Antibiotic stewardship in the NICU

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Antibiotic stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration.

Walker et al 2017

Antimicrobial stewardship is recognized as critical patient safety and quality imperative to combat the emergence of antimicrobial resistance and preserve the activity of existing agents.

Patel and Saiman 2012

THE LANCET • Vol 355 • March 18, 2000

An antibiotic policy to prevent emergence of resistant bacilli

P de Man, B A N Verhoeven, H A Verbrugh, M C Vos, J N van den Anker

- 2 identical NICUs, different empirical antibiotic regimens
- NICU B: PenG/Tobramycin EOS
  Flucloxacillin/Tobra LOS
- NICU A: Ampicillin/Cefotaxim EOS
  Flucloxacillin/Cefotaxim LOS
- After 6 months regimen change
- Weekly surveillance cultures (rectal and pharyngeal swabs)

THE LANCET • Vol 355 • March 18, 2000

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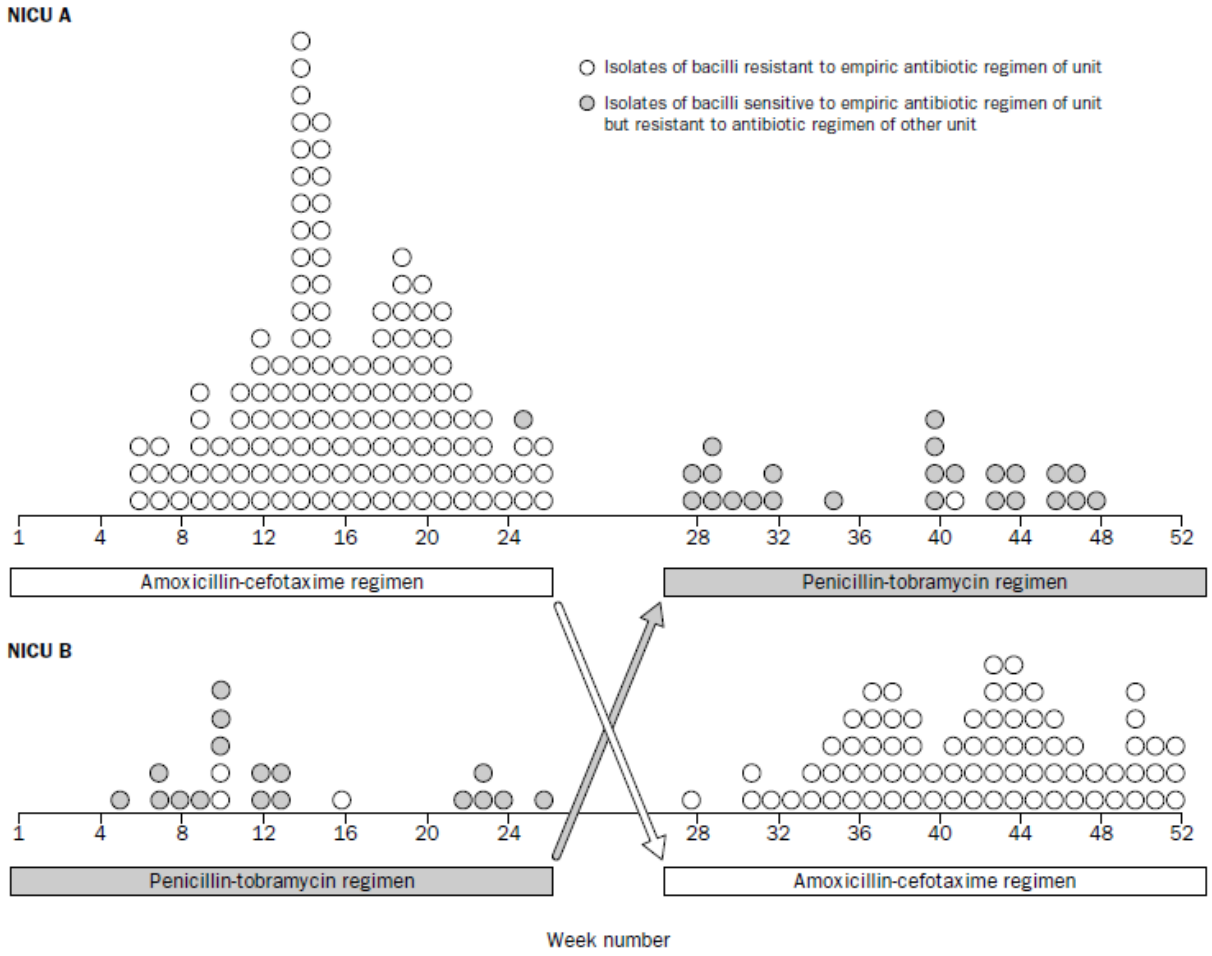


The high amount of antibiotic use, in combination with the low grade of colonisation of neonates at the time of their admissions, turns the NICU into an environment where antibiotic policy is likely to have a pronounced effect on the resistance problem.

