Uso y Abuso de Antibióticos en la Unidad de Cuidados Intensivos Neonatales

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NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

THE OHIO STATE UNIVERSITY

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Drug Use in NICUs

- 253,651 NICU patients, 1996 to 2005
  - What were the most-prescribed drugs?

Drug	Frequency
Ampicillin	186,799
Gentamicin	171,388
Ferrous sulfate	90,152
Multivitamins	64,329
Cefotaxime	55,455
Caffeine citrate	48,814
Furosemide	47,278
Vancomycin	44,218

Clark RH, et al, *Pediatrics* 2006:117:1979

ANTIBIOTIC USE IN NICU

◆**Antibiotics: most-prescribed medications in NICU!**

◆**Clark et al, *Pediatrics* 2006**

– **253,651 distinct NICU patients managed by Pediatrix from 1996 to 2005:**

TABLE 2	Most Commonly Reported Medications	
Medication Name		**Frequency, A**
Ampicillin ←		186 799
Gentamicin ←		171 388
Ferrous sulfate		90 152
Vitamin (multivitamin)		64 329
Cefotaxime ←		55 455
Caffeine citrate		48 814
Furosemide		47 278
Vancomycin ←		44 218

ANTIBIOTIC THERAPY

- ◆ The GOOD

- ◆ The BAD

- ◆ The SHAMEFUL!

"ANTIBIOTIC"

◆**Definition:**

– **Chemical substance produced by various microorganisms or made synthetically that is capable of destroying or inhibiting the growth of other organisms, and, in particular, bacteria**

– **Webster dictionary: antibiotics prevent, inhibit, or destroy life**

◆**Coined in 1889 by Louis Pasteur's pupil, Paul Vuillemin, that means a process by which life could be used to destroy life**

Prolonged Initial Antibiotic Treatment in ELBW Infants

Cotton et al. *Pediatrics* 2009;123;58

◆ **Retrospective cohort study; 1998-2001**

◆ **5693 ELBW (BW<1000 g) infants admitted to 19 NRN centers: 4039 survived >5 days, received initial empiric antibiotic treatment, and had sterile cultures through the 1st 3 days of age**

Prolonged Initial Antibiotic Treatment in ELBW Infants (cont)

◆ **Median duration of therapy: 5 days (range 1-36 d)**

◆ **2147 (53%) infants received prolonged empirical therapy (≥5 days): center range, 27%-85%**

– **Lower gestational age, lower Apgar scores**

– **Multivariate analysis: prolonged therapy associated with increased odds of NEC or death and of death**

– **Each empirical treatment day was associated with increased odds of death, NEC and the composite of NEC/death**

Prolonged Initial Antibiotic Treatment in Preterm Infants

◆ **Retrospective cohort study; 2000-2004**

◆ **365 infants (≤32 wks, ≤1500 g) infants who survived free of sepsis and NEC for 7 days**

◆ **36% received prolonged initial empiric antibiotics (≥5 days)**

◆ **Multivariate logistic regression:**

– **LOS (OR, 2.45; 95% CI, 1.3-4.7)**

– **LOS/NEC, or death (OR 2.7; 95% CI, 1.1-6.3)**

Antibiotic Exposure and NEC

◆ **Retrospective, 2:1 control-case study: 2000-2008**

◆ **124 NEC cases matched to 248 control subjects: gestational age, birth weight, birth year**

◆ **Cases less likely to have RDS (p=0.02), more likely to reach full enteral feeds (p=0.03) and have culture-proven sepsis (p<0.0001)**

◆ **After removal of neonates with sepsis from cohort, risk of NEC increased significantly with duration of antibiotic exposure**

◆ **Exposure for >10 days resulted in a nearly threefold increase in risk of NEC**

NEONATAL SEPSIS: ANTIBIOTIC THERAPY

Antimicrobial utilization practices in NICUs impact on the types of microorganisms responsible for neonatal sepsis and their antibiotic resistance patterns!

EMPIRIC ANTIBIOTIC THERAPY AND RESISTANT BACILLI

◆ **Prospective cross-over trial, 6-month intervals (12/96-12/97): 2 NICUs (Netherlands)**

◆ **Empiric antibiotic regimens:**

– **Penicillin / tobramycin (EOS); flucloxacillin / tobramycin (LOS)**

– **Amoxicillin IV / cefotaxime (EOS); flucloxacillin / cefotaxime (LOS)**

◆ **Weekly rectal, respiratory aspirate cultures; clinical isolates monitored**

de Man et al, Lancet 2000;355:973

EMPIRIC ANTIBIOTIC THERAPY AND RESISTANT BACILLI

◆ **Penicillin (flucloxacillin) / tobramycin regimen:**

  – *E. coli* predominant Gram-neg isolate (53%)

