Stewardship Begins in the NICU

Rita Drummond Olans,
DNP, CPNP-PC, APRN-BC, RN
3.18.19
I have nothing to disclose
Learning Objectives

Define developing concepts of antimicrobial stewardship

Identify opportunities for stewardship in your NICU world

Explain the role of parents in stewardship
Learning Objectives

Define developing concepts of antimicrobial stewardship

Identify opportunities for stewardship in your NICU world

Explain the role of parents in stewardship
Stewardship (noun)

the conducting, supervising, or management of something

especially: the careful and responsible management of something entrusted to someone’s care

Merriam Webster https://www.merriam-webster.com/dictionary/stewardship
Antimicrobial Stewardship is a quality paradigm whose desired goal is the optimal use of antibiotics to accomplish a lower rate of antibiotic resistance while achieving the most optimal clinical outcome(s).

TATFAR (2011). *Recommendations for the future collaboration between the U.S. and EU.*
Antimicrobial Stewardship

- Systematic
- Data Driven
- Intuitive
- Pragmatic
The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism.

“*I hope this evil can be averted*”
Penicillin cures gonorrhea in 4 hours. See your doctor today.
GC’s March to Resistance

1930s: Introduction of sulfonamide antimicrobials to treat GC

1940: Due to increasing resistance, penicillin and tetracycline no longer recommended to treat GC

1940s: Due to increasing resistance, sulfonamides no longer recommended for GC treatment; penicillin becomes treatment of choice

1950

1960

1970

1980

1990

2000

2010

2015

1980s: Fluoroquinolones become predominant treatment

2007: Fluoroquinolones no longer recommended; cephalosporins (incl. injectable ceftriaxone and oral cefiximine) become backbone of GC treatment

2012: Cefixime no longer recommended as first-line regimen, leaving ceftriaxone-based dual treatment as last recommended treatment

2015: Ceftriaxone plus azithromycin is the only recommended treatment for treating GC

The Evolution of Bacteria on a “Mega-Plate” Petri Dish (Kishony Lab)
The Critical Role of the Staff Nurse in Antimicrobial Stewardship—Unrecognized, but Already There

Richard N. Olans, R. D. Olans, and Alfred DeMaria Jr

An essential participant in antimicrobial stewardship who has been unrecognized and underutilized is the “staff nurse.” Although the role of staff nurses has not formally been recognized in guidelines for implementing and operating antimicrobial stewardship programs (ASPs) or defined in the medical literature, they have always performed numerous functions that are integral to successful antimicrobial stewardship. Nurses are antibiotic first responders, central communicators, coordinators of care, as well as 24-hour monitors of patient status, safety, and response to antibiotic therapy. An operational analysis of inpatient admissions evaluates these nursing stewardship activities and analyzes the potential benefits of nurses’ formal education about, and inclusion into, ASPs.

**Keywords.** antimicrobial stewardship; antimicrobial stewardship program; antibiotic resistance; nursing, turnaround time.
Nurses, and Antimicrobial Stewardship

Nurses already perform activities of stewardship, but current models of stewardship programs in hospitals do not integrate their contributions in the stewardship paradigm.

Olans, Olans, & Demaria. (2016). Clinical Infectious Diseases, 62(1), 84-89
What Happens When Nurses Are Engaged

Pennsylvania

FIGURE. Central line–associated bloodstream infection rate* in 66 intensive care units (ICUs), by ICU type and semiannual period — southwestern Pennsylvania, April 2001–March 2005

- All other unit types
- Medical/surgical units

Rate

<table>
<thead>
<tr>
<th>Year</th>
<th>April</th>
<th>October</th>
<th>April</th>
<th>October</th>
<th>April</th>
<th>October</th>
<th>April</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2002</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2003</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2004</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2005</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Semiannual period

*Pooled mean rate per 1,000 central line days.

Includes cardiothoracic, coronary, surgical, neurosurgical, trauma, medical, burn, and pediatric ICUs.

P<0.001

MMWR 2005;54:1013-16

Michigan

103 ICUs at 67 Michigan hospitals, 18 months


[Slide courtesy of Arjun Srinivasan, MD]
Critical Role of Bedside Nurses
Lessons Learned From CLABSI Prevention

• Nurses can play a critical role when they know the process and can watch for omissions.

• Nurses are key in prompting the provider/team to perform key actions that might get overlooked.