DeMan, Lancet 2000

Challenges in the NICU

- Prolonged ICU stay (frequent instrumentation, central lines, parenteral nutrition, repeated courses of antibiotics, mechanical ventilation, surgeries)
- Immature immune system
- Developmental Care - parents and siblings integrated in care – 24h visiting policy
- Open wards – no isolation rooms
- High turnover in perinatal centers – understaffing

High amount of antibiotic use in NICUs

- Point prevalence study of 29 US NICUs - 47% of 827 infants on antibiotics on day of survey (Grohskopf et al. PIDJ 2005)
- 72% of infants in level III US NICUs received at least 1 antibiotic course, only 5% prescribed for culture-proven infection (Scout study, Cantey et al. PIDJ 2015)
- Survey of 127 NICUs across California: 40-fold variation from 2,4% - 97,1% (mean 24,5%) of patient days - „Antibiotic usage in NICUs often is excessive and considerable proportion of antibiotic use lacks clear indication“ (Schulman et al. Pediatrics 2015)

Obviously, concerns about consequences of not treating infections outweigh concerns about the consequences of antibiotic overuse…….

……however, antimicrobial overuse in the NICU population can have grave unintended consequences for individual patients far beyond the emergence of drug-resistant pathogens

Patel and Saiman. Semin Perinatol 2012

Association between 3rd gen cephalosporins and invasive candidiasis in ELBWI

3701 ELBWI 12 centers, 284 (7,7%) invasive candidiasis

Center candidiasis incidence: 2.4% - 24%

Correlation with average use of 3rd gen cephalosporins

TABLE 2 Logistic Regression Analysis of Risk Factors for Invasive Candidiasis Among Infants in 12 NICUs, 1998–2001

Variable	Odds Ratio, Point Estimate	95% Confidence Interval
Center (same as Table 1)		
1	Reference[a]	Reference[a]
2	1.873	0.642–5.465
3	2.187	0.752–6.365
4	2.382	0.983–5.770
5	2.041	0.767–5.432
6	1.877	0.691–5.104
7	2.81	1.206–6.549
8	3.211	1.383–7.455
9	3.532	1.439–8.670
10	3.792	1.383–10.396
11	4.924	2.072–11.703
12	6.542	2.865–14.941
Noncenter variables with $P < .15$		
Exposure to BSA	2.157	1.422–3.271
Gestational age	0.752	0.672–0.841
Maternal hypertension	0.532	0.323–0.877
Gravida status	1.073	0.999–1.153
ROM >24 h	1.530	1.077–2.174
Age at first enteral feed	1.032	1.015–1.049
≥2 doses surfactant	1.438	1.007–2.052
PDA no surgery vs no PDA	1.935	1.340–2.793
PDA surgery vs no PDA	1.586	1.003–2.507
SGA status	1.666	0.925–2.999

Cotton et al. Pediatrics 2006

Association between prolonged duration of initial empirical antibiotics and NEC

5639 ELBWI 19 centers NICHD, sterile cultures

Prolonged duration of initial empirical antibiotic treatment (≥5d) associated with 30% increased rates of NEC and death

Each empirical treatment day associated with 4% increased odds of NEC/death after adjustment for GA, APGAR and race

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

ORs were adjusted for study center, gestational age, small-for-gestational age status, gender, black race, 5-minute Apgar score of <5, rupture of membranes for >24 hours, outborn, prenatal steroid treatment, intrapartum antibiotic treatment, maternal hypertension, maternal hemorrhage, and multiple birth. The total numbers of infants shown represent the numbers of infants with nonmissing outcome and covariate data who were included in each model.

