Duration of Empiric Antibiotic Therapy for Neonatal Sepsis

How much is Enough?

Ken Zangwill

OASCN learning Session #10

July 8, 2021

Empiric Tx: 2d v 5d v 7d v 10d?
How do we Sort This Out?

- RCT or Cohort studies?
- Useful info from treatment of confirmed disease?
  - GBS bacteremia: 10d (shorter courses reported)
  - Pneumonia: 4-7 days
- Stewardship Trials?
  - What effect on AUR and morbidity when stop at 36-48 hours?
- **Guidelines/Expert Opinion?**

AAP COFD and COID Guideline - **>35 weeks**

Among term infants with unexplained… cardiorespiratory illness…antibiotic therapy may be justified even in the absence of culture-confirmed infection. Most often…**therapy should be discontinued when blood cultures are sterile at 36-48 hours** unless there is…site-specific infection. Continuing therapy in response to [a] laboratory test… alone is rarely justified…

Puopolo K. Pediatrics 2018;142(6)

AAP COFD and COID Guideline - **<35 weeks**

…[should be] discontinued by 36-48 hours…unless… evidence of site-specific infection. Persistent cardiorespiratory instability is common among…**VLBW…not alone an indication for prolonged empirical antibiotic[s]…**Continuing [therapy] in response to [a] laboratory test…alone is rarely justified, particularly among preterm[s]…in the setting of maternal… conditions known to affect fetal hematopoiesis.

Puopolo K. Pediatrics 2018;142(6)

Do we Generally Adhere to Guidelines?
142 VON units audited in Feb 2016

- No center had all 7 CDC ASP Core Elements
  - Only 6% "[internally] report", 15% "track"
  - NICU level didn't matter
- 94/725 (13%) Tx'ed infants with no blood Cx sent first
- 412 patients on >48 hours of antibiotics
  - 25% with (+) Cx, 17% no Cx, 69% had ≥ 1 (-) Cx

Ho T. Pediatrics 2018;142(6)

We Use Too Much Empiric Drug (Probably)

CPQCC Data

- Wide variation in drug use (2-97% of pt-days; median 25%)
  - Independent of infection, NEC, surgical volume, mortality
  - 11-336 infants Tx'ed/EOS case (mean 95)
  - 2-105 infants Tx'ed/LOS case (mean 20)
- Did not correlate with BSI

Schulman J. Pediatrics 2019;144; Schulman J. Pediatrics 2015:135

Opportunities for (Empiric Use) Stewardship

- R/O sepsis to 44-70% of NICU use
- Cx (-) sepsis 20-25%
  - Empiric use >5d was 26% of all use
- "Pneumonia" 15%
- NEC 8%

Culture-confirmed in <15-20% typically

Cantey JB et al. Lancet Infect Dis 2016; Patel SJ PIDJ 2009;28:1047; Ho T. Pediatrics 2018;142(6)

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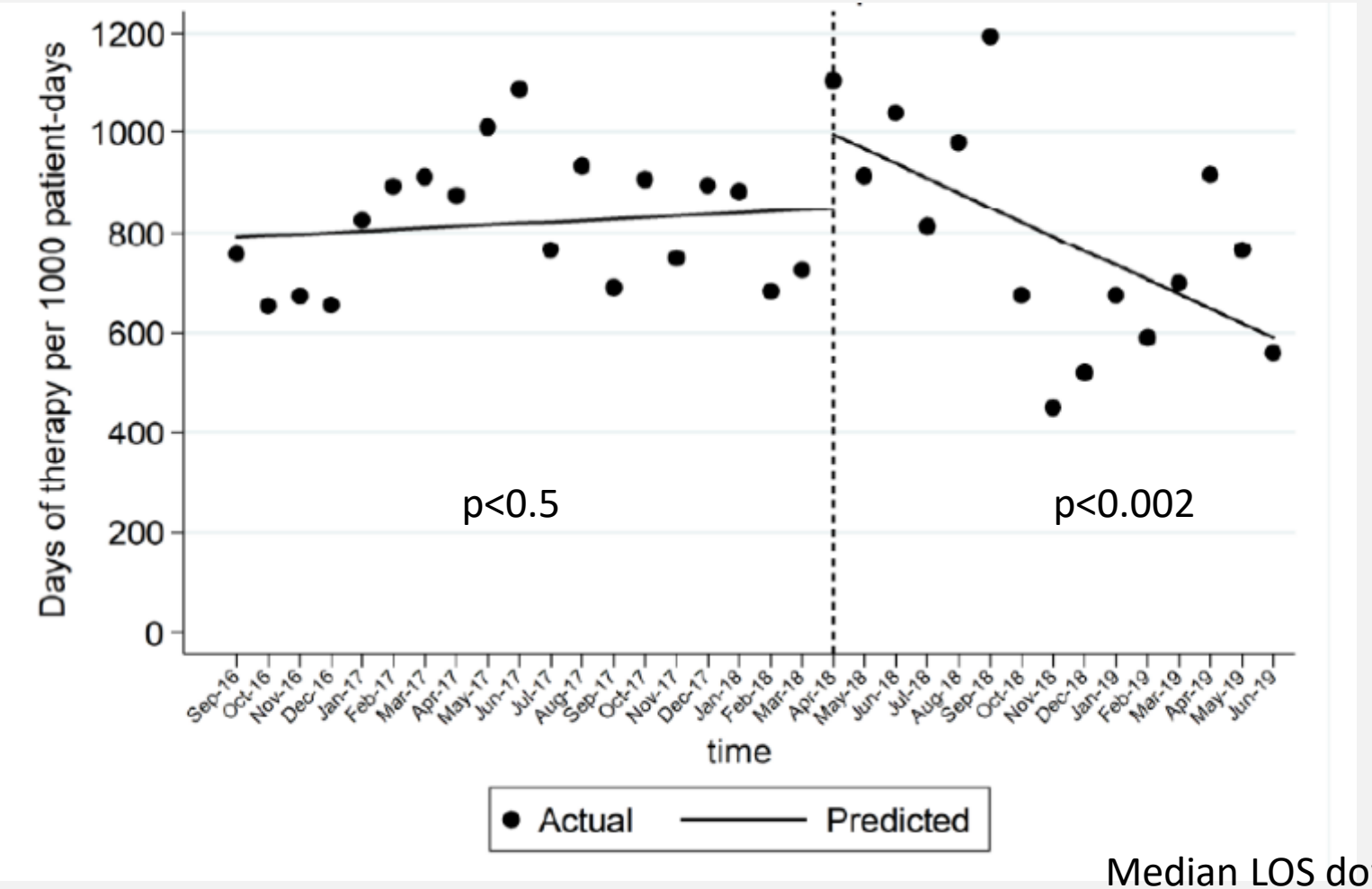
"Low Hanging Fruit"; Stop by <5 Days