◆ **Amoxicillin (flucloxacillin) / cefotaxime regimen:**

  – *Enterobacter* sp. predominant Gram-neg (77%)

  – Emergence of resistance higher:

    • Cefotaxime-R Gram-neg: RR 3

    • Cefotaxime-R *Enterobacter sp*.: RR 3

    • Gram-neg bacilli resistant to empiric rx: 41 vs 3 infants (p<0.001); RR 18

EMPIRIC ANTIBIOTIC THERAPY AND RESISTANT BACILLI

◆ **Penicillin (flucloxacillin) / tobramycin regimen:**

– **Shorter hospital stay, less CVLs**

◆ **Amoxicillin (flucloxacillin) / cefotaxime group:**

– **Higher vancomycin use**

◆ **No significant differences in deaths**

◆ **CoNS predominant pathogen in both groups!**

*de Man et al, Lancet 2000;355:973

ANTIBIOTIC USE AND RESISTANCE: CAUSAL ASSOCIATION?

◆ **Changes in antibiotic usage paralleled by changes in prevalence of resistance**

◆ **Resistance more prevalent in nosocomial vs. community-acquired bacterial strains**

◆ **Patients infected with resistant strains are more likely to have received prior antibiotics**

◆ **Hospital areas with highest resistance rates have highest antibiotic use rates**

◆ **Increasing duration of patient exposure to antibiotics increases likelihood of colonization with resistant organisms**

Campaign to Prevent Antimicrobial Resistance

prevent infection

diagnose and treat infection

use antimicrobials wisely

prevent transmission

Centers for Disease Control and Prevention

National Center for Infectious Diseases

Division of Healthcare Quality Promotion

➢ *Campaign to Prevent Antimicrobial Resistance Online*
➢ *Federal Action Plan to Combat Antimicrobial Resistance*