Cotton et al. Arch Dis Child 2010

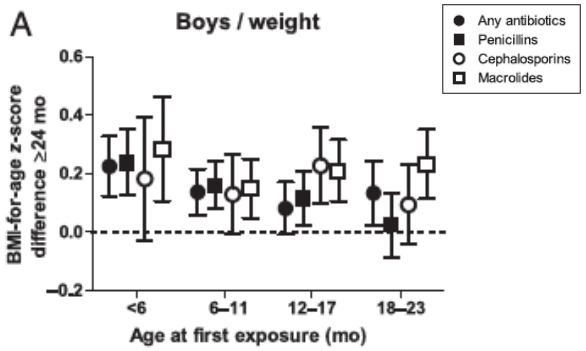
Association between prolonged duration of initial empirical antibiotics and BPD

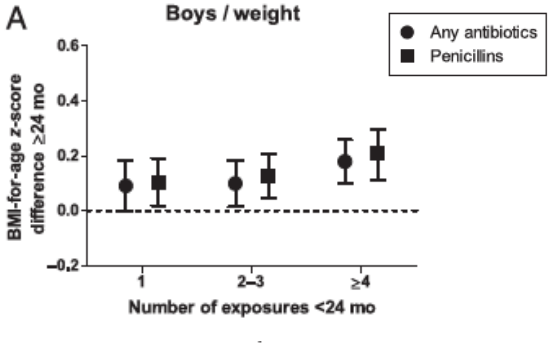
After controlling for severity of illness, each additional day of antibiotic therapy in first 14 DOL was associated with increased risk for and severity of bronchopulmonary dysplasia (patients with sepsis and NEC excluded)

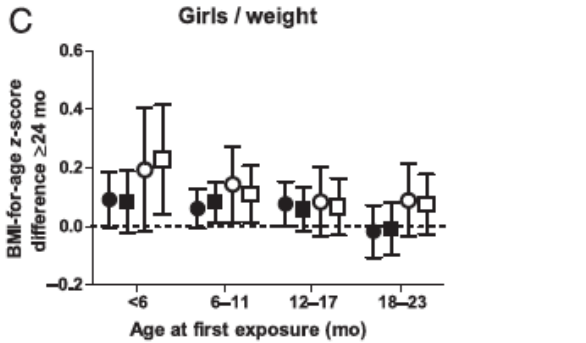
Table II. Multivariable analysis of factors associated with risk for death or BPD and severity of BPD in VLBW infants

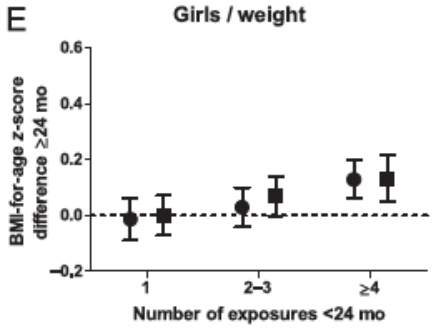
	OR (95% CI)		
Risk factors	**All infants**	**Infants ≤ 28 weeks gestation**	**Infants ≥ 29 weeks gestation**
Primary outcome			
Death or BPD			
CRIB-II score	1.8 (1.65-1.96)	1.73 (1.51-1.98)	1.39 (1.17-1.64)
Days of antibiotic therapy	1.13 (1.09-1.16)	1.13 (1.09-1.18)	1.11 (1.06-1.17)
Postnatal steroids	10.17 (3.17-32.62)	*	20 (4.13-96.75)
Secondary outcomes			
Mild BPD			
CRIB-II score	1.71 (1.32-2.34)	1.93 (1.45-2.87)	1.36 (1.04-1.91)
Days of antibiotic therapy	1.02 (0.96-1.11)	1.08 (0.99-1.22)	1.00 (0.87-1.16)
Moderate BPD			
CRIB-II score	1.77 (1.58-2.03)	1.8 (1.34-2.26)	1.39 (0.93-2.04)
Days of antibiotic therapy	1.14 (0.86-1.68)	1.14 (0.62-1.81)	1.1 (0.58-2.10)
Severe BPD			
CRIB-II score	1.91 (1.54-2.31)	2.11 (1.45-2.89)	1.76 (1.32-2.18)
Days of antibiotic therapy	1.16 (1.04-1.33)	1.15 (1.08-1.27)	1.19 (1.03-1.54)
Sepsis	1.76 (1.08-3.14)	1.65 (0.87-2.63)	1.88 (0.92-4.51)
Increased severity of BPD			
CRIB-II score	1.44 (1.36-1.52)	1.36 (1.27-1.46)	1.44 (1.22-1.71)
Days of antibiotic therapy	1.06 (1.04-1.08)	1.07 (1.05-1.10)	1.11 (1.05-1.16)
Sepsis	1.39 (1.22-1.57)	1.56 (1.08-2.32)	*
Surfactant doses	2.34 (1.85-2.96)	*	*

Antibiotics in early infancy and adverse long-term outcome









Statistical adjustments:
Maternal smoking after first trimester, parental relationships,
mode of delivery, birth weight and birth length

>12.000 healthy infants, antibiotic exposure before 6 months of age or repeatedly during infancy was associated with increased body mass in healthy children.

