Treatment	
	OR (95% CI)	*P*	OR (95% CI)	*P*
NEC or death (total, $N = 3883$; with outcome, $n = 884$)	1.04 (1.02–1.06)	<.01	1.30 (1.10–1.54)	<.01
NEC (total, $N = 3899$; with outcome, $n = 427$)	1.07 (1.04–1.10)	<.001	1.21 (0.98–1.51)	.08
Death (total, $N = 3882$; with outcome, $n = 631$)	1.16 (1.08–1.24)	<.001	1.46 (1.19–1.78)	<.001

C. Michael Cotton et al, for the NICHD Neonatal Research Network; Prolonged Duration of Initial Empirical Antibiotic Treatment Is Associated With Increased Rates of Necrotizing Enterocolitis and Death for Extremely Low Birth Weight Infants. Pediatrics January 2009; 123 (1): 58–66. 10.1542/peds.2007-3423

Harms of antibiotic administration in neonates

Table II. Characteristics of infants with or without the composite outcome of late-onset sepsis, NEC, and death

	Composite outcome (sepsis, NEC, or death >14 days of age)		
	Yes	No	*P* value
n			
Maternal age, years	28 (22-32)	28 (22-33)	.66
Maternal parity	2 (1-3)	2 (1-3)	.40
Maternal hypertension	33 (47%)	133 (44%)	.69
Maternal chorioamnionitis	6 (9%)	32 (11%)	.71
Maternal betamethasone	35 (50%)	139 (41%)	.41
Prolonged rupture of membranes (≥18 hours)	12 (17%)	58 (19%)	.66
Intrapartum antibiotic prophylaxis	35 (50%)	161 (46%)	.66
Vaginal delivery	20 (29%)	79 (26%)	.62
Birth weight, grams	895 (787-1225)	1160 (940-1330)	<.0001
Gestational age, weeks	28 (25-30)	29 (27-30)	.001
Multiple gestation	15 (21%)	75 (25%)	.18
Male sex	50 (71%)	149 (49%)	.002
1-minute Apgar	4 (2-5)	5 (3-6)	.0013
5-minute Apgar	6 (4-8)	7 (6-8)	<.0001
Spontaneous intestinal perforation	2 (3%)	6 (2%)	.65
Days of mechanical ventilation	9 (4-16)	6 (2-12)	<.0001
Days of vasopressor medication (range)	0 (0-11)	0 (0-6)	.22
Central line days	14 (9-23)	10 (7-18)	.003
Days to full enteral feeding	13 (8-19)	9 (7-15)	<.0001
CRIB II score	10 (7-12)	7 (5-10)	.0001
CRIB II score predicted mortality risk	12% (4-25%)	4% (1-12%)	.0001
DOT ≤14 days of age, median (range)	14 (4-42)	5.5 (0-25)	<.0001
LOT ≤14 days of age, median (range)	7 (2-14)	3 (0-14)	<.0001
Length of stay, days	91 (73-127)	70 (51-97)	.0001

Data shown as median (IQR) or percentage unless otherwise indicated.

Composite outcome sepsis, NEC, or death > 14 days of age
Late-onset sepsis

DOT ≤ 14 days of age 14 versus 5.5 (p<0.0001)

LOT ≤ 14 days of age 7 versus 3 (p<0.0001)

Joseph B. Cantey et al, Early Antibiotic Exposure and Adverse Outcomes in Preterm, Very Low Birth Weight Infants, The Journal of Pediatrics, Volume 203, 2018, Pages 62-67, doi.org/10.1016/j.jpeds.2018.07.036

Harms of antibiotic administration in neonates

TABLE 3 Distribution of Mortality and Morbidities and the Composite Outcome Among VLBW Infants

Outcome	Antibiotic Exposure			aOR[a] (95% CI) 1–3 d Versus None[b]	aOR[a] (95% CI) 4–7 d Versus None[b]	aOR[a] (95% CI) 4–7 d Versus 1–3 d[c]
	None (N = 2950), n (%)	1–3 d (N = 5401), n (%)	4–7 d (N = 5856), n (%)			
Composite outcome[d]	646 (22)	1987 (37)	3403 (58)	0.90 (0.79–1.02)	1.24 (1.09–1.41)	1.38 (1.25–1.51)
Composite outcome II[e]	631 (21)	1935 (36)	3334 (57)	0.89 (0.78–1.00)	1.21 (1.06–1.37)	1.36 (1.24–1.50)
Mortality after 7 d of age	30 (1)	144 (3)	354 (6)	1.11 (0.72–1.69)	1.20 (0.78–1.83)	1.08 (0.87–1.34)
Severe neurologic injury[f]	55 (2)	255 (5)	564 (10)	1.48 (1.08–2.03)	1.87 (1.37–2.57)	1.27 (1.07–1.50)
PDA requiring treatment	263 (9)	1101 (20)	2004 (34)	1.16 (0.98–1.38)	1.29 (1.09–1.53)	1.11 (0.99–1.23)
Greater than or equal to stage 2 NEC	81 (3)	177 (3)	273 (5)	0.74 (0.55–0.99)	0.75 (0.56–1.02)	1.02 (0.83–1.25)
HAI	258 (9)	666 (12)	1149 (20)	0.83 (0.70–0.99)	0.93 (0.78–1.10)	1.11 (0.99–1.25)
CLD	391 (16)	1358 (27)	2497 (46)	0.89 (0.77–1.03)	1.22 (1.06–1.41)	1.37 (1.25–1.51)
Greater than or equal to stage 3 ROP or ROP treated	42 (3)	203 (7)	580 (14)	0.76 (0.52–1.11)	0.98 (0.68–1.42)	1.29 (1.07–1.56)
PVL	31 (1)	111 (2)	219 (4)	1.26 (0.82–1.94)	1.49 (0.97–2.30)	1.18 (0.92–1.52)

[a] Adjusted for GA, SNAP-II score >20, extensive CPR, PROM ≥24 h, multiple births, surfactant use, mechanical ventilation for all first 3 d, inotropes in any of first 3 d, iNO in any of first 3 d, and pneumothorax treated with chest tube in a logistic regression model (significant variables identified by using univariate tests between 0, 1–3, and 4–7 d). Chorioamnionitis was not included in the model because of too many missing values.