15 of 17 Public NICUs in Greece

N=1025 ≥*37wkrs, >70% C-section, >80% no chorio, >90% no PROM*



Median LOS down 1-3d

Kopsidas I et al. Antibiotics 2021;10:275

36h Stop, 5d for Cx (-) sepsis & Pneumonia
Parkland Memorial, 2502 infants

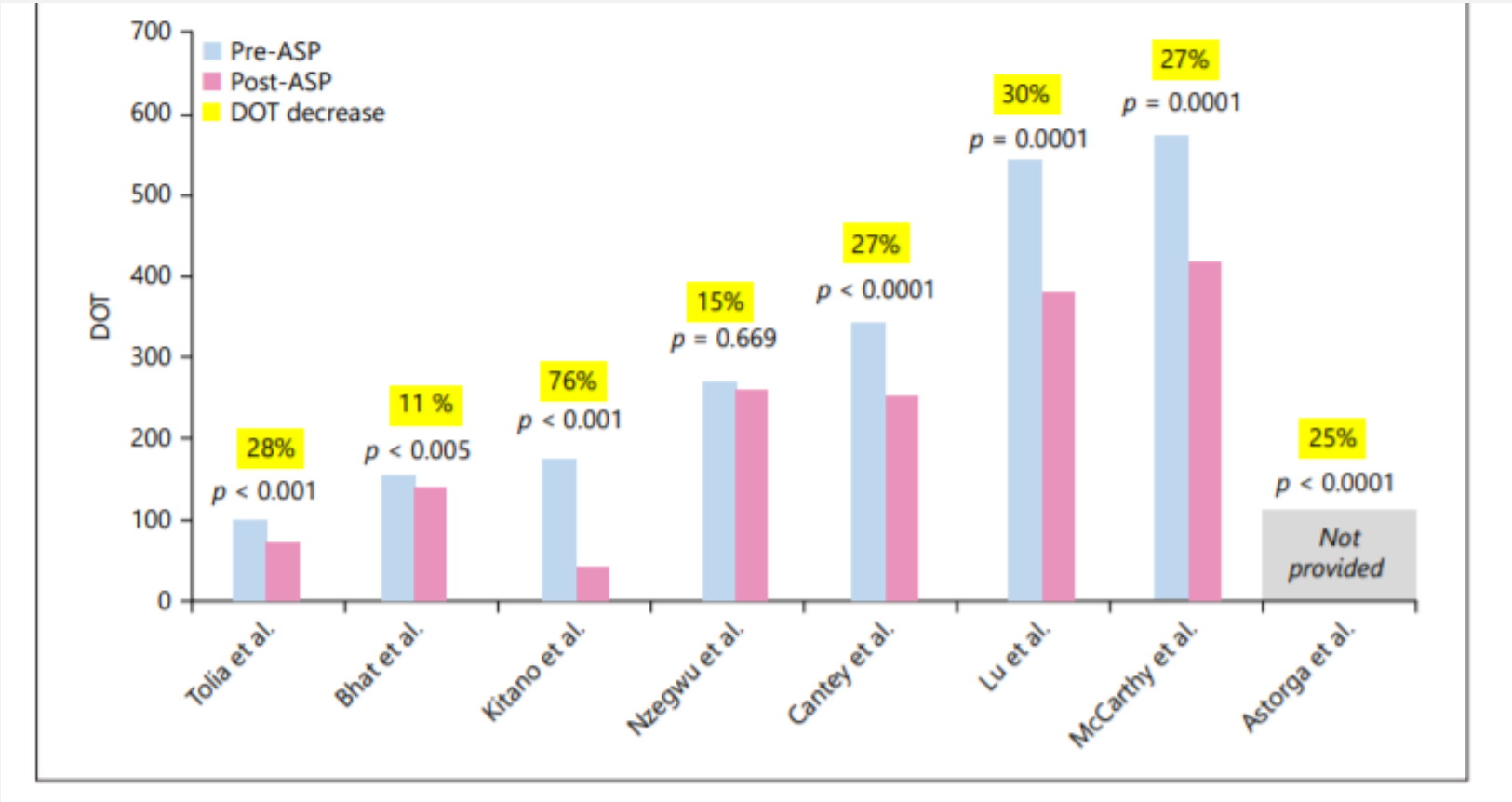
- Stewardship actions:
  - 48h hard stop for EOS R/O sepsis
  - Rec: ≤5d for pneumonia and Cx (-) sepsis
- 48h: 32% to 95%, p<0.0001
- Pneumonia: 36% ≤5d to 72%, p<0.0001
- Cx (-) sepsis: 31% ≤5d to 62%, p<0.04