Antibiotics in early infancy and Asthma

- Prospective birth cohort study Tokyo
- 1550 newborns 2003-2005
- 48% of children received antibiotics within first 2 years of life

⇒ Antibiotic exposure in first 2 years of life associated with asthma, atopic dermatitis and allergic rhinitis at 5 years of age

Associations of Antibiotic Use in Children Younger Than 3 Years With Wheeze and Allergy Outcomes in Children at 5 Years Old

	Crude OR	95% CI		*P* value	Adjusted OR[a]	95% CI		*P* value	Power[b]
		Lower	Upper			Lower	Upper		
Current wheeze									
All antibiotics	1.36	0.95	1.94	.089	1.24	0.86	1.78	.255	
Penicillin	1.11	0.60	2.09	.736	1.16	0.61	2.18	.653	
Cephem	1.44	0.96	2.16	.075	1.39	0.92	2.09	.122	
Macrolide	1.20	0.78	1.85	.410	1.04	0.66	1.64	.856	
Current asthma									
All antibiotics	1.78	1.15	2.75	.009	1.72	1.10	2.70	.017	0.75
Penicillin	1.88	0.58	2.53	.602	1.21	0.58	2.56	.612	
Cephem	2.02	1.28	3.20	.003	1.97	1.23	3.16	.005	0.84
Macrolide	2.59	0.97	2.60	.064	1.46	0.88	2.44	.145	
Current atopic eczema									
All antibiotics	1.42	1.03	1.95	.032	1.40	1.01	1.94	.044	0.55
Penicillin	1.42	0.83	2.44	.203	1.41	0.82	2.43	.219	
Cephem	1.41	0.98	2.04	.068	1.37	0.94	1.99	.103	
Macrolide	1.59	1.09	2.32	.016	1.58	1.07	2.33	.022	0.64
Current rhinitis									
All antibiotics	1.82	1.18	2.80	.007	1.65	1.05	2.58	.030	0.68
Penicillin	1.29	0.23	1.52	.278	0.58	0.22	1.51	.264	
Cephem	1.88	1.19	2.98	.007	1.82	1.12	2.93	.015	0.73
Macrolide	1.77	1.10	1.52	.020	1.50	0.90	2.49	.121	

[a]Adjusted for maternal history of allergy (asthma, atopic dermatitis, or allergic rhinitis), maternal education level, maternal age at pregnancy, maternal body mass index, maternal smoking during pregnancy, mode of delivery, gestational age at delivery, previous live births, daycare, bronchitis, and sex of the child.

Antibiotics in first year of life and inflammatory bowel disease

- Case control study, 36 cases, 360 controls
- Mean age at IBD diagnosis 8.4 years.
- 21 cases (58 %) had one or more antibiotic courses in first year of life compared with 39 % of controls.
- Crohn's disease diagnosed in 75 % of IBD cases
- Odds for being an IBD case 2.9 times higher when receiving one or more courses of antibiotics (95% 1.2-7.0)

	Case	Controls[a]	Total
Overall no. (% of total)	36	360	396
Age at diagnosis[b] (year)			
Mean	8.4±2.5	8.4±2.5	
Median	9	9	
Range	2–12	2–12	
Antibiotic dispensations—no. (%)			
0	15 (42)	221 (61)	236 (60)
1+	21 (58)	139 (39)	160 (40)
Mean	1.6±1.9	0.9±1.5	
Median	1	0	
Range	0–6	0–8	

Shaw. Am J Gastroenterol 2010

.....urgent need for effective antibiotic stewardship efforts in the NICU setting.....