• Nursing time-outs in this model enhanced the patient safety and have demonstrably achieved superior outcomes.
Pedi CAUTI

Monthly CAUTI rates, July 2009 through June 2012. Upper control limit set at 3 o: red lines; mean CAUTI rate: green lines. Lower control limits were below zero for both pre- and postintervention periods.
Fig 4. Members of the comprehensive multidisciplinary antibiotic management program (AMP) team at the Hospital of the University of Pennsylvania (Philadelphia, PA). P&T, Pharmacy and Therapeutics.

WHO is MISSING?
Low Hanging Fruit
Recognized Nurses’ Strengths

Communication
Patient Safety Protection
History Taking
Operationalizing Protocols
Attention to Detail
Observation
Nurses document well
Cultures

Cultures are taken before initiation of antibiotics except in the case of sepsis. Cultures are collected appropriately, documented appropriately and transported appropriately.
Allergy History

“Penicillin Allergy” label: Consequences

- Increased MDROs
- Increased *Clostridium difficile*
- Increased post-operative infections
- Increased lengths of stay
- Increased hospital costs
Timely conversion from IV -> PO

Nurse alerts the prescribing physician the patient has progressed from NPO to fluids & food by mouth.
Redefining the Antibiotic Stewardship Team:
Recommendations from the American Nurses Association/Centers for Disease Control and Prevention Workgroup on the Role of Registered Nurses in Hospital Antibiotic Stewardship Practices
Effective Date: 2017

https://www.cdc.gov/antibiotic-use/healthcare/pdfs/ANA-CDC-whitepaper.pdf
Learning Objectives

Define
Define developing concepts of antimicrobial stewardship

Identify
Identify opportunities for stewardship in your NICU world

Explain
Explain the role of parents in stewardship
1. Leadership Commitment: Dedicating necessary human, financial and information technology resources

2. Accountability: Appointing a single leader responsible for program outcomes. Experience with successful programs show that a physician leader is effective

3. Drug Expertise: Appointing a single pharmacist leader responsible for working to improve antibiotic use.

4. Action: Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e. “antibiotic time out” after 48 hours)

5. Tracking: Monitoring antibiotic prescribing and resistance patterns

6. Reporting: Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff

7. Education: Educating clinicians about resistance and optimal prescribing

CDC. (2017). Core elements of hospital antibiotic stewardship programs.
1. **Leadership Commitment**: Dedicating necessary human, financial and information technology resources

2. **Accountability**: Appointing a single leader responsible for program outcomes. Experience with successful programs show that a physician leader is effective.

3. **Drug Expertise**: Appointing a single pharmacist leader responsible for working to improve antibiotic use.

4. **Action**: Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e. “antibiotic time out” after 48 hours).

5. **Tracking**: Monitoring antibiotic prescribing and resistance patterns.

6. **Reporting**: Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff.

7. **Education**: Educating clinicians about resistance and optimal prescribing.

---

CDC. (2017). Core elements of hospital antibiotic stewardship programs.
How Are CDC Guidelines Stewardship Guidelines Being Implemented in Nurseries and NICU’s?

143 centers completed structured self-assessments. No center addressed all 7 core elements.

CONCLUSIONS: Significant gaps exist between CDC recommendations to improve antibiotic use and antibiotic practices during the newborn period. Three-quarters of infants who received antibiotics for >48 hours did not have infections proven by using cultures.

Ho, T. et al. (2018). Adherence of newborn-specific antibiotic stewardship programs to CDC recommendations. Pediatrics, 142(6)
Antibiotic Stewardship in the Neonatal Intensive Care Unit: Lessons From Oxygen and,
Duration of Initial Empirical Antibiotic Therapy and Outcomes in Very Low Birth Weight Infants

Both can be found in *Pediatrics*, March 2019, vol. 143, Issue 3
Early Onset Sepsis

- Overall 0.77 to 1 per 1000 Live births
- Incidence 11-20 per 1000 VLBW (<1500 g) births over past 2 decades
  - <1000 grams- 26 per 1000
- Increases with lower gestational age and birthweight
- 30-50% mortality in infants 22-28 weeks