[b] Reference is 0 d.

[c] Reference is 1–3 d.

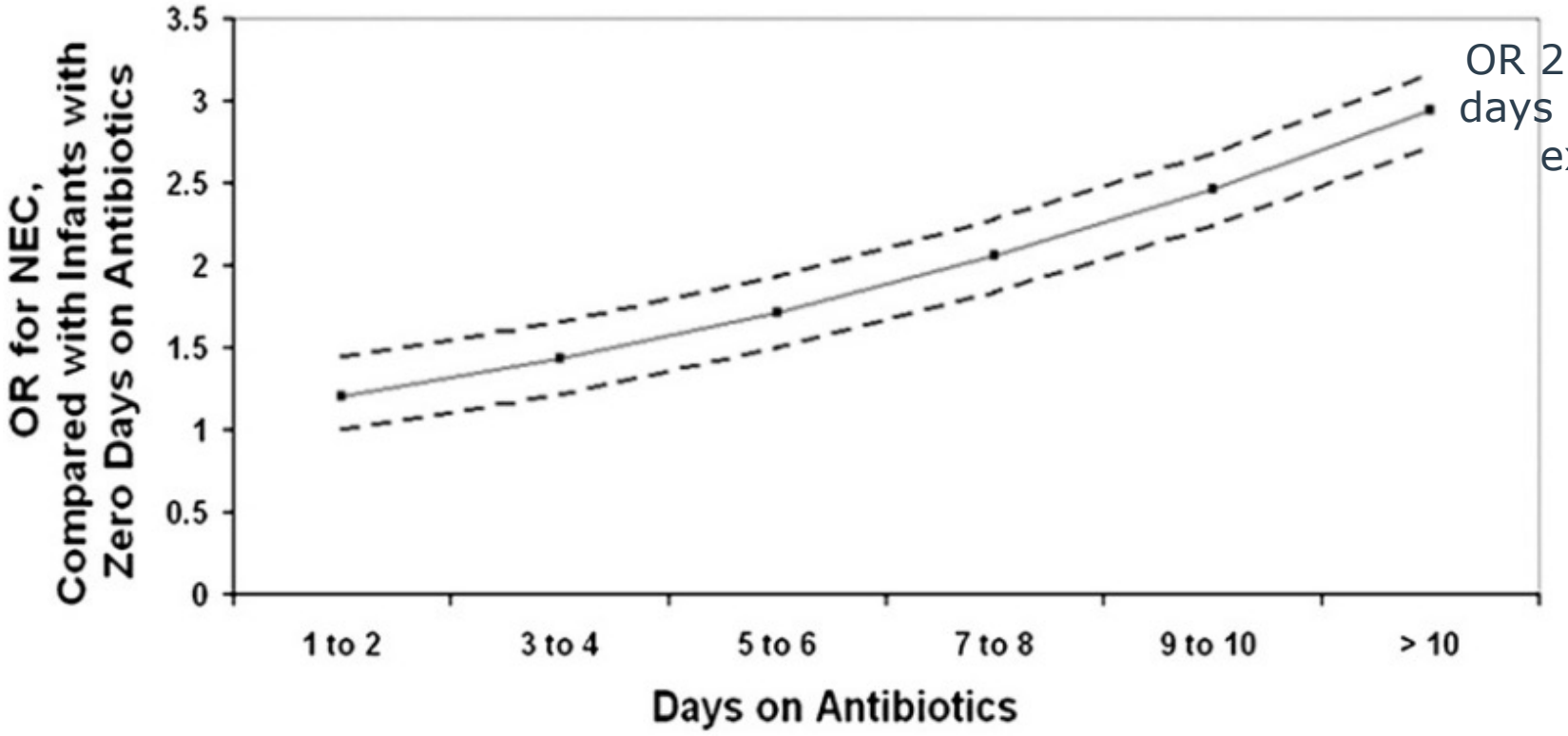
[d] Composite outcome is any severe IVH (grade 3 or 4), NEC (greater than or equal to stage 2), CLD, severe ROP (greater than or equal to stage 3), HAI, or death.

[e] Composite outcome II is any PVL, NEC (greater than or equal to stage 2), CLD, severe ROP (greater than or equal to stage 3), HAI, or death.

[f] Severe neurologic injury is IVH grade 3 or 4 or PVL.

Ting JY et al; Canadian Neonatal Network Investigators. Duration of Initial Empirical Antibiotic Therapy and Outcomes in Very Low Birth Weight Infants. Pediatrics. 2019 Mar;143(3):e20182286. doi: 10.1542/peds.2018-2286.