Cantey 2017

Not only increased risk of antibiotic resistance but also increased individual risk for adverse outcomes after prolonged antibiotic use in preterm infants

CDC AT A GLANCE

CDC Campaign to Prevent Antimicrobial Resistance in Healthcare Settings

12 Steps to Prevent Antimicrobial Resistance Among Hospitalized Children

Strategy: Prevent Infection

Step 1. Vaccinate hospitalized children and staff
- Vaccinate according to AAP/ACIP/AAFP recommendations
- Review immunization records and catch-up with routine vaccinations
- Give influenza vaccine to at-risk infants and children
- Give influenza vaccine to all health workers

Step 2. Get the devices out
- Insert catheters and devices only when essential
- Use proper insertion techniques and follow guidelines for catheter-care
- Remove catheters and other devices when no longer essential

Strategy: Diagnose and Treat Infection Effectively

Step 3. Use appropriate methods for diagnosis
- Order appropriate laboratory tests
- Obtain appropriate specimens

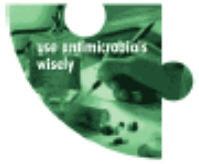
Step 4. Target the pathogen
- Target empiric antimicrobial therapy to likely pathogens
- Target definitive antimicrobial therapy to known pathogens

Step 5. Access the experts
- Consult infectious disease experts for complicated infections

Strategy: Use Antimicrobials Wisely

Step 6. Practice antimicrobial control
- Optimize timing, regimen, dose, route, and duration of antimicrobial treatment and prophylaxis
- Follow policies and protocols in your institution

Step 7. Use local data
- Know your regional, institutional, and high-risk unit-specific antibiograms
- Know your formulary
- Know your patient population (birthweight, age, and setting)



Step 8. Treat infection, not contamination or colonization
- Use proper antisepsis for drawing blood cultures
- Avoid routine culturing of catheter tips
- Treat bacteremia, not catheter colonization or contamination

Step 9. Know when to say "no"
- Avoid routine use of vancomycin, extended-spectrum cephalosporins,* carbapenems, oral quinolones, and linezolid
- Follow antimicrobial prescribing guidelines from CDC, AAP, and other professional societies

Step 10. Stop treatment
- When infection in unlikely
- When culture results indicate no clinical need for antimicrobials
- When infection is cured

Strategy: Prevent Transmission

Step 11. Practice infection control
- Be familiar with recommended infection control precautions
- Consult infection control teams
- Stay home when you are sick
- Restrict visitors with symptoms of respiratory or gastrointestinal tract infections from contact with your patients

Step 12. Practice hand hygiene
- Wash your hands or use an alcohol-based hand rub before and after patient contact
- Set an example

Get Smart Campaign - BeAntibioticsAware

- CDC antimicrobial stewardship initiative for **acute care setting 2011**
- Goal: promotion of timely and appropriate antibiotic utilization for hospitalized patients
  - Ongoing evaluation of need for antibiotics
  - Appropriate selection of a regimen
  - Optimization of dose, route and duration of therapy
- Applied to
  - Empiric use
  - Definitive use
  - Prophylaxis

BE ANTIBIOTICS AWARE
SMART USE, BEST CARE

CDC CAMPAIGN TO PREVENT ANTIMICROBIAL RESISTANCE IN HEALTHCARE SETTINGS

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Diagnosis of neonatal sepsis

- Blood culture gold standard
- **Use minimum of 1ml of blood when ever possible**
- S… used
- C… less t…
- E… a…
- A… n a…

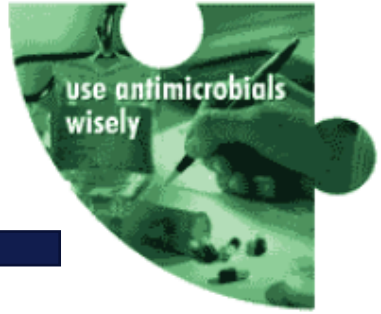
„To end the culture of culture-negative sepsis, providers must systematically obtain appropriate blood cultures . . . and then trust them.“

Cantey and Baird 2017

Biomarkers for ruling out neonatal infections

- Normal I:T ratio or 2 negative CRP values 24hrs apart can rule out EOS with high accuracy
- Frantz et al.: IL-8 plus CRP vs CRP alone reduces antibiotic use by 73% in preterm infants with suspected LOS without increasing missed infections
- PCT - higher sensitivity compared to CRP for neonatal sepsis
- **Interpret biomarkers always in combination with clinical picture**

Strategy: Use Antimicrobials Wisely



Step 6. Practice antimicrobial control
- Optimize timing, regimen, dose, route, and duration of antimicrobial treatment and prophylaxis
- Follow policies and protocols in your institution