Simonsen KA, Anderson-Berry AL CMR 2014
Mukhopadhyay S, Puopolo K PIDJ 2017

[Slide Courtesy of Dr. Jason Newland]
Early Onset Sepsis - Incidence

Simonsen KA, Anderson-Berry AL CMR 2014

Cases/1000 live births

Term Preterm

Black Non-Black

Simonsen KA, Anderson-Berry AL CMR 2014

[Slide Courtesy of Dr. Jason Newland]
Early Onset Sepsis - Term Infants

GBS
E. coli
Viridans Strep
S. aureus

Simonsen KA, Anderson-Berry AL CMR 2014
Very Low Birth Weight (<1500 grams)-EOS

• Retrospective study from Brigham and Women’s Hospital
• January 1, 1990 to May 31, 2015
• 2 blood cultures routinely performed (aerobic and anaerobic)
• Commensals (eg. Coag neg Staph) only a case if grown from 2 cultures and treated

Mukhopadhyay S, Puopolo K PIDJ 2017
Very Low Birth Weight (<1500 grams)-EOS

- 109 with culture confirmed (rate 20.5 cases/1000 VLBW
- Which of the following was the most common bacteria isolated:
  - Group B streptococcus 20.2%
  - *Escherichia coli* 36.7%
  - *Listeria monocytogenes* 1.8%
  - *Bacteroides species* 13.8%
  - *Staphylococcus aureus* 2.8%

Mukhopadhyay S, Puopolo K PIDJ 2017
Early Onset Sepsis - Preterm Infants

Simonsen KA, Anderson-Berry AL CMR 2014

[Slide courtesy of Dr. Jason Newland]
Very Low Birth Weight (<1500 grams)

• 106 (97%) of culture confirmed EOS had preterm labor, preterm rupture of membranes or chorioamnionitis
  • 2 infants with Listeria

Subgroup Analysis-

• 605 did not have above risk factors and were delivered by C-section for pre-eclampsia treatment
  • Only 1 (1.7 per 1000) had EOS and was a patient with 1 of 2 positive blood cultures that had repeat negative culture on a non effective antibiotic

• Among 2143 with the above risk factors, 45 (21 per 1000) had EOS

Mukhopadhyay S, Puopolo K PIDJ 2017
Early-Onset Sepsis-Extremely Premature

• Identifying those low risk infants for early onset sepsis
• Infants 22 to 28 weeks in Neonatal Research Network Centers from 2006 to 2014, weighed 401-1500 grams, and no congenital anomalies
• Low risk= Cesaerean section, membranes ruptured at birth and no clinical chorioamnionitis
• Evaluated the following
  • Frequency of prolonged antibiotics (≥ 5 days)
  • Risks of mortality, EOS and comorbidities including NEC, LOS, ICH, and BPD

Puopolo K et al Pediatrics Nov 2017
Early-Onset Sepsis-Extremely Premature

- 5759 Low Risk infants; 9674 Comparison group (not low-risk)
- Mortality in first 12 hours
  - Low risk- 119 (2.1%); Comparison- 1252 (12.9%)

<table>
<thead>
<tr>
<th></th>
<th>Low Risk</th>
<th>Comparison</th>
<th>Adjusted RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants survived &gt;12h</td>
<td>5640</td>
<td>8422</td>
<td></td>
</tr>
<tr>
<td>EOS</td>
<td>29 (0.5)</td>
<td>209 (2.5)</td>
<td>0.24 (0.16-0.36)</td>
</tr>
<tr>
<td>EOS incl. CONS</td>
<td>46 (0.8)</td>
<td>232 (2.8)</td>
<td>0.33 (0.24-0.46)</td>
</tr>
</tbody>
</table>

Puopolo K et al Pediatrics Nov 2017
Early-Onset Sepsis-Extremely Premature

• Low Risk Infants
  • 1771 Received Prolonged Antibiotics (≥ 5 days); 2563 not prolonged
  • Prolonged more likely to be younger, smaller, boys, and 5 minute Apgars <5

• Outcomes
  • Prolonged antibiotics with
    • BPD after 36 weeks (ARR 1.28 (1.2-1.36))
    • NEC > 7d or death before discharge (ARR 1.22 (1.07-1.40)
    • SIP > 7d (ARR 1.86 (1.23-2.82))

Puopolo K et al Pediatrics Nov 2017

[Slide courtesy of Dr. Jason Newland]
Early onset Sepsis calculator
• Does your NICU utilize the Early Onset Sepsis calculator for infants born at 35 weeks or greater?
  • Yes
  • No
  • I don’t know

Puopolo K et al Pediatrics Nov 2017
• Does your NICU utilize the Early Onset Sepsis calculator for infants born at 35 weeks or greater?
  • Yes
  • No
  • I don’t know