Number of and proportion Tx'ed for R/O sepsis and pneumonia didn't change.
No infant required additional antibiotics.

Cantey JB et al. Lancet Infect Dis 2016; doi.org/10.1016/S1473-3099(16)30205-5

Can Less Prolonged Therapy be Accomplished?

Decrease in Duration of Therapy

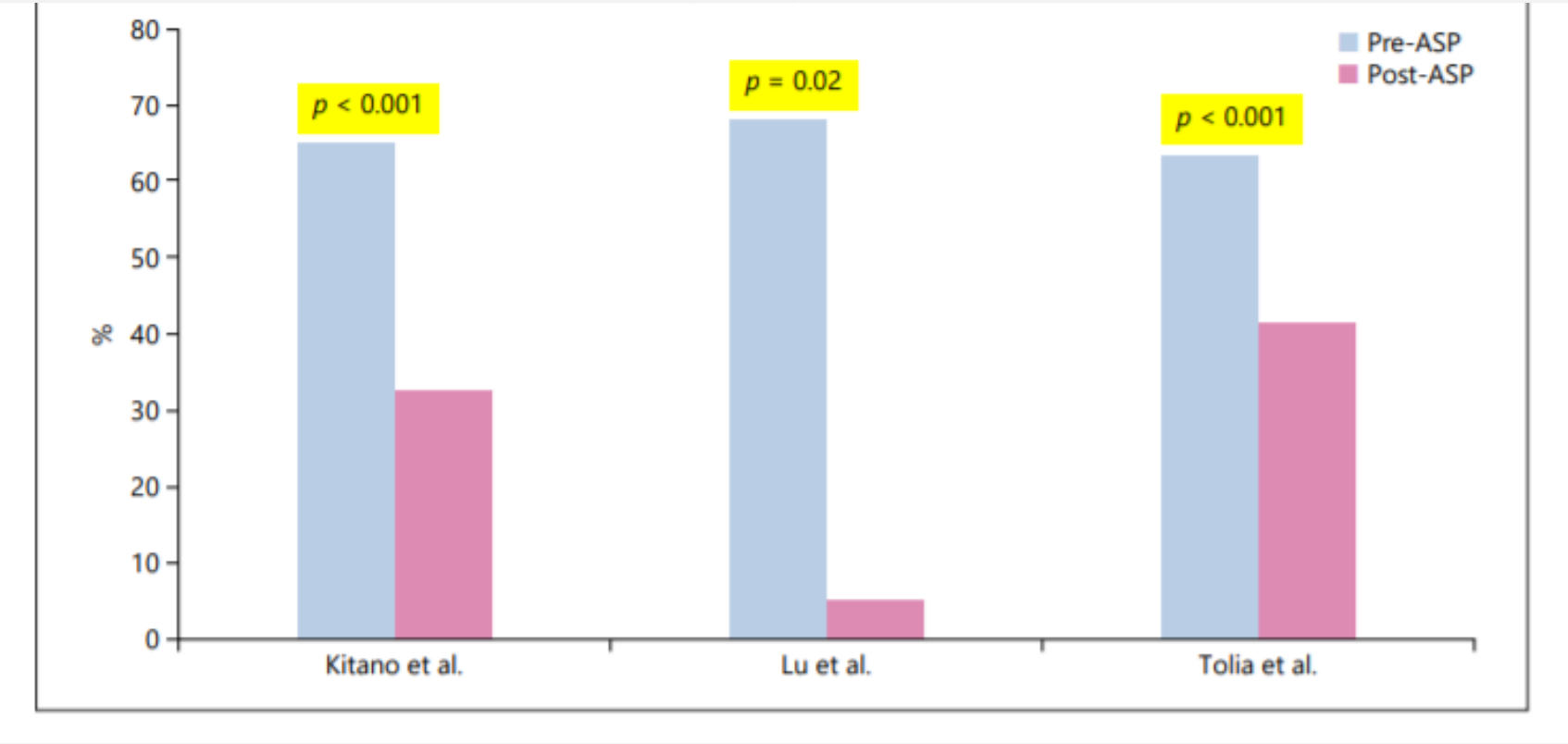


48h stop & education	Clinical algorithm	48h stop	Prosp Audit & feedbk	48h stop; 5d pneumonia & Cx (-) sepsis	48h stop	36h stop	48h stop

