Optimization of Antibiotics Practices by Applying Antibiotic Stewardship Principles

Joel Weiner, MD

September 12, 2014
Disclosure

Nothing to disclose
Reducing Initial Antibiotic Exposure in Selected Infants During Early Rule-out Sepsis Evaluations-Impact on Infectious Outcomes

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Antibiotics in the NICU: Less is More?

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O Has Perinatal community turned delivery & newborns (especially PT) into infectious dx?
O In process of aiming to help, have infants been made susceptible to increased risk of long-term effects (LOS, NEC, Death)?
O NICU’s are not exempt from overuse of antibiotics
O Is implementation of approach limiting antibiotic use realistic/achievable?
Goals

- (1) Review of some relevant studies
- (2) Late-Onset Sepsis- incidence in various NICU’s
- (4) Preliminary results on-going study at U Mass Memorial Hospital
- (5) Conclusions
Ampicillin & Bleeding Time in VLBW (Sheffield, J Peri, 2011)

- 20 VLBW on Amp, 23-30 wks, 500-1410 gms
  - 10 d/c’d Amp 4-7 doses, 10 w/ 10-15 doses
- Short: no diff BT start & finish; long: BT ~2X longer at stop vs start (clinically insig)
- BUT: all w/ (-) bld cx, no diff WBC, CRP, clinical course or explanation in progress notes
Use Antimicrobial Agents in U.S. NICU/PICU’s
(Grohskopf, PID, 05)

- 29 NICU’s, 1580 pts, 45% levels 3 or 4, 21% level 3, 28% level 2/3, 22.7% level 1
- 43.3% NICU pts receiving abs; median # abs = 2 (range 1-5)
- Amp/Gent/Vanc most common
- Median # pts on abs 45.8% (15.2-85.7%); Aminoglycoside use 25% (4.4-71.4%); Vancomycin use 8.8% (0-35.4%)
- Most rx is **empiric** (55-68%), not therapeutic
Prolonged Duration of Initial Empirical Antibiotic Treatment (Cotton, Peds, 09)

- 5693 ELBW, 19 centers, 4039 (71%) survived > 5 days, received initial abs, all w/ (-) bld cx
  
- Median duration abs = 5 days (1-36)

- 2147 (53%) rx ≥ 5 days

- NNH = 22

- > 4 days abs associated w/ ↑ risk NEC or death (1.3) & death (1.5) as well as LOS & death (1.21)
Risk NEC & Abs in NICU
(Alexander, JOP, 2011)

- 124 NEC cases & 248 controls
- Eliminating sepsis, risk NEC sig ↑ w/ duration abs
- Nearly 3X greater risk if > 10 days rx
- ~93% entire cohort rx > 5 days abs
- Risk NEC ↑ ~20%/day exposure
Prolonged Antibiotics for Cx (-) Sepsis in PT (Kuppala, JOP, 2011)

- > 5 days abs to 36% of 365 PT (< 32 wks/BW < 1500 gms) who survived free sepsis/NEC in first week
- Assoc w/ sig ↑ LOS (2.45) & LOS/NEC/Death (2.66)
- Each day ab associated w/ ↑ risk LOS/NEC/Death
- NNH = 3
Duration of Empiric Antibiotics
(Cordero, Infect Control, 03)

- 790 ELBW, 30 NICU’s, 24 states
- 94% (744) w/ bld cxs obtained, 47 (6.3%) (+)
- BC (-): 40% rx < 3 d, 26% rx 4-6 d, 34% > 7 d
  - No diff tests, clinical dx, sx
- Avg total days abs: 23 for < 3 d vs 38 > 7 d
- No diff LOS (1.3 episodes/pt)
- In ½ hospitals ≥ 50% ELBW rx > 3 d w/ (-) BC
Association IP Abs & LOS (Glasgow, Peds, 2005)

- 1998-2002: 35% term mothers rx abs
- Eval 1999-2003, ≥ 37 wks & 7-90 d/o
- 90 infants w/ LOS; IPA exposure 41% vs 27% controls (OR 1.96, CI 1.05-3.66)
- Pen not associated w/ ↑ risk LOS or resistant organisms; all other abs w/ sig risk both
Effect of Antibiotics on Intestinal Colonization
(Turcu, Ped Res, 06)

- Early exposure to abs associated w/ ↓ diversity scores
- # species ↓ further during and after ab rx
- Flora improves by 1 mth age
- Included only term infants
Bacterial Gut Microflora in ELBW (Jacquot, JOP, 2011)

- 29 consecutive ELBW, microflora in stool samples days 3-56 w/ direct molecular fingerprinting