Puopolo K et al Pediatrics Nov 2017
• If yes, is the neonatal early onset sepsis calculator incorporated in your electronic health record system?
  • Yes
  • No
  • I don’t know

Puopolo K et al Pediatrics Nov 2017
Early-Onset Sepsis-Maternal Risk Factors

- Nested Case Control Study of infants ≥ 34 weeks gestation at 12 Kaiser Permanente Medical Care Programs and 2 Boston Hospitals
- January 1993 to December 2007
- Positive blood or CSF culture before 72 hours of age
- Coagulase negative Staphylococcus included if treated for > 5 days
- 3 controls per case
- Exclusions: birth outside the hospital, congenital anomalies, chromosomal abnormalities

Puopolo K et al Pediatrics 2011
Early-Onset Sepsis-Maternal Risk Factors

- 350 cases of 608,014 live births (0.58 cases per 1000 live births)
- 1063 controls
- Pathogens
  - GBS- 53%
  - *E. coli*- 20.3%
  - Other bacteria included- *S. aureus*, Listeria, Enterococci, Bacteroides, Klebsiella. Only 1 case of *S. epidermidis* was included

Puopolo K et al Pediatrics 2011

[Slide courtesy of Dr. Jason Newland]
Early-Onset Sepsis-Maternal Risk Factors

• Factors Identified
  • GBS status- categorical
  • Gestational age- continuous variable
  • Duration of ROM- continuous variable transformed
  • Highest intrapartum fever- continuous variable to 0.1° F
  • Intrapartum antibiotics- categorical variable
    • None
    • GBS IAP on time or anytime
    • Broad spectrum on time

Puopolo K et al Pediatrics 2011

[Slide courtesy of Dr. Jason Newland]
Early-Onset Sepsis-Maternal Risk Factors

- Contribution of Predictors to the multivariate model

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Entire Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age</td>
<td>16.7%</td>
</tr>
<tr>
<td>GBS Status</td>
<td>2.3%</td>
</tr>
<tr>
<td>Highest intrapartum temp</td>
<td>58.4%</td>
</tr>
<tr>
<td>ROM time</td>
<td>12.6%</td>
</tr>
<tr>
<td>Intrapartum Abx Treatment</td>
<td>10%</td>
</tr>
</tbody>
</table>

Puopolo K et al Pediatrics 2011
Early-Onset Sepsis-Risk Stratification

Goal- Define a simple strategy to guide newborn care

Steps:
1. Prior probability- baseline EOS incidence (varies based on location and setting- ranges 0.5 to 1.2 and potentially higher) plus maternal risk factors
2. Posterior Probability determined based neonatal clinical appearance could be increased or decreased
3. Treatment algorithm for 3 different clinical appearances

Escobar GJ et al Pediatrics 2013
Early-Onset Sepsis-Risk Stratification

3 Clinical Presentations within first 12 hours

- **Clinical Illness (Sick)** - 5 min Apgar < 5, mechanically ventilated or nasal cpap, vasoactive drugs, seizure, respiratory distress
  - Likelihood Ratio for EOS- 14.7

- **Equivocal** - 2 instances of one of the following:
  - HR >160, RR > 60, Temp > 100.4 or < 97.5, respiratory distress
  - LR for EOS- 3.75

- **Well appearing** - Not in above groups
  - LR for EOS- 0.36

Escobar GJ et al Pediatrics 2013

[Slide courtesy of Dr. Jason Newland]
# Early-Onset Sepsis-Risk Stratification

Prior Probability including Maternal Risk Factors

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>&lt;.65/1000 live births</th>
<th>0.65-1.54/1000</th>
<th>≥ 1.54/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well Appearing</td>
<td>OBSERVE (85%)</td>
<td>OBSERVE and EVALUATE (11%)</td>
<td></td>
</tr>
<tr>
<td>Equivocal</td>
<td>OBSERVE and EVALUATE NNT-823</td>
<td></td>
<td>TREAT EMPIRICALLY (4%) NNT=118</td>
</tr>
<tr>
<td>Clinical Illness</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Escobar GJ et al Pediatrics 2013

[Slide courtesy of Dr. Jason Newland]
Early-Onset Sepsis Calculator-Validation

- Infants born at 35 weeks in Kaiser Permanente
- Jan 1, 2010 to Dec 31, 2015
- 3 time periods
  - National recommended guidelines (1/1/10-11/30/12)
  - Multivariable risk estimates/learning period (1/1/12-6/30/14)
  - Multivariable risk estimates plus infant clinical condition- EOS calculator period (1/1/14-6/30/14)