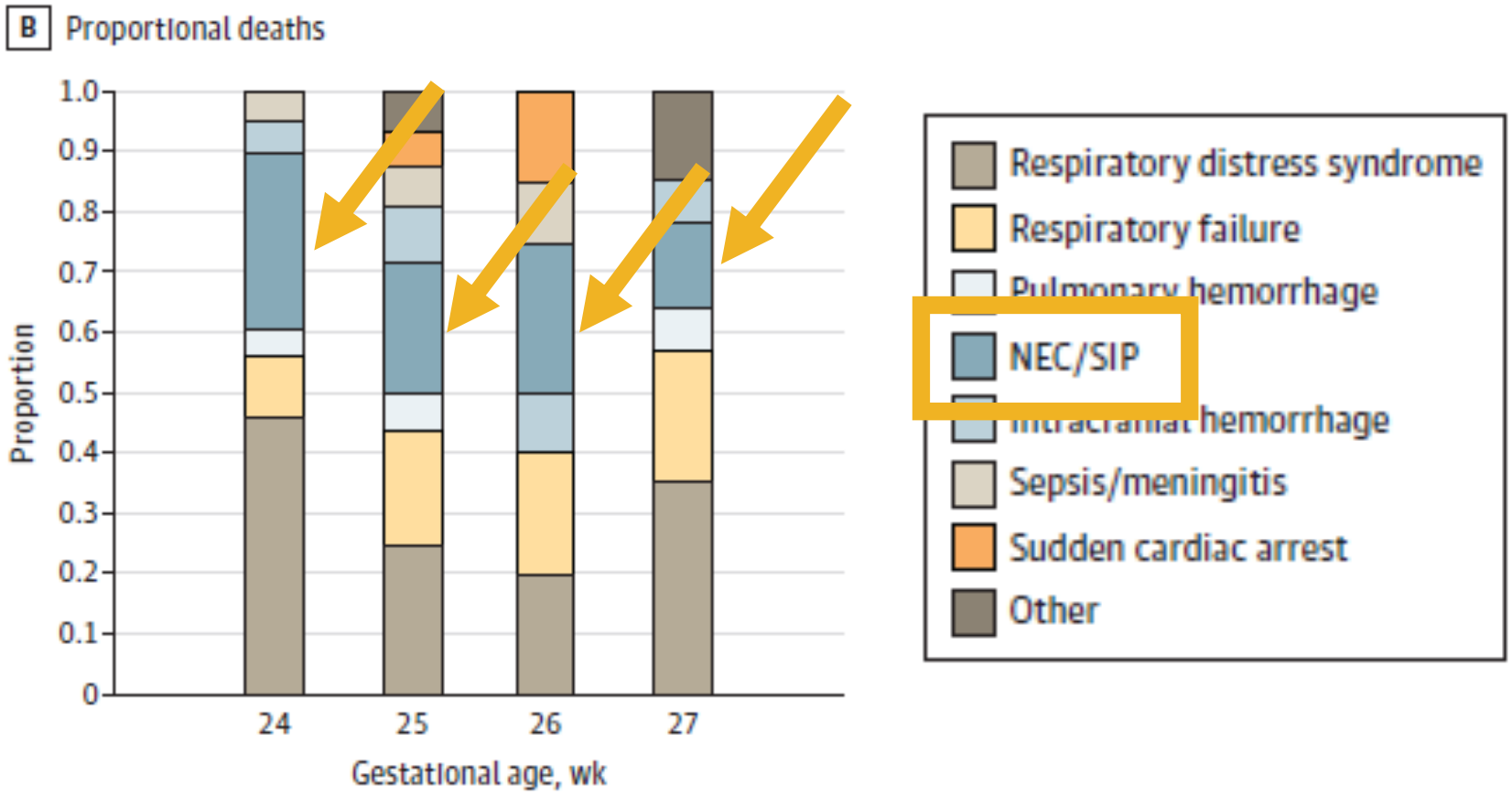
Harms of antibiotic administration in neonates



OR 2.94 for >10 days of antibiotic exposure

Alexander VN, Northrup V, Bizzarro MJ. Antibiotic exposure in the newborn intensive care unit and the risk of necrotizing enterocolitis. J Pediatr. 2011 Sep;159(3):392-7. doi: 10.1016/j.jpeds.2011.02.035.

NICU Mortality



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Necrotizing Enterocolitis (NEC)

The most common, serious gastrointestinal disease affecting newborn infants. Healthcare providers consider this disease as a medical and surgical emergency.

NICHD estimates for NEC:

- 9,000 / 480,000 (~2%)
- 7% of very low birth weight infants
- leading causes of illness and death among preterm infants
- 15 to 40% mortality

https://www.nichd.nih.gov/health/topics/nec/conditioninfo/risk

NEC – Staging / Severity

Stage 1, suspected NEC

- Symptomatic: bloody stools, diminished activity (lethargy), slow heart rate, an unstable temperature, mild abdominal bloating, and vomiting

Stage 2, definite NEC Stage 1 +

- lab abnormalities (reduced blood platelet levels, lactic acidosis)
- Worsening symptoms absent bowel sounds, abdominal tenderness
- Radiologic pneumatosis intestinalis (gas-filled spaces in the walls of the intestine)

Stage 3, advanced NEC Stages 1, 2 +

- Signs and symptoms of sepsis, free air in the belly, spontaneous intestinal perforation