- 6 wk biodiversity score inversely correlated w/ duration abs & parenteral feeding, ↑ wt gain w/ ↑ diversity

- Johnson (Peds, 12): complete recovery of initial bacterial composition rarely achieved after initial alteration d/t abs
Early Empiric Antibiotic Use & Preterm Infants (Greenwood, JOP, 2014)

- 74 NB, ≤ 32 wks, rx 0 d (18%), 1-4 d (64%) & 5-7 d (18%)
- All free NEC/Sepsis/Death in 1st wk of life
- Serial stool samples over 1st three wks life
- Sig assoc 5-7 d abs w/ NEC/Sepsis/Death & profound alteration intestinal microbiota
Late-Onset Sepsis

- Marked variation in incidence
- Role of antibiotics
  - Total days
  - Specific antibiotic exposures
- Fluconazole prophylaxis
Late-Onset Sepsis

- Indomethacin Prophylaxis vs Expectant Rx of PDA in ELBW (Cordero, J Peri, 2007)
  - Overall Incidence LOS: 36.8% (36 & 38%)

- Aggressive vs Conservative Phototherapy (Morris, NEJM, 2008)
  - OA: 41.4% (41 & 44%)

- Outcomes ELBW at 18-22 Months (Gargus, Peds, 2008)
  - OA: 39% (29.3 & 48.7%)
Late-Onset Sepsis

- SUPPORT Trial-Target Ranges of O2 Saturation (NICHD, NEJM, 2010)
  - OA: 36% (35.6 & 36.5%)
- Seizures in ELBW & Outcomes (Davis, JOP, 2010)
  - OA: 38.1% (37 & 61%)
- Breast Milk & NEC (Sullivan, JOP, 2010)
  - OA: 22.7% (19 & 21 & 28%)
Late-Onset Sepsis

- Outcomes Early HAL (Trinitis, J Peri, 2010)
  - OA: 15.3% (15 & 16%)
  - OA: 32.4%
- Effect Persistent PDA on M & M in VLBW (Tauzin, Acta Peds, 2012)
  - OA: 46% (45 & 48%)
Late-Onset Sepsis

  - OA: 21.1% in 2000 & 15% in 2009

- Neuro Outcomes s/p Selective vs Early PDA Ligation (Wickremasinghe, JOP, 2012)
  - OA: 47.5% (45 & 51%)

- Outcome UAC related Thrombus (Ergaz, J Peri, 2012)
  - OA: 35% (22 & 63.2%)
Late-Onset Sepsis

- Outcome ELBW Requiring CPR in DR (Wyckoff, JOP, 2012)
  - OA: 35.4% (35 & 38%)
- Randomized Trial Cycling HAL (Salvador, JOP, 2012)
  - OA: 31.4% (31 & 32%)
- Timing PDA Tx & Respiratory Outcome (Sosenko, JOP, 2012)
  - OA: 42.9% (42 & 45%)
Late-Onset Sepsis

- Human Milk vs Preterm Formula in PT (Cristofalo, J Peds, 2013)
  - OA: 17% (14 & 21%)
- Probiotic Effects on LOS in Very PT (Jacobs, Peds, 2013)
  - OA: 25% (23.5 & 26.5%)
- Noninvasive Ventilation Strategies in ELBW (Kirpalani, NEJM, 2013)
  - OA: 38.8% (38.5 & 39.2%)
Late-Onset Sepsis

- High-Flow Nasal Cannula after Extubation (Manley, NEJM, 2013)
  - OA: 18.5% (17.1 & 19.9%)

- Indomethacin vs Ibuprofen for Tx PDA (Sivanandan, J Peri, 2013)
  - OA: 27% (both)

- Enteral Feeding During Indo & Ibu Tx PDA (Clyman, JOP, 2013)
  - OA: 44.5% (44 & 45%)
Late-Onset Sepsis

- Cohort Study of Probiotics in NA NICU’s (Janvier, JOP, 2014)
  - OA: 18.2% (17 & 18.4%)

- Trends in Caffeine Use in VLBW (Dobson, JOP, 2014)
  - OA: 24.9% (21.1 & 29.8%)

- Risk for LOS in VLBW SGA (Troger, PID, 2014)
  - OA: 15% (14.3 & 20.1%)
Late-Onset Sepsis

- IVH & Neurodev Outcomes in Extremely PT (Bolisetty, Peds, 2014)
  - OA: 37.4% (28.4 & 40.6%)
- LOS in VLBW (Boghossian, JOP, 2013)
  - OA: 25%
Fluconazole Prophylaxis
(Kaufman, NEJM, 2001)