CDC CAMPAIGN: 12 STEPS

◆ **Use Antimicrobials Wisely:**

6. **Practice antimicrobial control**

7. **Use local data**

8. **Treat infection, not contamination or colonization**

9. **Know when to say "no"**

10. **Stop treatment**

◆ **Prevent Transmission:**

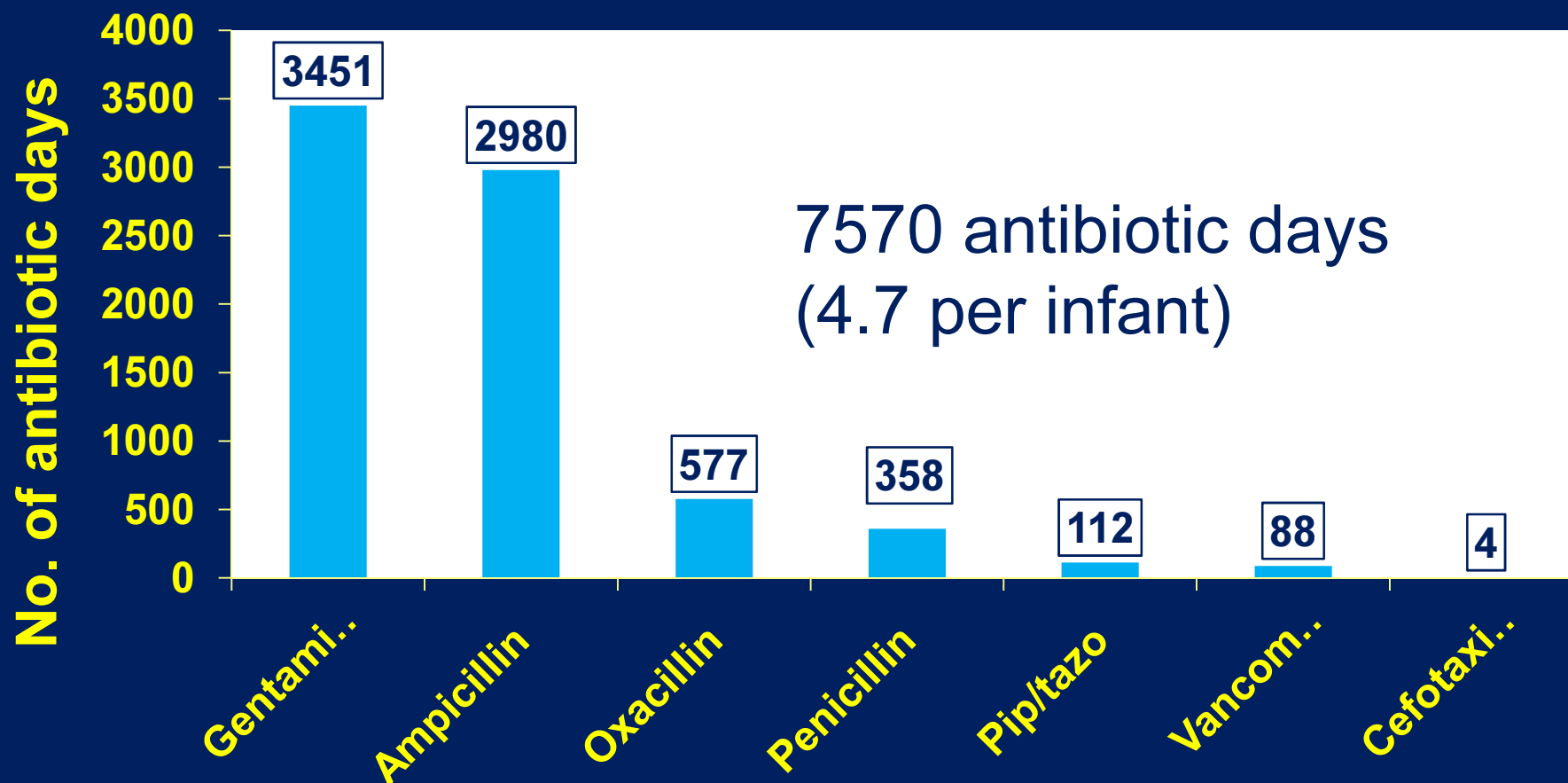11. **Practice infection control**

12. **Practice hand hygiene**

Antimicrobial Stewardship

"Selection, dose, and duration of antibiotic treatment resulting in best clinical outcome… minimal toxicity… minimal subsequent resistance."

Owens RC, Pharmacotherapy 2004

Vancomycin-Reduction Protocol: *The Boston* Experience
Chiu et al. PIDJ 2011;30:273

◆ 2 NICUs: Brigham & Women's Hospital (BWH), Mass Gen Hospital (MGH); low MRSA rates

◆ 2006: vancomycin use guideline implemented that restricted its use for empiric therapy of late-onset infection; data collected pre/post periods

◆ Nafcillin (BWH) or oxacillin (MGH) with gent

◆ Causes of death, duration of bacteremia, and incidence of complications or deaths attributable to LOS did not change significantly

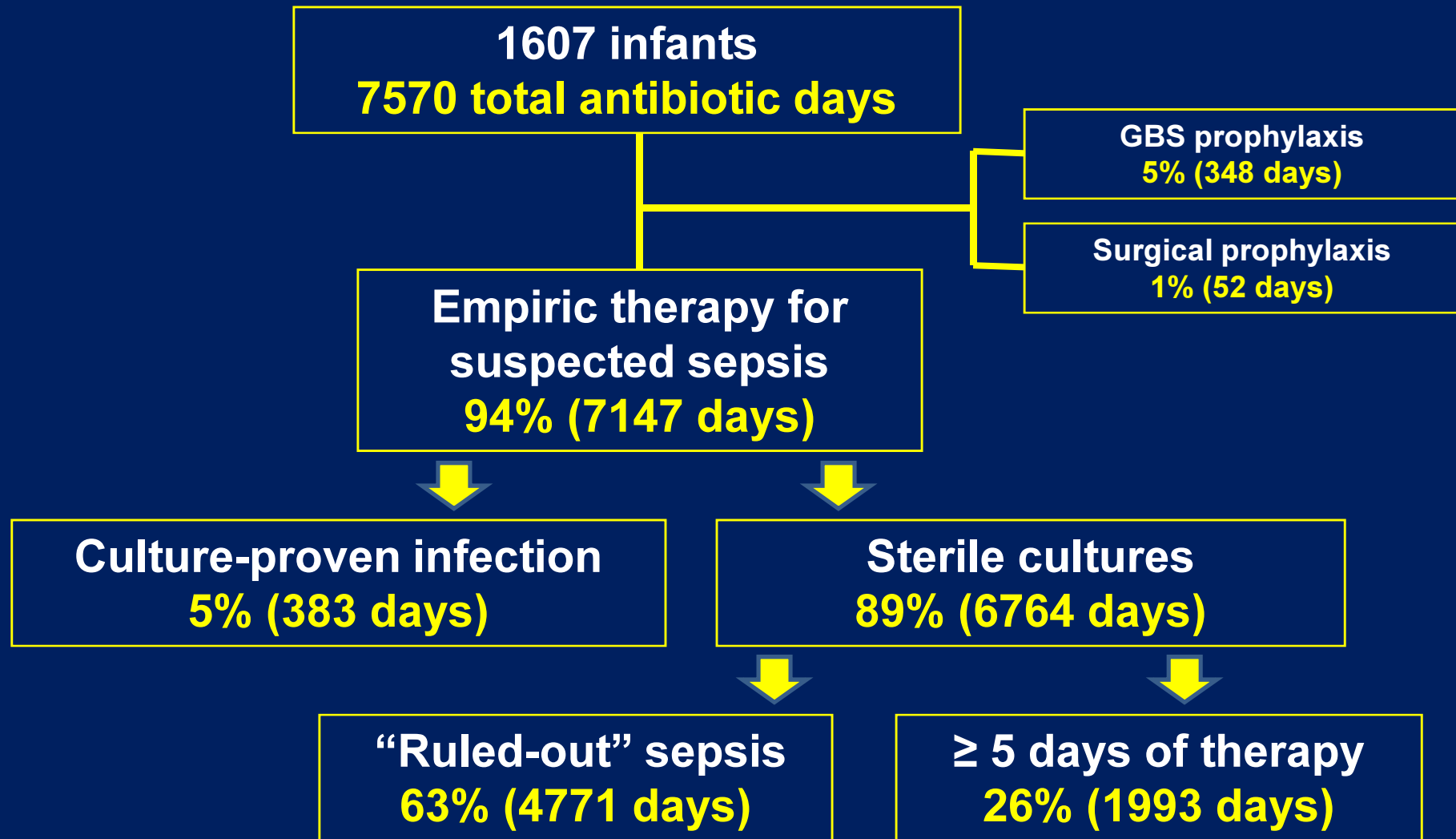# Vancomycin-Reduction Protocol: *The Boston* Experience