Step 7. Use local data
- Know your regional, institutional, and high-risk unit-specific antibiograms
- Know your formulary
- Know your patient population (birthweight, age, and setting)

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Step 10. Stop treatment
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Selecting Empiric Therapy

- Promt treatment reduces mortality of early neonatal sepsis ⇒ start early already at sepsis suspicion (e.g. ampicillin or PenG plus gentamicin), stop after 48hrs if cultures and laboratory parameters remain negative
- Know blood-culture isolates of your ward in order to establish an empirical regimen for nosocomial sepsis (e.g. vancomycin or oxacillin plus gentamicin)
- Avoid agents with overlapping spectrum of activity (no evidence of increased efficacy, potential of increased toxicity)
- Avoid using 3rd generation cephalosporins in the NICU
- Do not use carbapenems empirically

Re-evaluating Antibiotic Regimen

- Evaluate daily whether antibiotics are still necessary (>97% of blood cultures with clinically meaningful bacterial growth are positive within 48hrs)
- Stop antibiotics in case of negative cultures and stable patient by 48hrs
- Limit perioperative prophylaxis to maximum of 48hrs after surgery (max 72hrs after cardiac surgery)
- Switch to antibiotic with narrower spectrum if possible
- Do not treat positive cultures from non-sterile body sites (e.g. tracheal aspirates) when clinical course is not suggestive of infection

Patel and Saiman, Semin Perinatol 2012

Examples of how to translate these principles into specific action

Utilize local epidemiology data	Avoid using meropenem for suspected LOS if rates of MDR gram-negative organisms is low
Avoid therapy with overlapping activity	Do not simultaneously use pip/taz or meropenem with metronidazole to treat NEC
Give the right dose and interval of drug	Target vancomycin trough levels at 15-20mg/L to treat MRSA pneumonia
Review culture results and adjust antibiotics - narrow antibiotic coverage promptly	MSSA - switch from vancomycin to flucloxacillin or oxacillin Discontinue vancomycin when gram-neg bacilli are isolated
Stop therapy if indicated by culture results	Discontinue antibiotics after 48hrs if blood culture is negative and ongoing infection is not suspected

Patel and Saiman, Semin Perinatol 2012

Antibiotic Use in NICUs and Adherence with CDC 12 Step Campaign to Prevent Antimicrobial Resistance

- Multicenter retrospective analysis - 4 tertiary NICUs US
- 50 infants of each NICU studied
- Analysis of appropriateness of antibiotic use (after 72hrs of life) based on CDC guidelines

Patel et al. PIDJ 2009

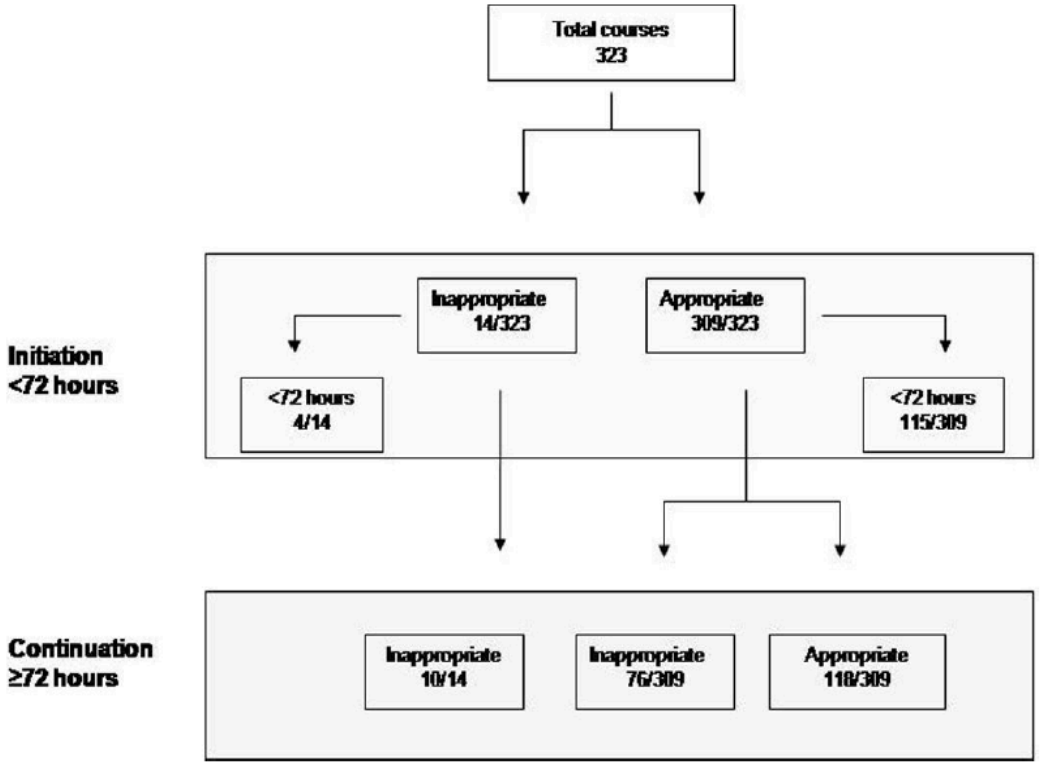
Selected CDC 12 steps and examples of inappropriate use in NICUs