Kuzniewicz MW et al JAMA Peds 2013
Early-Onset Sepsis Calculator-Validation

Results

• 204,485 Infants 35 weeks and older
  • 95,343 in baseline, 52,881 learning period, 56,261 EOS Calculator
  • No difference in EOS rates across periods (0.02-0.03%)  
• Significant reduction in blood culture use (7.7%) and antibiotic use (1.8%)

Kuzniewicz MW et al JAMA Peds 2013
Early-Onset Sepsis Calculator-Validation

Adverse Events

• No difference in readmissions across periods

• EOS Calculator Period
  • 12 infants with EOS
    • 6 symptomatic and treated
    • 5 well appearing, developed symptoms and were treated
    • 1 met CDC guidelines to treat (maternal fever 38.0)- EOS risk 0.15 developed tachypnea and then had cultures obtained and grew *E. coli*

Kuzniewicz MW et al JAMA Peds 2013
Early Onset Sepsis Calculator

https://neonatalsepsiscalculator.kaiserpermanente.org/

[Slide courtesy of Dr. Jason Newland]
Early Onset Sepsis Calculator

https://neonatalsepsiscalculator.kaiserpermanente.org/

[Slide courtesy of Dr. Jason Newland]
Early Onset Sepsis Calculator

https://neonatalsepsiscalculator.kaiserpermanente.org/

[Slide courtesy of Dr. Jason Newland]
Do you use the Early Onset Sepsis Calculator in eligible infants born to mom’s with clinical chorioamnionitis?

☐ Yes
☐ No
Early-Onset Sepsis Calculator and Clinical Chorioamnionitis

Committee on Fetus and Newborn recommendations for clinical chorioamnionitis:

• Blood culture, WBC, CRP at birth and empirically treat with antibiotics

• Negative blood culture, well baby and abnormal labs- the recommendation is to treat

Polin RA Pediatrics 2012
Early-Onset Sepsis Calculator and Clinical Chorioamnionitis

Survey of Neonatologist in AAP

• 23.5% response rate
• 25% of respondents use the EOS Calculator
  • Level III more likely to use than Level II
• 4.8% would perform LP in well-appearing infant with abnormal CBC and CRP, 39% if labs still abnormal at 24 hours
• 44% will not stop antibiotics if labs abnormal and baby well appearing

Ayrapetyan M et al Am J Perinatol 2018
Antibiotic Recommendations

• Ampicillin- best antibiotic for Group B streptococcus
• Gentamicin- Covers most *E. coli*
• Cefotaxime- only would use in infants with concerns for CNS involvement
  • National shortages have led to varying recommendations- ceftazidime recommended by AAP
• Acyclovir should be considered in clinically septic infant
Culture Results

It is always helpful to know what is out there to better inform our clinical decisions. Probably the most important take-home point of this study is the fact that, potentially, 11% of the infants would not have been well served by treating empirically with only a third-generation cephalosporin. If practitioners can remember only one thing from this study, that is probably the most important thing. The individual contributions of each bacterial type are both harder to remember and less helpful in everyday clinical practice.

The other important take-home point is that while knowing what you're treating is always a great idea, **adjusting medications as needed once isolates and their sensitivities are finalized may be even more important.** Given high contributions of *E coli* and *Enterococcus* species and their associated greater resistance frequencies, this is more important than ever in this current era of increasing antimicrobial resistance. Good antimicrobial stewardship is always a good idea, and that is true for even the youngest infants.

Learning Objectives

**Define**
- Define developing concepts of antimicrobial stewardship

**Identify**
- Identify opportunities for stewardship in your NICU world

**Explain**
- Explain the role of parents in stewardship
Antimicrobial Stewardship Workflow Communication
Improving Antibiotic Use
Roles for Nurses

- History taking to include recent antibiotic use in mother
- Careful, recent parental STI history
- Timely, & yet appropriate, culture taking & transport
- Monitoring patient responses
- Interdisciplinary communication
- Strengthening cross-disciplinary liaisons between microbiologists, pharmacists, prescribing clinicians, & infection preventionists
Nurses need to be aware of their influence on patients and families and with good communication skills, nurses can be able to assist patients and families in [understanding the implications of inappropriate antibiotic use].

References


References