Adapted from Rajar P. Neonatology 2020l117:673

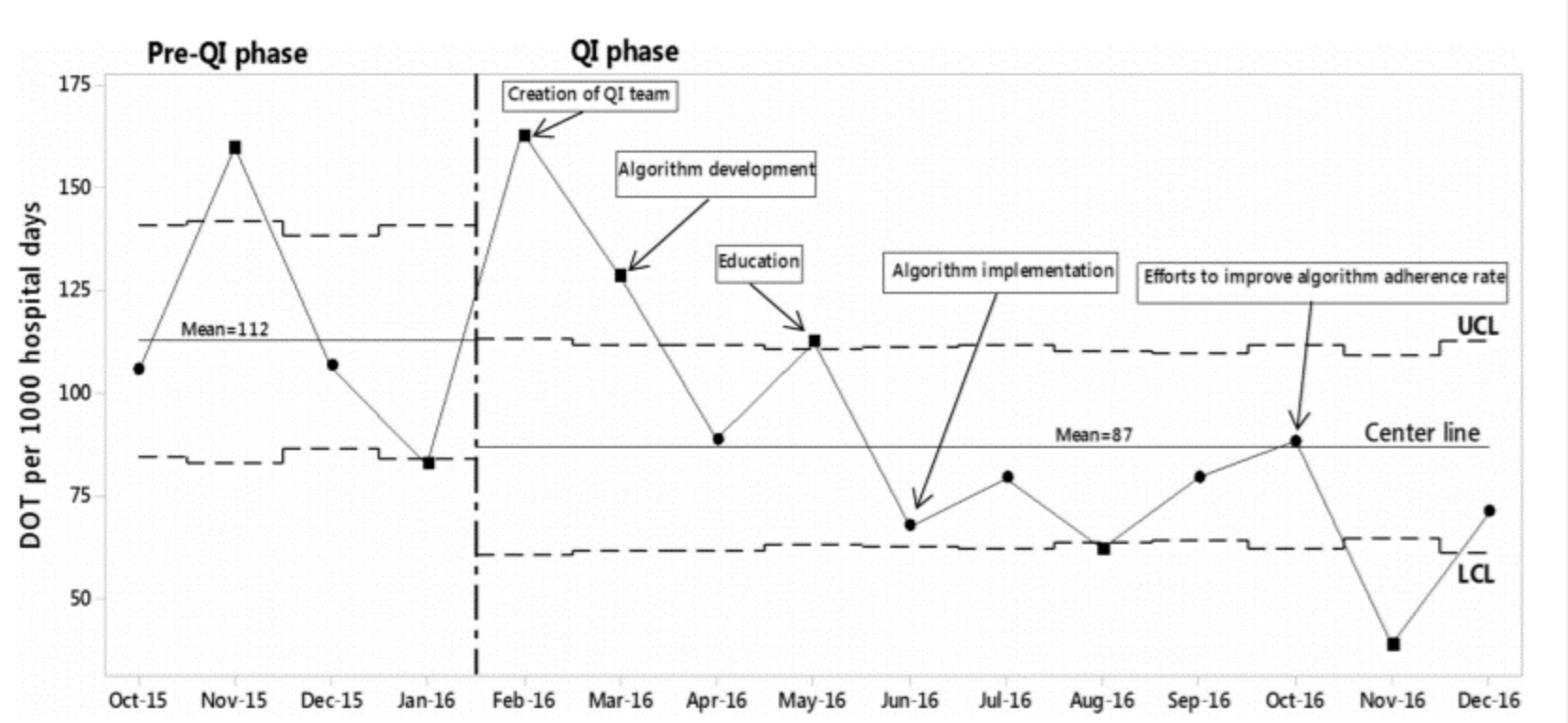
Can <48hr be Accomplished?