NEC

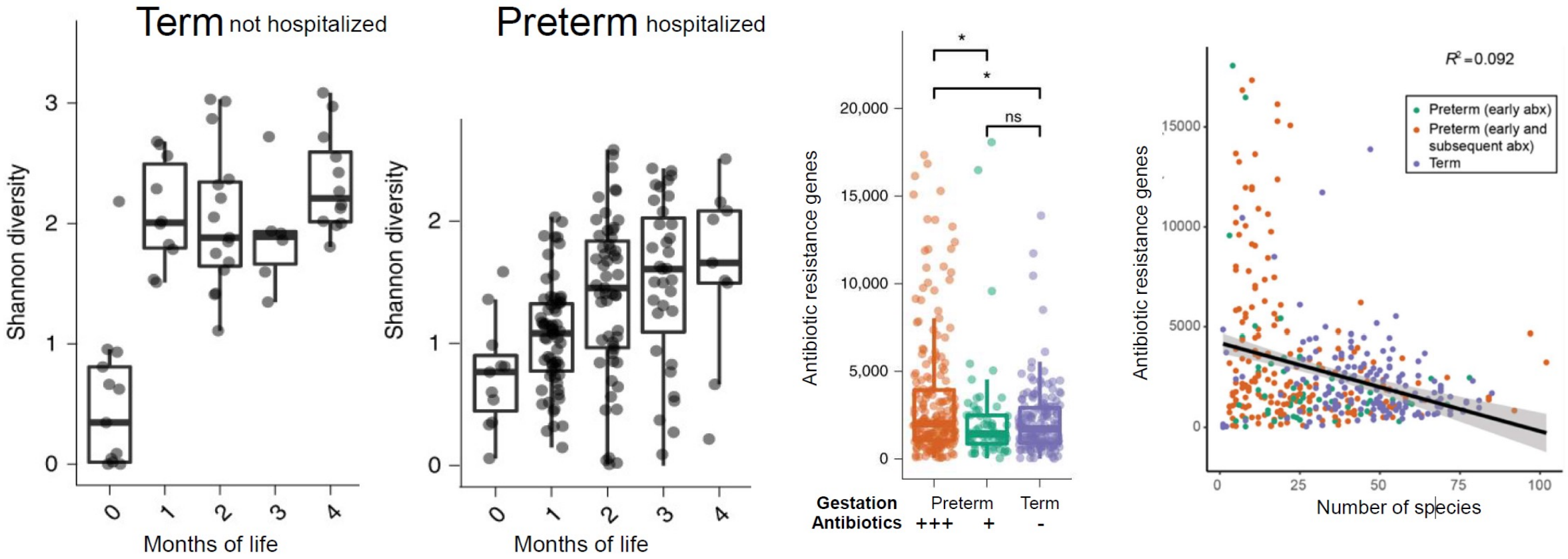
The cause of NEC is not well known

May be related to the immaturity of the digestive system.

Infection and inflammation in the gut may stem from dysbiosis *"the growth of dangerous bacteria or the growth of bacteria in parts of the intestine where they do not usually live"*

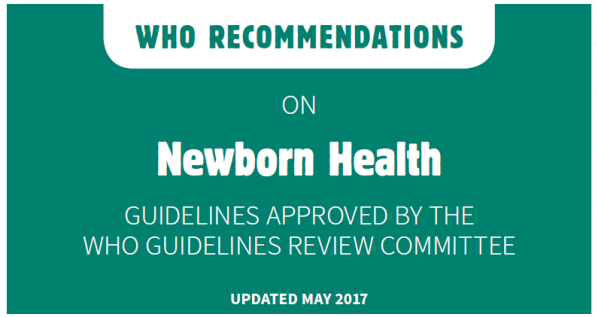
https://www.nichd.nih.gov/health/topics/nec/conditioninfo/causes

Neonatal microbiome



Gasparrini, A.J et al. Persistent metagenomic signatures of early-life hospitalization and antibiotic treatment in the infant gut microbiota and resistome. Nat Microbiol 4, 2285–2297 (2019). https://doi.org/10.1038/s41564-019-0550-2

Current situation



Necrotizing enterocolitis

Antibiotics for treatment of necrotizing enterocolitis

- Young neonates with suspected necrotizing enterocolitis should be treated with IV or IM ampicillin (or penicillin) and gentamicin as first line antibiotic treatment for 10 days. *(Strong recommendation, low quality evidence).* Source

Current Situation

PART II Clinical Syndromes and Cardinal Features of Infectious Diseases: Approach to Diagnosis and Initial Management
SECTION H Gastrointestinal Tract Infections and Intoxications

58 Necrotizing Enterocolitis

Kanecia Zimmerman and Daniel K. Benjamin, Jr.

"Recommendations for initial antimicrobial therapy vary among experts. Some experts advocate the routine use of ampicillin and gentamicin. When perforation is diagnosed or necrosis is suspected, providers should add an agent with activity against anaerobes (e.g., clindamycin or metronidazole)."

Survey from Pediatric ID listserv – 9/2020

University of North Carolina School of Medicine Chapel Hill, NC	amp/gent adding metronidazole if there's a perforation
Le Bonheur Children's Hospital *Memphis, TN*	Modified Bell's stage IIa – Ampicillin and Gentamicin for 5 days Modified Bell's stage IIb – Ampicillin and Gentamicin for 7 days Modified Bell's stage IIIa – Ampicillin, Gentamicin, Metronidazole for 10 days Modified Bell's stage IIIb – Ampicillin, Gentamicin, Metronidazole for 14 days
The Hospital for Sick Children Toronto, ON	Amp/Tobra/Metro - skip the Metronidazole in Stage 1-2A, but that hasn't been very well-accepted.
St. Louis Children's Hospital	Modified Bell's stage I – Ampicillin* and Gentamicin for 3 days Modified Bell's stage II – Ampicillin* and Gentamicin for 7 days Modified Bell's stage III – Ampicillin*, Gentamicin, Metronidazole for 10 days
UCSF	**NICU** Modified Bell's stage I – Nafcillin* and Gentamicin for 48 hours Modified Bell's stage IIa – Ampicillin, Gentamicin Modified Bell's stage IIb, III – Ampicillin, Gentamicin and metronidazole Pip/tazo only stage II-III with renal impairment **PICU** Modified Bell's stage I – Pip/tazo for 48 hours Modified Bell's stage II-III- Pip/tazo
Rainbow Babies and Children's Hospital Cleveland, OH	ampicillin + gentamicin + metronidazole
Nicklaus Children's Hospital	Modified Bell's stage I – Ampicillin* and Gentamicin for 48 hours Modified Bell's stage IIa – Ampicillin*, Gentamicin and metronidazole OR pip/tazo for 7 days Modified Bell's stage IIb – Ampicillin*, Gentamicin and metronidazole OR pip/tazo for 10 days Modified Bell's stage III – Ampicillin*, Gentamicin and metronidazole OR pip/tazo for 14 days
CS Mott Children's Hospital University of Michigan	Modified Bell's stage I – Ampicillin* and Gentamicin for 48 hours Modified Bell's stage IIa – Ampicillin* and Gentamicin for 7 days Modified Bell's stage IIb – vancomycin# and pip/tazo for 10 days Modified Bell's stage IIIa – vancomycin# and pip/tazo for 10 days Modified Bell's stage IIIb –vancomycin#, pip/tazo and flucon for 14 days
Doernbecher Children's Hospital Portland, Oregon	r/o NEC- Ampicillin and Gentamicin for 48 hours Modified Bell's stage IIb $^{+}$- Ampicillin, Gentamicin, metro OR pip/tazo If MRSA concern- vanco, gen, metro OR vanco and pip/tazo
John Hopkins	Age < 7 days: amp, gen (or ceftaz if CNS concern), metro Age > 7 days: vanco, ceftaz or ceftrx or cefepime, metro
CHOP	Pip/tazo x 7-10 day if symptoms improve within 48 hours Pip/tazo x 10-14 day if surgical NEC
University of Texas Health San A	Modified Bell's stage I, II – pip/tazo Modified Bell's stage III – pip/tazo and fluconazole