◆ Vancomycin start rates:

– BWH: 6.9 to 4.5 per 1000 patient-days
  • 35% reduction; $p = 0.01$

– MSG: 17 to 6.4 per 1000 patient-days
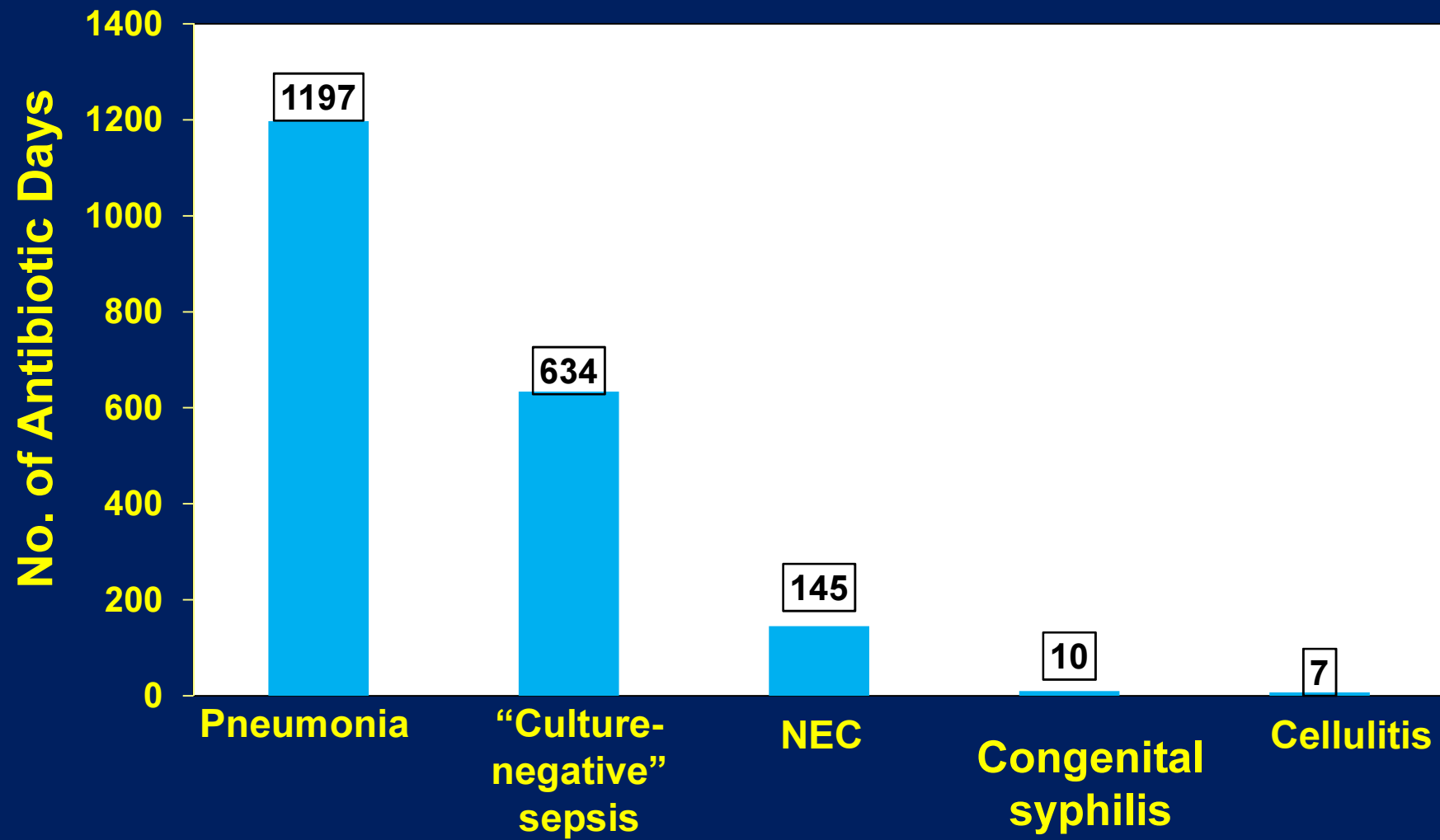 • 62% reduction; $p < 0.0001$