Antibiotics >48 Hours



Rajar P. Neonatology 2020l117:673

Guidance Algorithms (emphasis on 36hr stop) 25-34 wks GA only

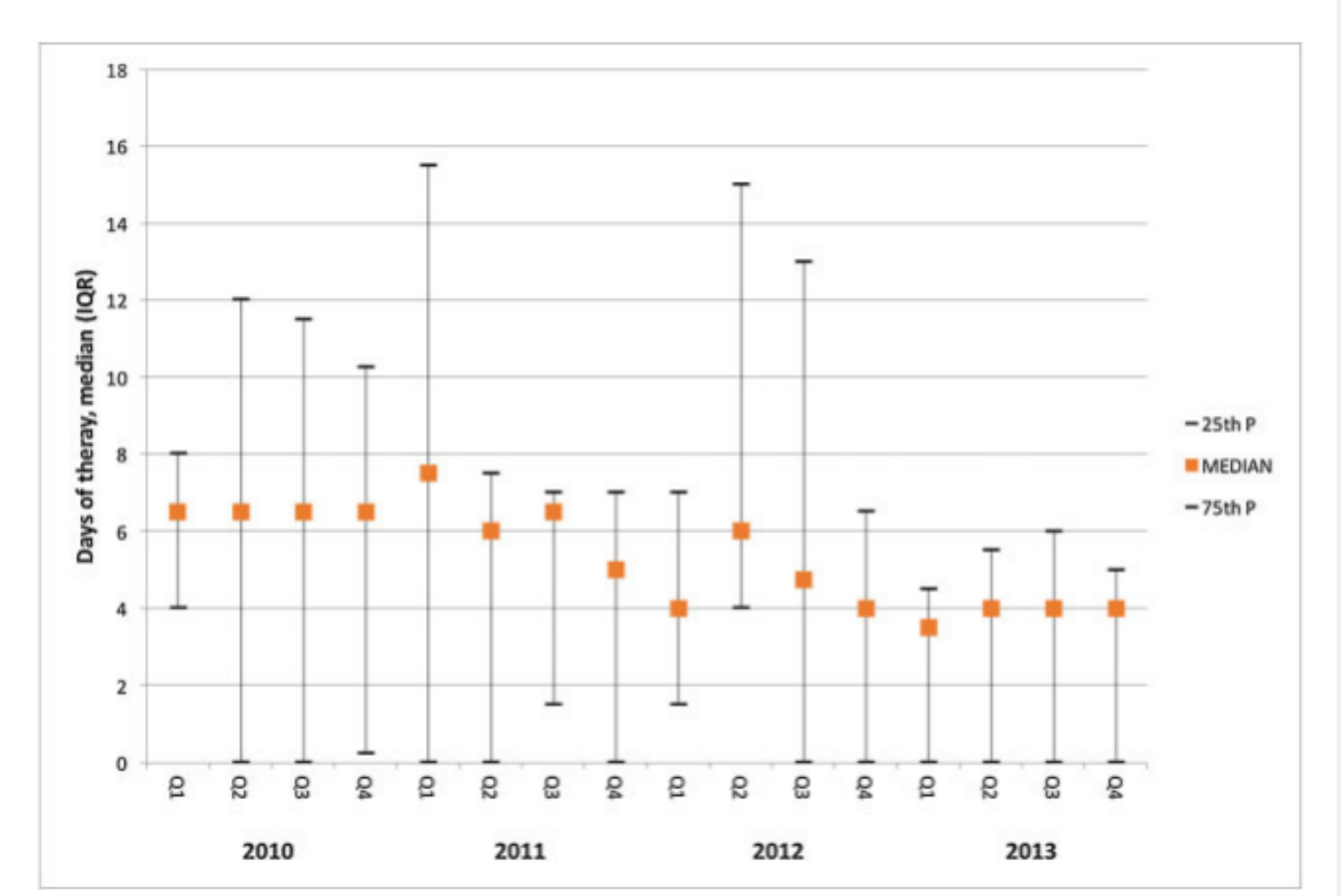


"Empirical AUR"