Cochrane Library

Cochrane Database of Systematic Reviews

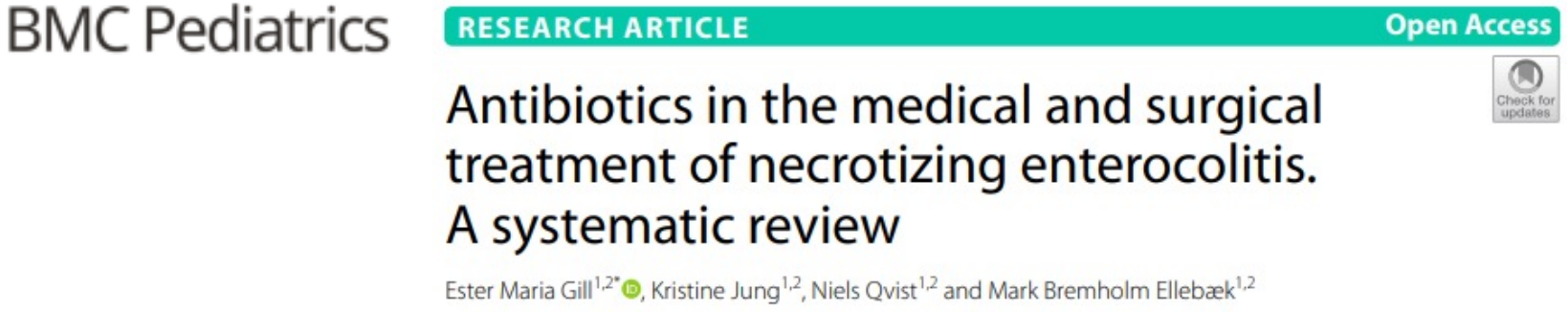
Antibiotic regimens for the empirical treatment of newborn infants with necrotising enterocolitis (Review)

Shah D, Sinn JKH

Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 1, 2012), Oxford Database of Perinatal Trials, MEDLINE (1966 to February 2012), EMBASE (1980 to February 2012) and CINAHL (1982 to February 2012).
MeSH terms:
enterocolitis, Necrotizing OR enterocolitis OR NEC AND anti-bacterial agents OR antibiotics AND therapeutics OR therapy AND infant, newborn/OR infant, low birth weight/OR infant, very low birth weight/OR infant, premature/OR Infant, Premature, Diseases OR (neonate: OR prematur*: OR newborn) AND controlled clinical trial OR randomised controlled trial OR cohort studies.

Only two RCT studies Hansen et al and Faix et al

"…there was insufficient evidence to recommend a particular antibiotic regimen for NEC."



Embase, Medline, Cochrane, Clinicaltrials.gov, Prospero, Opengrey.eu
Increased search terms

Only had three additional studies to Cochrane:

- Vermeylen et al (prospective cohort), Scheifele et al prospective cohort), Luo et al (retrospective cohort)

5 total studies included, 4 antibiotic regimens

"we were not able to demonstrate consistent results to recommend neither the type of antibiotics, the route of administration or the duration of treatment."

CMHH NEC Treatment Guideline

GUIDELINES FOR THE MANAGEMENT OF NECROTIZING ENTEROCOLITIS AT THE CHILDREN'S MEMORIAL HERMANN HOSPITAL NEONATAL INTENSIVE CARE UNIT

Mary Arbuthnot; Naahanna Bryan Akahara; Li Wen; Cynthia Ault; Bettina Herbert; Christine Domonoske; Megan Forbes; Dolly Rinehart; Mykela Deckinga; Michael L Chang; Allison Speer; Rajesh Pandey; KuoJen Tsao; Chiamaka Aneji

While other institutions may utilize piperacillin/tazobactam, this choice is based on each institutions internal antibiograms. The susceptibilities for gentamicin and piperacillin/tazobactam in our NICU are comparable. After careful consideration, it has been decided to utilize the following guidelines:

Modified Bell's Stage	Initial Antibiotic Regimen	Anticipated Duration of Therapy
IA and IB (suspected)	Ampicillin/gentamicin	48-72 hours
IIA (mildly ill)	Ampicillin/gentamicin	7 days
IIB (moderately ill)	Ampicillin/gentamicin/metronidazole	7-10 days
IIIA and IIIB (advanced)	Ampicillin/gentamicin/metronidazole	10-14 days*

*Duration should be counted from the time of source control (i.e. peritoneal drain placement or initial exploratory laparotomy with bowel removal)

Is Stewardship Possible?

Elements for effective NICU antimicrobial optimization

MEMORIAL HERMANN

Gastroschisis

Full-thickness abdominal wall defect
Variable amounts of intestine and occasionally other abdominal organs herniated through the abdominal wall defect

- 3 out of every 10,000 births.
- A 20-fold increase in the prevalence of gastroschisis in the United States (US) since 1980
- Overall mortality for newborns with gastroschisis is estimated to be 5%

Broad-spectrum empiric antibiotic therapy is recommended

Journal of Perinatology

Gastroschisis and low incidence of early-onset infection: a case for antimicrobial stewardship

Stefanie Riddle[1✉], Nidhi Agarwal[2], Beth Haberman[1], Heidi Karpen[3], Franscesca Miquel-Verges[2], Sujir Pritha Nayak[4], Kevin Sullivan[5], Sadie Williams[6], Isabella Zaniletti[7], Elizabeth Jacobson[8] and Children's Hospitals Neonatal Consortium Gastroschisis Focus Group*

Table 2. Infections and complications.