◆ Number of infants exposed to vancomycin:

– BWH: 5.2 to 3.1 per 1000 patient-days
  • 40% reduction; $p = 0.008$

– MGH: 10.8 to 5.5 per 1000 patient-days
  • 49% reduction; $p = 0.009$

Parkland Memorial Hospital:
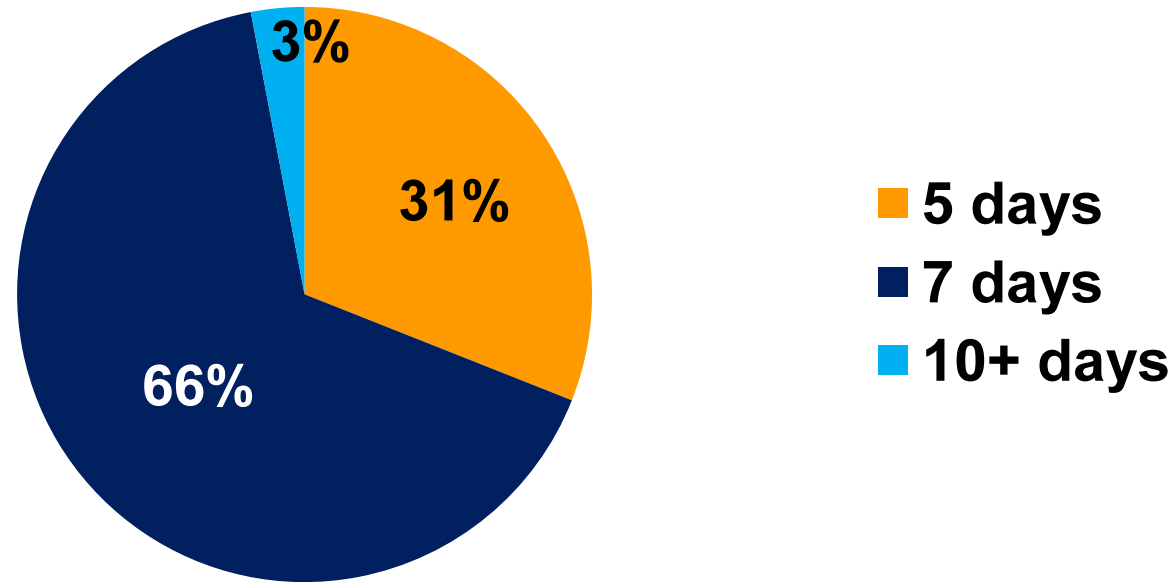One Year Prospective Surveillance

1607 infants
7570 total antibiotic days

GBS prophylaxis
5% (348 days)

Surgical prophylaxis
1% (52 days)

Empiric therapy for
suspected sepsis
94% (7147 days)

Culture-proven infection
5% (383 days)

Sterile cultures
89% (6764 days)

"Ruled-out" sepsis
63% (4771 days)

≥ 5 days of therapy
26% (1993 days)

PMH: "Culture-Negative Sepsis"