Bhat R. J Perinatology 2018;38:421

VLBW Only, Hard Stop at 36-48 HOL

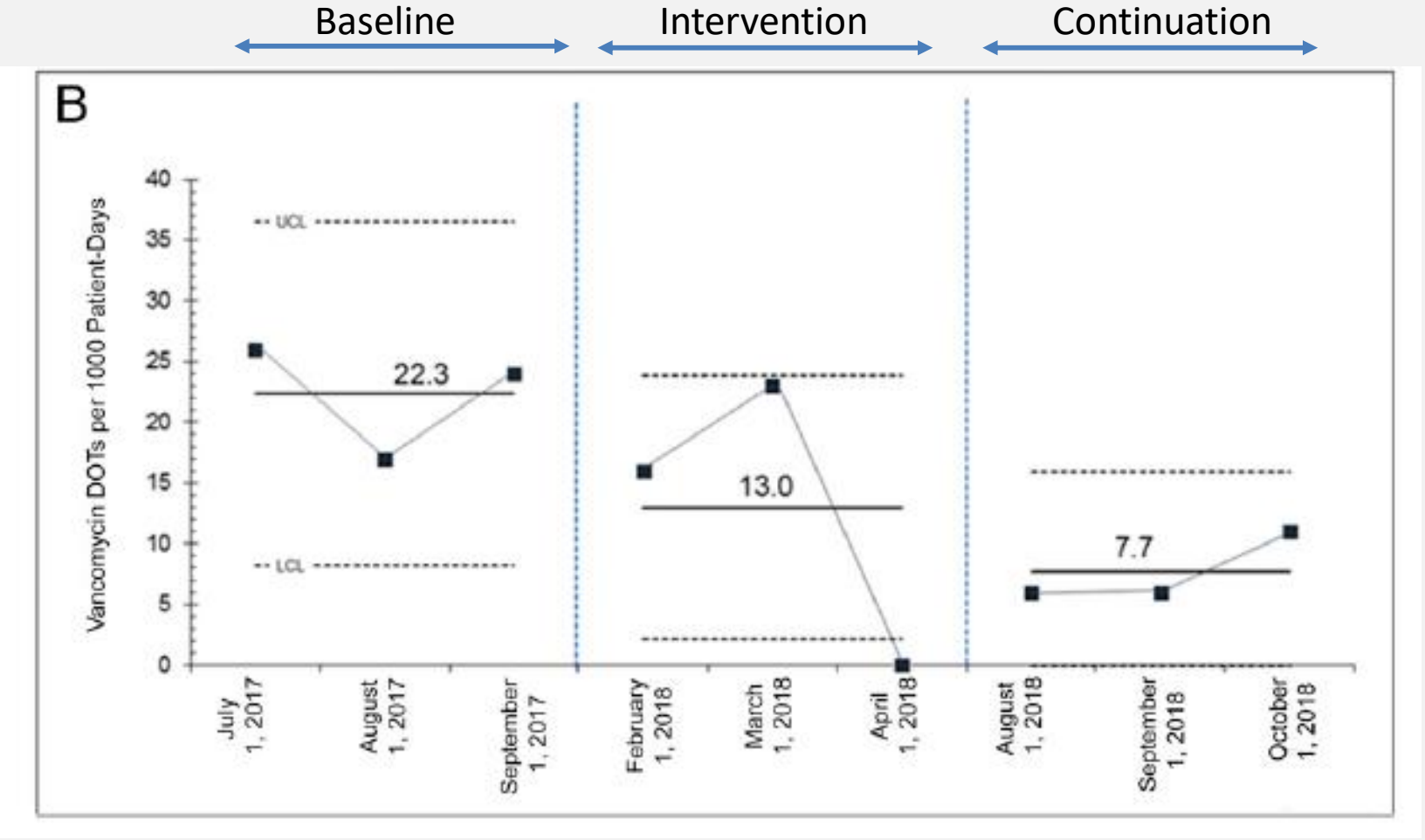
No Other Intervention



Tolia VN. Am J Perinatol 2017;3:105

If Tx'ed, got drug beyond 48 HOL: 88% down to 64%

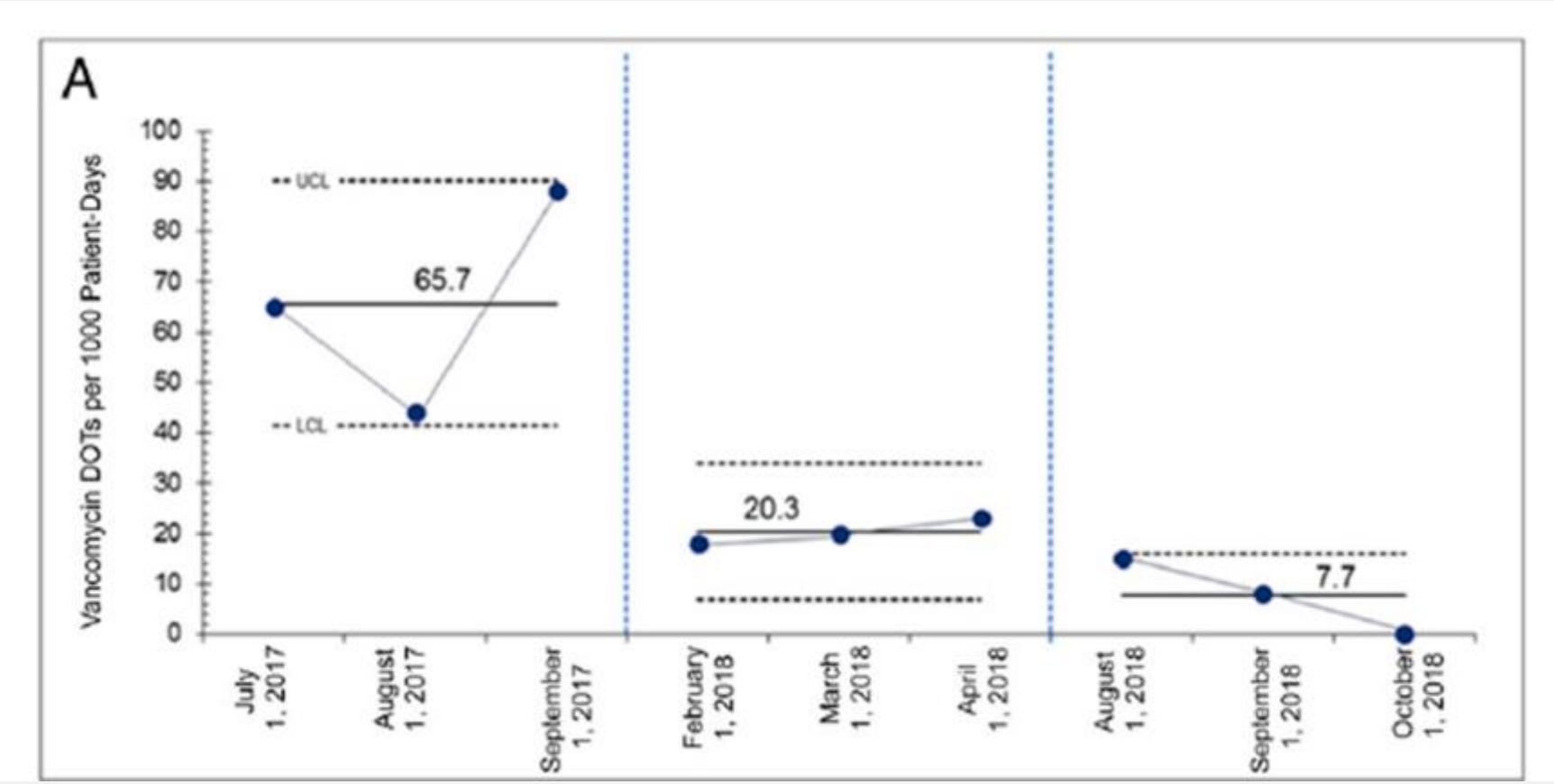
Stop Vancomycin at 48 Hours (for LOS)



63% decrease, No change in Gram (+) disease rates

Hamdy R et al. Pediatrics 2020;146(2)

Stop Vancomycin at 48 Hours (for NEC)