	N = 2021	Simple, *N* = 1672	Complex, *N* = 349	*P* value (Simple vs Complex)
Positive culture at birth, *N* (%)	13 (0.64)	9 (0.54)	4 (1.15)	0.258
Received initial antibiotics, *N* (%)	1898 (93.9)	1575 (94.2)	323 (92.6)	0.267
Antibiotic days	7 [3,9]	6 [3,8]	7 [3,10]	<0.0001
Central line days, median [IQR]	27 [20,44]	25 [19,36]	76 [38,117]	<0.0001
Infections during hospitalization				
BSI, *N* (%)	143 (7.1)	80 (4.8)	63 (18.1)	<0.0001
UTI, *N* (%)	56 (2.8)	34 (2)	22 (6.3)	<0.0001
Pneumonia, *N* (%)[a]	23 (1.1)	14 (0.8)	9 (2.6)	0.010
Meningitis, *N* (%)[b]	1 (0.1)	1 (0.1)	0 (0)	0.999
Post-Closure, Wound, *N* (%)	91 (4.5)	69 (4.1)	22 (6.3)	0.087
Other Misc (includes Culture Negative Dx), *N* (%)	479 (23.7)	346 (20.7)	133 (38.1)	<0.0001
Necrotizing enterocolitis				
Medical NEC, *N* (%)	93 (4.6)	48 (2.9)	45 (12.9)	<0.0001
Surgical NEC, *N* (%)	11 (0.5)	1 (0.1)	10 (2.9)	<0.0001

[a]Pneumonia is defined in the MOP as infection confirmed by positive tracheal aspirate or clinical pneumonia without causative organism, treated with >5 days of antibiotic therapy.

[b]Other miscellaneous infections are defined in the MOP as any other Congenital, Viral and Atypical Organisms, and infections in "Other" sites (e.g.: wound, endocarditis) and not defined elsewhere. These also can include clinical sepsis diagnosis where no positive culture is present, but patients are treated with ≥7 days of antibiotic therapy.

Gastroschisis – Antibiotic variability

Retrospective observational study utilizing data extracted from the Pediatric Health Information System® (PHIS)

Uncomplicated newborn gastroschisis patients

- discharged from a PHIS participating hospital
- between November 1, 2016 through June 30, 2019
- Gastroschisis cases = ICD-10 diagnosis code of Q79.3 for gastroschisis AND one of the following four procedure codes 0WQF0ZZ, 0WUF0JZ, 0WQF4ZZ, 0WQF4JZ for abdominal wall repair

Austin et al. Unpublished data

Gastroschisis – Antibiotic Variability

730 patients identified, 711 (97.4%) received antibiotics

- 20 out of 31 hospitals gave every patient antibiotic therapy
- Median days on therapy (11.1 days, IQR 9.4, 13.9)

20 different antibiotics were administered 8,682 total days of antibiotic therapy

- Ampicillin and gentamicin accounted for 66% of antibiotics given
- Cefazolin 9.8%
- Vancomycin 7.3%
- Piperacillin and tazobactam 6.2%

No correlation between gastroschisis volume and average days on antibiotic therapy

Austin et al. Unpublished data

MANAGEMENT GUIDELINE OF GASTROSCHISIS IN THE NICU

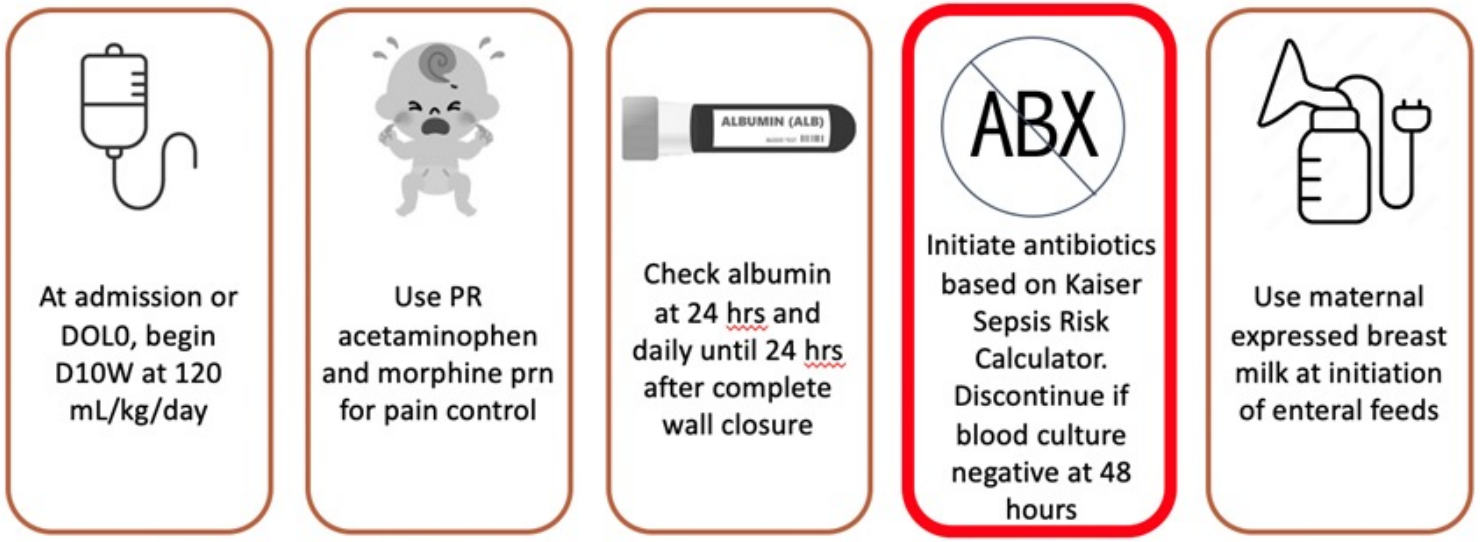
Mary Johnson MD, Kathryn Kuehn MD, Mary Austin MD, MPH, Eric Reynolds MD MPH,
Linda Li MD, Allison Speer MD, Michael Chang MD, Chiamaka Aneji MD, MPH

"**Evaluate for sepsis risk**. If present or patient clinically ill, send blood culture and initiate antibiotics. (*Monitoring the patient for sepsis with blood culture and without starting antibiotics can be considered if approved by the attending physician*).