Antibiotic Duration for "Culture-Negative" Sepsis

3%

31%

66%

- 5 days
- 7 days
- 10+ days

- **97%** of therapy initiated within 72 hours of birth (early-onset)
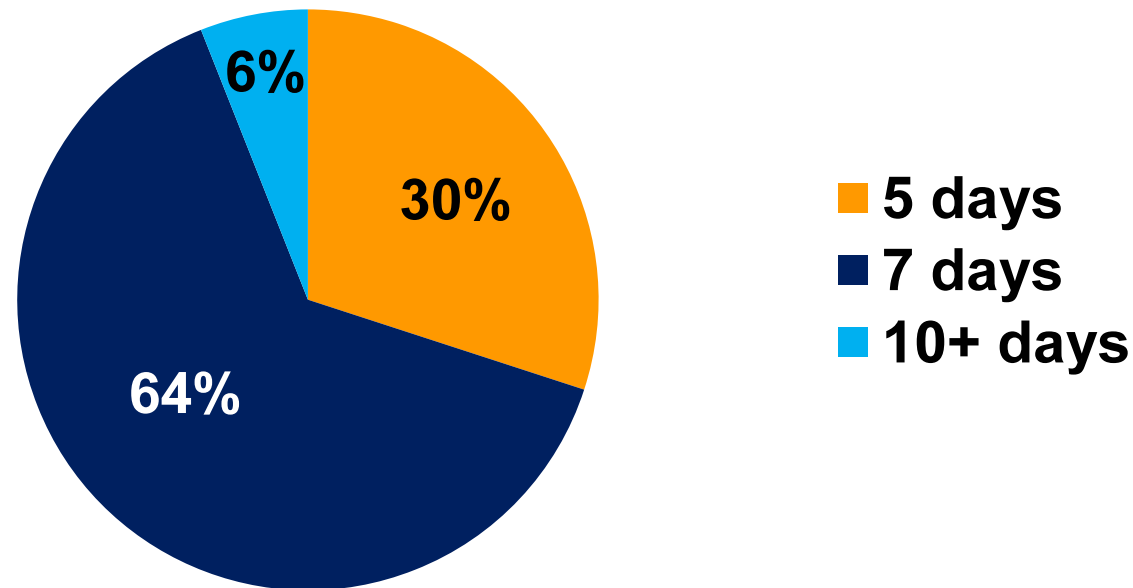
- **3%** initiated beyond 72 hours (late-onset)

Chorioamnionitis and the Asymptomatic Infant
GL Jackson et al, Pediatrics 2004;113:1173

- ◆ Prospective, observational study:
  - – 856 newborns, BW $\geq$2100 g, GA $\geq$35
  - – Exposed to maternal chorio (T$\geq$38)
  - – All received amp/gent x 48 hrs
- ◆ 96%: sterile cultures, A/G stopped at 48 hrs
- ◆ F/U (1-3 wks; 92%): all with abnormal WBC I/T; 50% of those with normal WBCs (even MR#)
- ◆ 99% had $\geq$1 abnormality (2427 WBCs)
  - – Specificity, 0.12-0.91; negative predictive value, 0.91-0.97; sensitivity, 0.27-0.76

PMH: Pneumonia

Antibiotic Duration for Pneumonia

- **94%** of therapy initiated within 72 hours of birth (early-onset)

- **6%** initiated beyond 72 hours (late-onset)

Neonatal Pneumonia
Engle et al. *J Perinatology* 2002;20:421

◆ 73 full term newborns: normal newborn nursery

◆ Presented with respiratory signs, abnormal CXR but no mod/thick meconium, prior antibiotic treatment >24 hrs, oxygen >8 hrs

◆ If asymptomatic at 48 hrs, randomized to 4 d (plus 24 hrs observation; n=35) vs 7 d (n=38) of amp/gent (all blood cultures sterile)

◆ No re-hospitalization for sepsis, pneumonia

◆ With 95% confidence, the true rate of success for the 4 d group was at least 92%

RESPIRATORY VIRUSES: NICU
Kidszun A et al, PIDJ, 2013

◆ Prospective study: 8/2010 – 3/2012

◆ 64 (14%) of 462 infants >72 hrs of age evaluated for late-onset sepsis and IV antibiotics started

   – Median GA 26 wk (24-40), BW 720 g (370-3650)

◆ Multiplex PCR (in-house): adenovirus, RSV, influenza A/B/H1N1, parainfluenza 1-4, metapneumovirus, coronavirus, picornavirus (rhino/entero)

RESPIRATORY VIRUSES: NICU
Kidszun A et al, PIDJ, 2013

◆ 60 infants (4 excluded - inadequate specimen)

◆ 6 (10%) RVP positive:

- RSV, 1; picornavirus, 5

◆ 3 (5%) had positive blood cx: CoNS, 2; *Klebsiella oxytoca*, 1

◆ 31 (52%) had "clinical sepsis" (antibiotics ≥5 d and/or CRP >15 mg/L) – RVP negative