Of 323 antibiotic courses, 90 (28%) courses and 806 (24%) antibiotic-days were judged to be nonadherent.

70 infants (35%) received at least 1 inappropriate course

Inappropriateness more common with continuation than initiation (39% vs 4%, $p<0.001$)

Failure to narrow or discontinue antibiotics represented 9% of all antibiotic use.

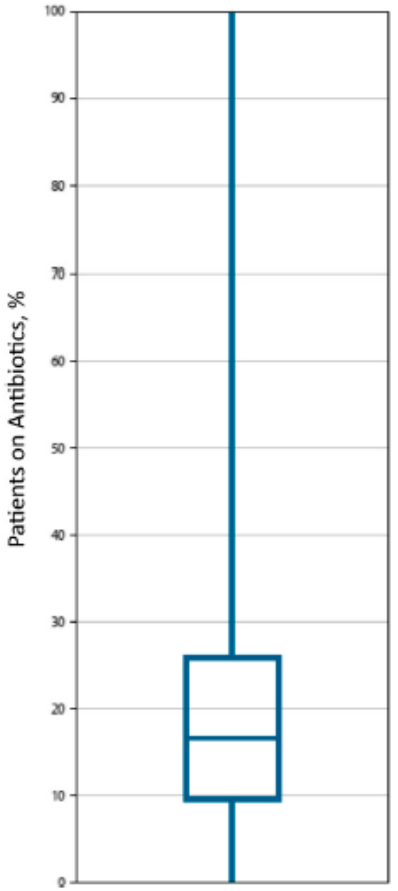


Patel et al. PIDJ 2009

Adherence of Newborn-Specific Antibiotic Stewardship Programs to CDC Recommendations

- Cross-sectional audit of VONN members Feb 2016
- 143 centers completed self-assessment
- 725/4127 on antibiotics (17%)
- Only 26% of infants on >48hrs of antibiotics had positive culture results

	No. (N = 725)	%
No culture obtained	93	13
Culture obtained, no organism identified	540	74
Organism identified	92	13
Known nonresistant organism	45	49[a]
Coagulase-negative *Staphylococcus*	20	22[a]
Methicillin-resistant *Staphylococcus aureus*	3	3[a]
Vancomycin-resistant *Enterococcus*	0	0[a]
Gram-negative bacilli resistant to third-generation cephalosporin	5	5[a]
Fungal pathogen	12	13[a]
Other	18	20[a]



Ho et al. Pediatrics 2018

Lancet Infect Dis 2016;
16: 1178–84

Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study

Joseph B Cantey, Phillip S Wozniak, Jessica E Pruszynski, Pablo J Sánchez

- All AB use in NICU patients monitored and analyzed during 14 months period - areas determined where AB use could be reduced - implement interventions while monitoring for safety
- Most inappropriate antibiotic use occured with continuation, not initiation of antibiotics
- Continuation of empirical therapy beyond 48h, pneumonia and culture-negative „sepsis“ selected as targets for intervention.