Gastroschisis by itself is not a sufficient justification to start antibiotics

Ampicillin and gentamicin are the antibiotics of choice to start with and should be managed according to unit practice"

Gastroschisis Quality Improvement

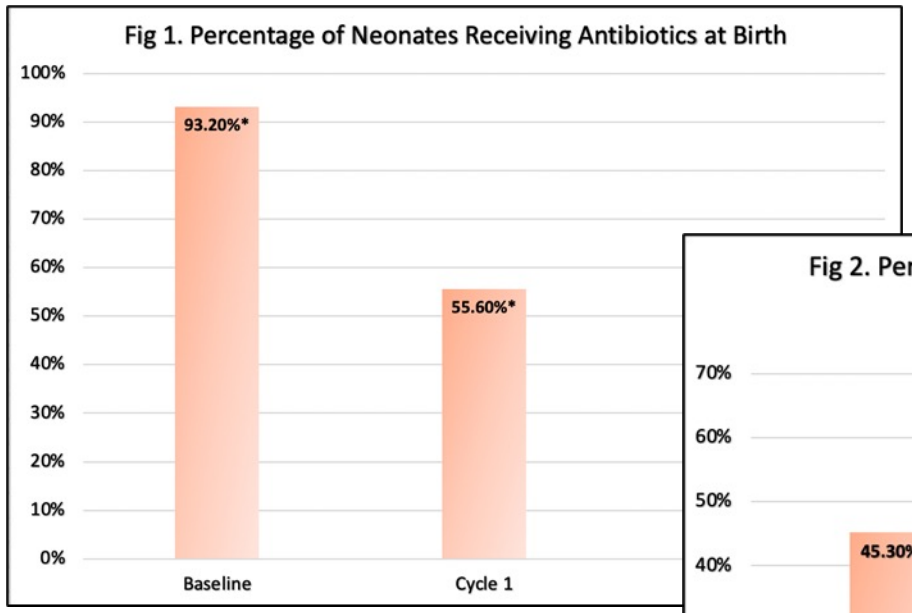


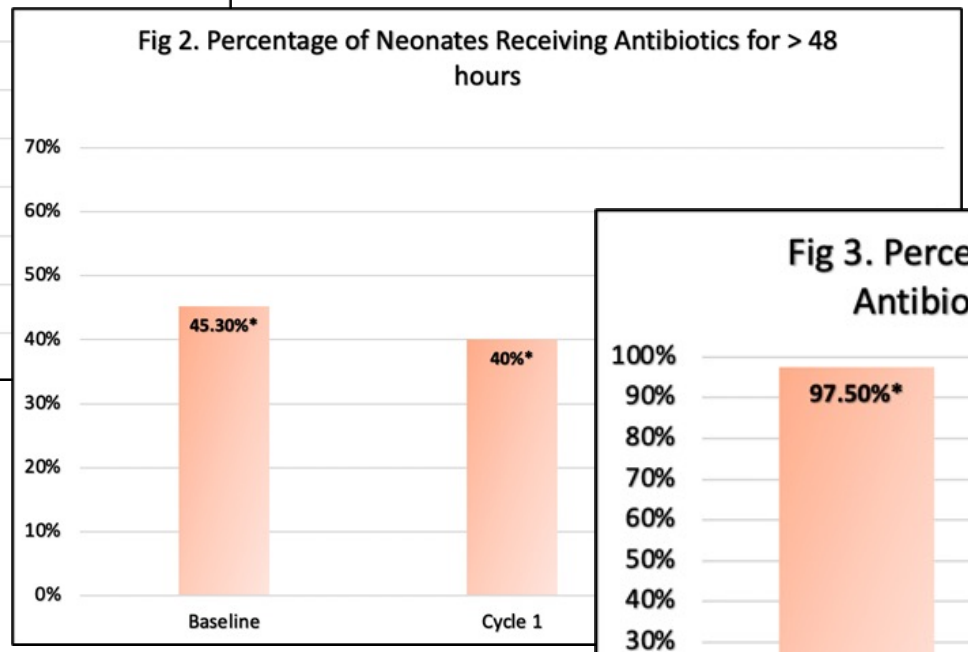
Baseline
10 years
retrospective data
n=161