◆ No specific presentation (clinical or labs) and signs same as bacterial sepsis (no URI-sx)

RESPIRATORY VIRUSES IN NICU:
THE VIRION-I Study
Ronchi et al, PAS, 2013

◆ **Prospective cohort study** performed at Parkland Hospital (Dallas) and Women & Infants Hospital (Brown University, Rhode Island – Michelow)

◆ **OBJECTIVE**: To determine the incidence of respiratory viral infections among infants who are >72 hours of age, evaluated for possible sepsis and antibiotics started while in NICU

RESPIRATORY VIRUSES IN NICU:
THE VIRION-I Study
Ronchi et al, PAS, 2013

◆ 1 year: 1/15/12 – 1/31/13

◆ Nasopharyngeal specimen for respiratory viral PCR:

  – Luminex®: 17 viruses (influenza A/B, RSV, metapneumovirus, rhinovirus/enterovirus, adenovirus, parainfluenza 1-4, coronavirus)

  – Genmark PCR (eSensor®): 14 viruses

RESPIRATORY VIRUSES IN NICU:
THE VIRION-I Study
Ronchi et al, PAS, 2013

◆ 100 (70%) of 142 eligible infants enrolled

- PMH: 94% (86/91)
  - GA (mean ± SD): 31 ± 5 wk
  - BW (mean ± SD): 1715 ± 969 g
- W & I: 27% (14/51)
  - GA (mean ± SD): 31 ± 5 wk
  - BW (mean ± SD): 1595 ± 814
- 135 sepsis evaluations / antibiotics

RESPIRATORY VIRUSES IN NICU:
THE VIRION-I Study
Ronchi et al, PAS, 2013

◆ 8 (8%) infants: positive respiratory viral PCR:
  – 7% (6/86) at PMH
  – 14% (2/14) at W&I
◆ 8 (6%) of 135 sepsis evaluations was associated with a positive respiratory viral PCR test
  – None had a positive bacterial or fungal blood/CSF culture.

RESPIRATORY VIRUSES IN NICU:
THE VIRION-I Study

- 8 infants (GA: 25-34 wk; BW 420-2705 g):
  - Rhino/entero: 4
  - Parainfluenza-3: 2
  - Coronavirus: 2
- Hypothermia (7), fever (1), tachypnea (7), apnea (6), congestion/rhinorhhea (2), bloody stool (2); 2 required mechanical ventilation
- 3 received antibiotics $\geq$5 days
- Clinical suspicion (75% of PCR-pos infants)

Summary and Conclusions

- Improving antimicrobial use in the NICU requires generating **local data** and engaging **key stakeholders**.

- Use **variability** in treatment to gain consensus.

- Start with **low hanging fruit** to achieve success!

- Assessment needs to include **safety**.

- **Disseminate outcomes** widely within your organization and publish your results!!!

GRACIAS!

Vignette Study

- Patel et al, *ICHE* 2011.
  - Survey consisting of 12 clinical vignettes describing scenarios of antibiotic use in the NICU
  - Sent to neonatology attendings and fellows, neonatal nurse practitioners, and residents in academic NICU's
  - 161 responders answered "appropriate," "inappropriate," or "not sure" to the antibiotic usage described in each vignette
  - Graded on correct usage as defined by CDC's 12-Step Campaign to Prevent Antimicrobial Resistance

Patel et al, continued

Antibiotic use described	% of responders calling use appropriate	Reason wrong
21 days of piperacillin/tazobactam for *P. aeruginosa* sepsis	11	Too long
10 days of cefazolin for chest tube placement	13	Prolonged prophylaxis
Metronidazole and meropenem for treatment of NEC	44	Redundant therapy
10 days of vancomycin for 1 positive BCx for CONS from PICC with negative peripheral BCx	48	Treating contamination