Intervention period:

- Empirical AB set to discontinue after 48h in electronic medical record
- Duration of therapy for pneumonia and culture-negative sepsis limited to 5 days

Lancet Infect Dis 2016;
16: 1178–84

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Primary outcome: antibiotic use, defined as days of therapy per 1000 patient days - baseline vs intervention period

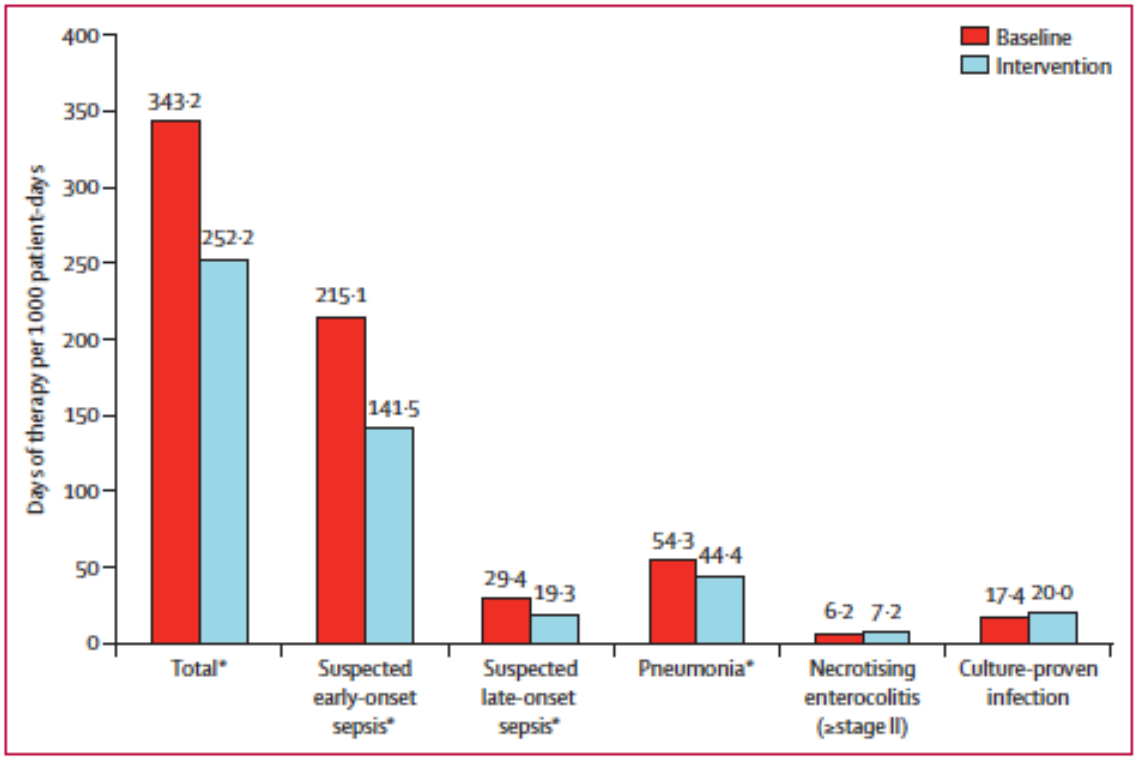

Figure 2: **Antibiotic use by indication during baseline and intervention periods**
*Statistically significant differences.

Statistically significant 27% reduction in AB use between baseline and intervention period (343 vs 252 days/1000 patient days, p<0.0001)

Lancet Infect Dis 2016;
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Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study

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No difference in safety outcomes

- Re-institution of AB within 14d after discontinuation for any

Antibiotic stewardship in the neonatal intensive care unit can be achieved safely.

al

ne

individual centre

⇒ Effective interventions to reduce antibiotic use can then be designed and implemented in a NICU without adverse effects

Take home messages.....

- Days on antibiotics are associated with increased risk of NEC, BPD, death and potential adverse long-term outcomes of preterm infants
- Antibiotic stewardship interventions are particularly important for NICU patients
- Always take blood-cultures (ideally min 1ml) before starting antibiotics
- Use local epidemiology to guide the selection of empiric therapy
- Develop local antibiotic policies to guide rational empirical treatment and to restrict broad-spectrum antibiotics
- Do not use empiric 3rd gen cephalosporin or penem - use aminoglycoside-based empirical regimens
- Do not use antibiotics with overlapping antimicrobial activity

Take home messages.....

- Do not treat colonisation
- Do not use prophylactic antibiotics in case of ventilation, chest tube, i.v. line, ...
- Limit perioperative prophylaxis to maximum of 48hrs after surgery (max 72hrs after cardiac surgery)
- Trust your microbiology - rely on blood culture results and adapt the empirical regimen when appropriate
- Stop antibiotics if cultures remain negative and child is clinically well after 48hrs
- Try your best to prevent infections by reinforcing infection control - HAND HYGIENE HAND HYGIENE HAND HYGIENE

Antibiotic stewardship in the NICU

Yes, we can!

Together we can provide better outcomes for our patients