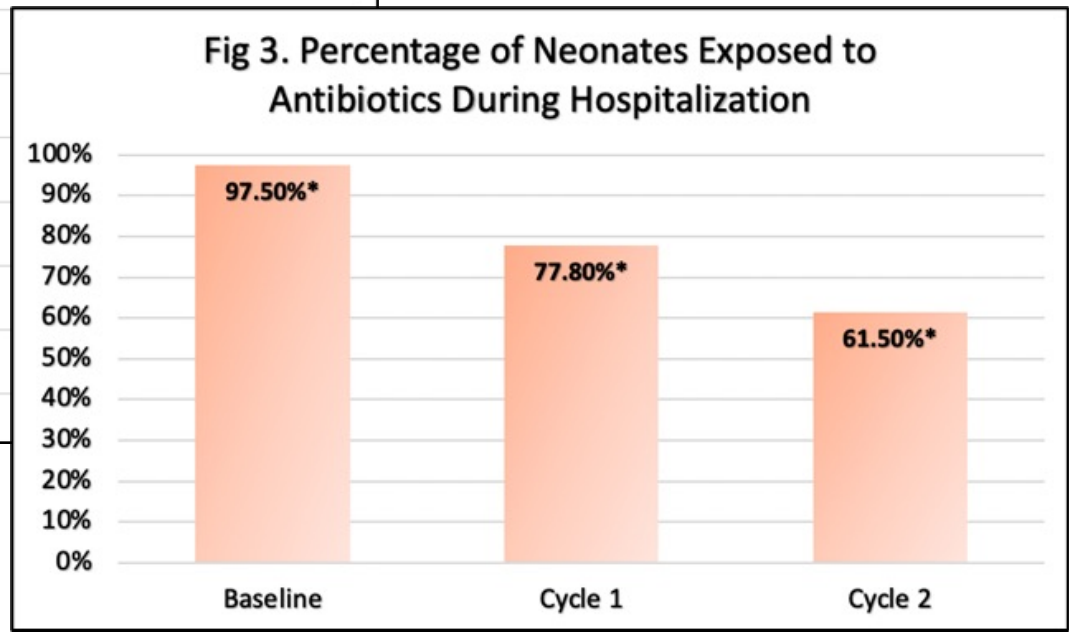
Cycle 1
0-6 months
n=9

Cycle 2
7-24 months
n=26

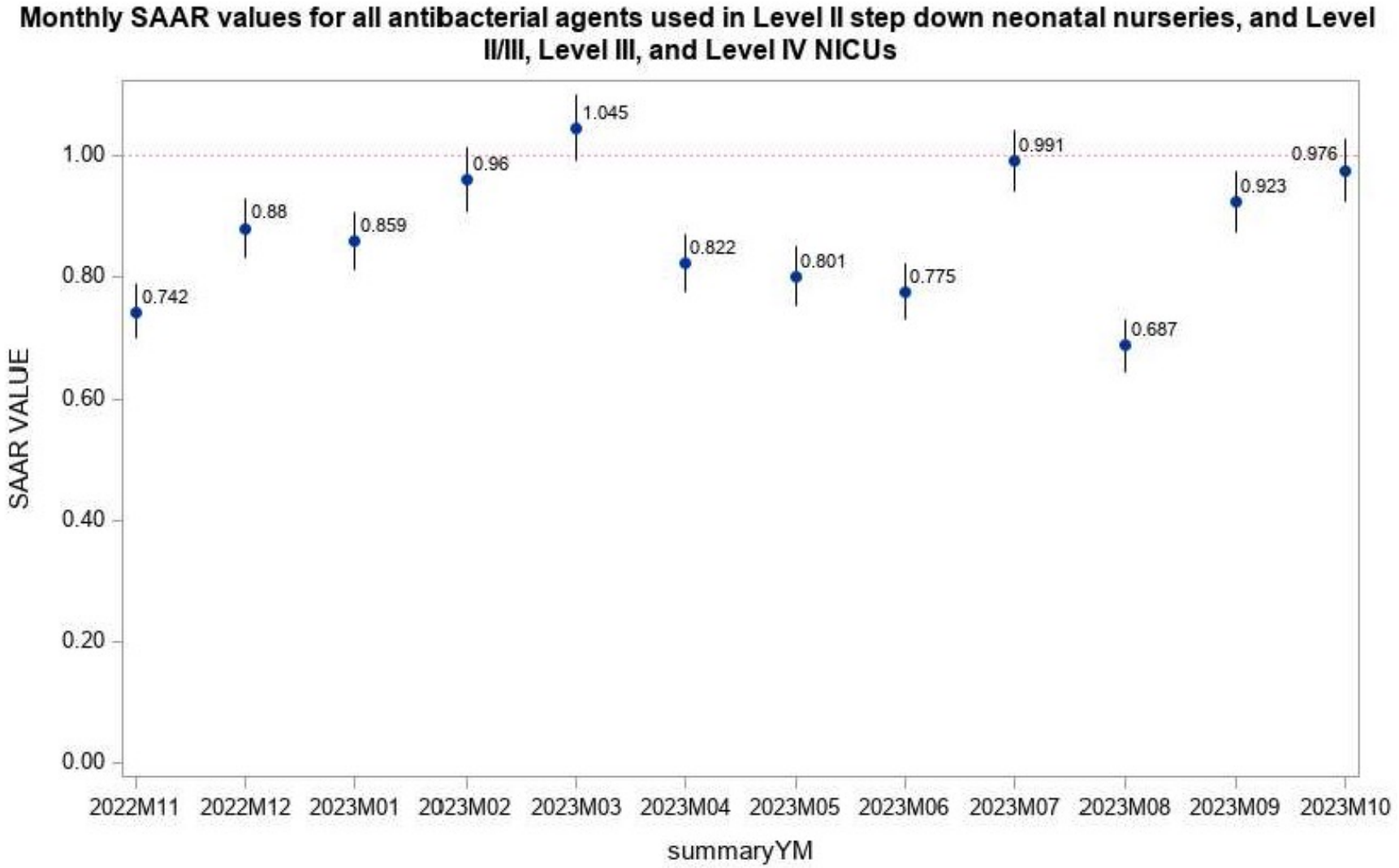
Gastroschisis Quality Improvement







NHSN AU SAAR – CMHH NICU



Team

- Neonatologists

Chiamaka Aneji

Amir Khan

- Pediatric surgeons

Mary Austin, Allison Speer, KuoJen Tsao

- NICU Clinical Specialist pharmacists

Christine Domonoske

Matthew Martin-Souza

Mamta Naik

- ASP pharmacist

Hoang Huynh

Culture-negative sepsis
Endotracheal aspirates

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Thank You!

Neonates are amazing!

Michael L. Chang, MD
Hoang Huynh, PharmD

January 19, 2024

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