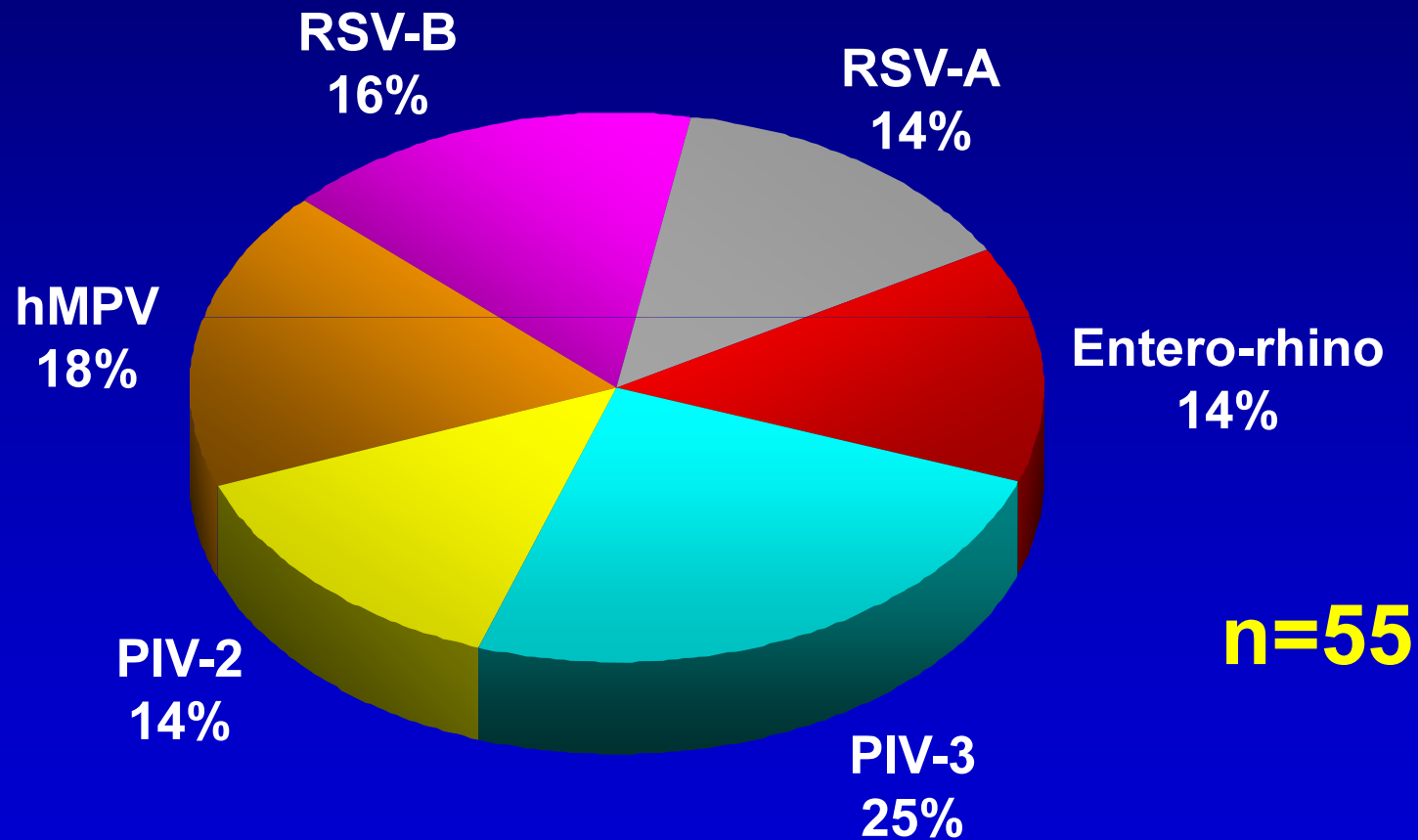# RESPIRATORY VIRUSES: NICU
Bennett NJ et al, *J Pediatr*, 2012

◆ Prospective, 1 year surveillance in 2 NICUs

◆ Preterm infants <33 wks GA (NICU since birth) had nasopharyngeal swabs for detection of respiratory viruses by multiplex PCR twice weekly within 3 days of birth until discharge

◆ Respiratory viral panel (Luminex): 17 different respiratory viruses (influenza A/B; RSV A/B; parainfluenza 1-4; coronavirus; adenovirus; rhinovirus/enterovirus; metapneumovirus)

RESPIRATORY VIRUSES: NICU
Bennett NJ et al, *J Pediatr*, 2012

◆ 52% (26/50) of infants tested positive for a respiratory virus at least once during the NICU stay (708 specimens obtained)

RESPIRATORY VIRUSES: NICU

Bennett NJ et al, *J Pediatr*, 2012

- 18 samples (28% of the positive swabs) included more than 1 virus

- 14 infants had sequentially positive specimens for the same virus over 3-13 days

- No long term outcomes

RESPIRATORY VIRUSES: NICU
Bennett NJ et al, *J Pediatr*, 2012

◆ Virus-positive infants:

- Longer length of stay (70 d vs 35 d, p=0.002)

- Need for intubation (65% vs 29%, p=0.01)

- Duration of intubation (19 vs 5 days, p=0.03)

- Duration of oxygen requirement (51 vs 13 d, p=0.002)

- BPD (46% vs 21%, p=0.05)

- More desaturation (p<0.0001) and clinical deterioration episodes (p=0.0001)

Another Challenge: Duration of Treatment?

- How long is *long enough*?