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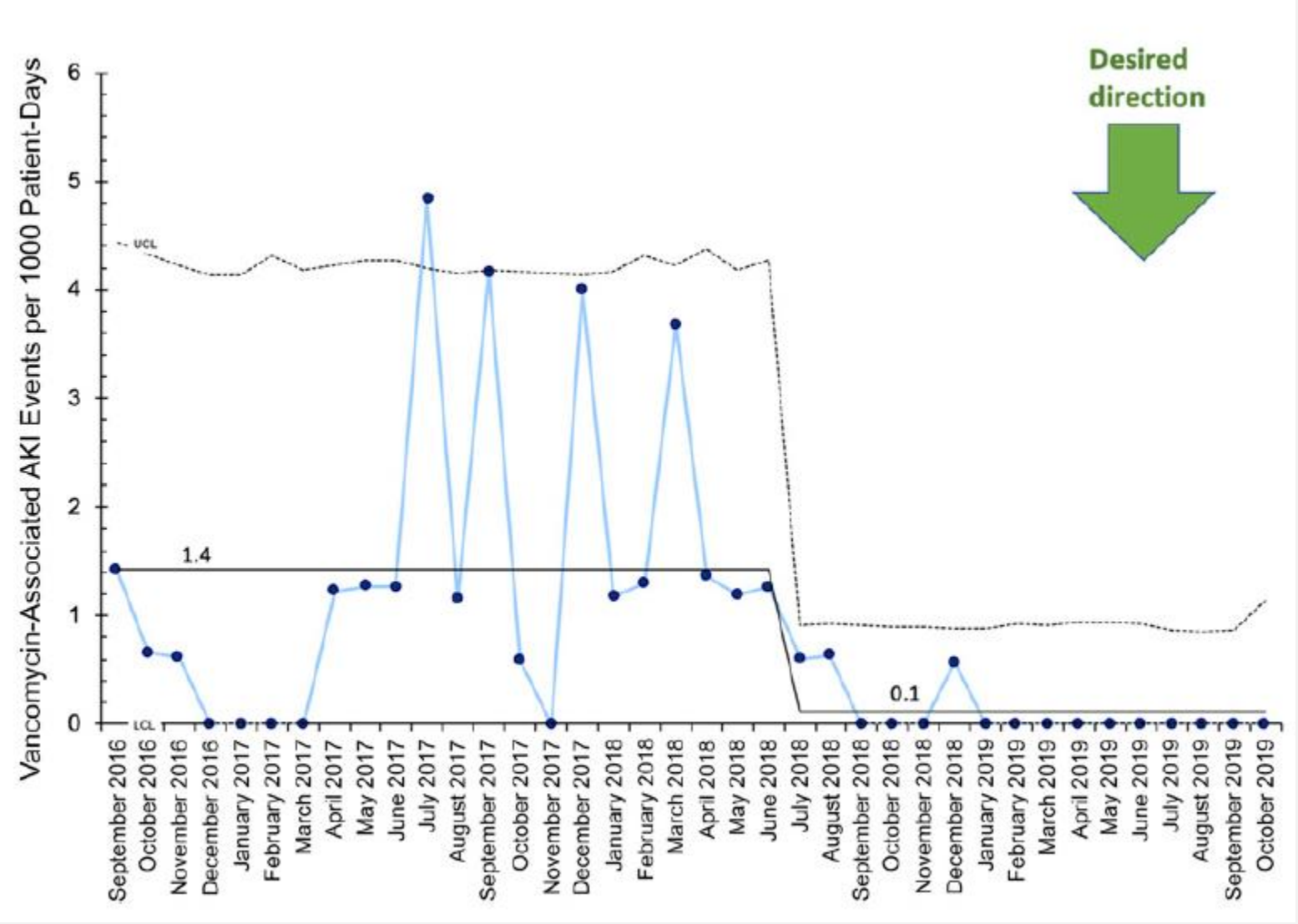
Hamdy R et al. Pediatrics 2020;146(2)

LOSA: Stop Vancomycin at 48 Hours

Change in in AKI Likelihood



Hamdy R et al. Pediatrics 2020;146(2)

In no NICU stewardship study was there a rise in clinical morbidity or mortality post-implementation.

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The evidence base directly comparing various durations of empiric therapy for clinical sepsis in newborns is weak.

RCTs/Cohort Data for Empiric Therapy?

- Pilot study, 52 ROS patients (>30 weeks GA/>1kg)
- Randomized: 2-4d v 7d
  - No diff in Tx failure
- 73 resp distress pts - then well 48h - (>35wk GA)
- Randomized: 4d v 7d
  - No difference in outcomes
    - 2 infants in 4d group had benign tachypnea in 24 obs period

Saini SS. Indian Pediatrics. 2011;48(1):19–24; Engle WD et al. J Perinatol 2000;20:421

RCTs/Cohort Data for Empiric Therapy?

- 695 Cx (-) treated ELBWs (<1000g)

Duration of Treatment (d)	Gestational Age (wk)		
	No. ≤ 26 (%)	No. ≥ 27 (%)	Total (%)
≤ 3	170 (38)	113 (46)	283 (40)
4–6	120 (27)	58 (23)	178 (26)
≥ 7	157 (35)	77 (31)	234 (34)
Total	447 (100)	248 (100)	695 (100)

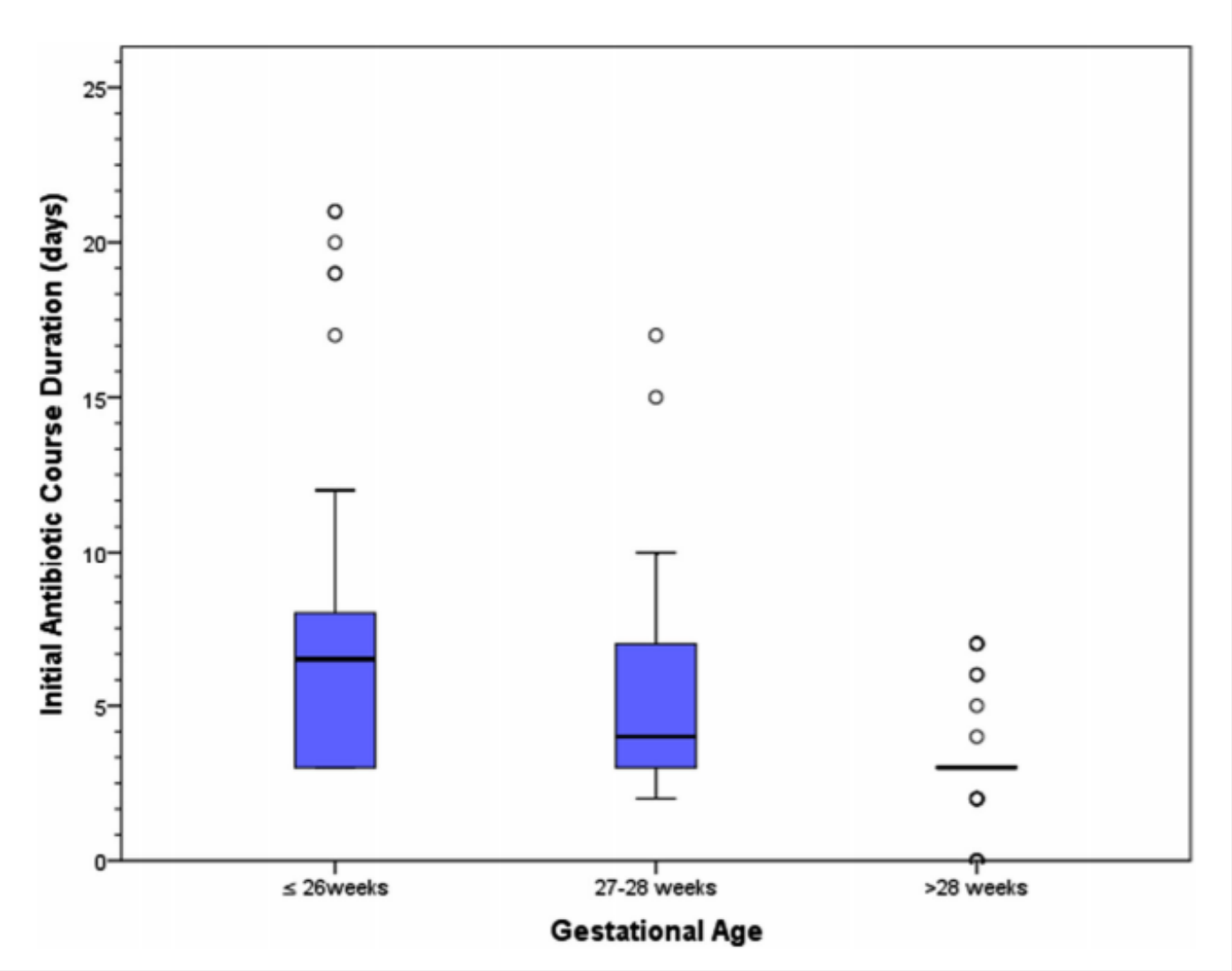
Similar in mortality, morbidity, maternal risks, CRIB scores

- 117 Cx (-) treated VLBWs
  - 59% got ≤3d, 11% 4-5d, 41% >5d
  - Multivariate predictor: Maximum vent support; lab values and risk factors didn't predict use

Cordero L. ICHE 2003;24(9):662–666; Charron et al. Infect Dis Ther 2019;8:209

What Drives Drug use for VLBWs?

Wash Univ, 2014



Charron et al. Infect Dis Ther 2019;8:209-17.

Prolonged Antibiotic Impacts on VLBWs

Canada

In addition to candidiasis and multi-drug resistance…:

Table 3. Regression Analyses Examining the Neonatal Outcomes in Infants Without Infection-Related Morbidities

Outcome	Adjusted Odds Ratio (95% CI)[a]
Composite primary outcome[b]	1.18 (1.13-1.23)
Mortality	2.04 (1.87-2.21)
Chronic lung disease	1.04 (1.00-1.10)
Persistent echogenicity or echolucency on neuroimaging	1.01 (0.96-1.05)
≥3 Stage retinopathy of prematurity	1.18 (1.06-1.32)

N= 2845 infants (w/o infection or NEC) controlled for GA, sex, SNAP-II >20, unit size, admission year, SGA, multiple births, C-section, birth at an outside institution, maternal antenatal corticosteroids

Ting JY. JAMA Pediatrics 2016;170:1181 and editorial by Mukhopadhyay S

Prolonged Antibiotic Impacts on VLBWs

Chicken or egg?

Increasing data suggest microbiome changes may result in systemic GALT responses.

Ting JY. JAMA Pediatrics 2016;170:1181 and editorial by Mukhopadhyay S

We Can (Further) Lessen Empiric Use…

- Stopping drug is the most visible goal now
  - Practice variation is substantial
- U.S. and UK guidelines are harmonized
- Few RCTs; but compelling stewardship data
  - Randomized, cohort, quasi-experimental
  - EOS, LOS & term, VLBW, ELBW
  - No evident bad outcomes
- >2d therapy may lead to bad outcomes