- < 1000 gms; IV Fluconazole vs placebo x 6 wks; 100 NB randomized
- Significant diff in incidence documented fungal infections (20% vs 0%)
- During Tx period (Flu vs placebo):
  - 74 & 72% rx steroids
  - 28 & 22% H-2 blockers
  - 62 & 72% rx Vanc; 74 & 68% Cephalosporin
- Ab days: 13 +/- 7 & 14 +/- 8
Use of Leukocyte Counts in Evaluation Early-Onset Sepsis (Murphy/Weiner, PID, 2012)

- Retrospective study w/ r/o sepsis in first 24 hours life, 1999-2008
- Also evaluated all pts w/ documented EO sepsis 1989-1998
- Defined normal limits:
  - WBC between 6,000 & 30,000 (x 2)
  - Band/Neutrophil ratio < 20%
  - (-) Bld cx at 24 hrs of age
<table>
<thead>
<tr>
<th>True/Presumed Infection</th>
<th>No Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 abn WBC &amp;/or (+) Bld cx at ≤ 24 hrs</td>
<td>23/119</td>
</tr>
<tr>
<td></td>
<td>PPV 8.8% Specificity 51%</td>
</tr>
<tr>
<td>2 normal WBC &amp; differentials &amp; (-) Bld cx at 24 hrs</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>NPV 100% Sensitivity 100%</td>
</tr>
</tbody>
</table>
1989-1998: all infants evaluated for EO sepsis w/ (+) blood cxs
   91 NB w/ documented EO-sepsis: all w/ at least one abn WBC &/or (+) bld cx ≤ 24 hrs

Cohort 1999-2008
   17% initial normal B/N ratio; all abn on rpt (2 GBS, 2 E coli)

Cohort 1988-1998
   97% w/ 1 or 2 abn WBC; 3 w/ 2 nl WBC, asx, (+) bld cx by 24 hrs
- 92% NB w/ abnormal WBC free proven/presumed sepsis

- No false-negative results in 25 years (1/4 century)
Potential Impact

- If applied in U.S. could reduce antibiotic doses for EO sepsis r/o by 900,000 to 1.8 million doses/year
- Fewer: IV placements, shorter length of stay, lower costs
- Decrease in resistant organisms, less alteration in GI flora
- Decrease in late-onset sepsis, NEC
Rapid Detection of Microorganisms in Bld Cx on NB Infants
(Garcia-Prats, Peds, 2000)

- Prospective study of all bld cx FT & PT, 93-97
- 23,078 LB, 81% FT; ~8% all w/ NB sepsis eval
- For EO sepsis evals: 97% (+) by 24 hrs & 99% (+) by 36 hrs (All GBS by 24 hrs, all E coli by 12 hrs)
- Rec consideration reducing duration ab tx to 24-36 hrs in EO r/o sepsis
Early r/o Sepsis Evaluations

- No data exists w/ defined numbers
- Pediatrix Medical Group Clinical Data Warehouse (2006): 70% of neonates admitted to NICU’s rx empirically
- Lieberman (Peds, 1997): Epidural Analgesia, IP fever & Neonatal Sepsis Evaluations
Epidural Anesthesia
(Lieberman, 1999, Peds)

- 1657 women, **FT**, 1047 (63%) w/ epidurals
- Incidence fever 14.5% vs 1% (OA 9.5%)
- With epidural, longer labor associated w/ ↑ risk fever:
  - Labor ≤ 6 hrs = 7%
  - Labor ≥ 18 hrs = 36%
- 96.2% IP fevers, 85.6% sepsis evals & 87.5% neonatal antibiotic tx in epidural group
<table>
<thead>
<tr>
<th></th>
<th>Epi (1067)</th>
<th>No epi (610)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis eval</td>
<td>356 (34%)</td>
<td>60 (9.8%)</td>
<td>416 (25%)</td>
</tr>
<tr>
<td>Any Ab Tx</td>
<td>161 (15.4%)</td>
<td>23 (3.8%)</td>
<td>194 (11%)</td>
</tr>
<tr>
<td>Abs ≥ 3 days</td>
<td>17 (1.8%)</td>
<td>3 (0.5%)</td>
<td>20 (1.2%)</td>
</tr>
<tr>
<td>Doc sepsis</td>
<td>3 (0.3%)</td>
<td>1 (0.2%)</td>
<td>4 (0.2%)</td>
</tr>
</tbody>
</table>
EO Sepsis Evals
(Mukhopadhyay, 2013, J Peri)

- EO sepsis evals among ≥ 35 wks, asx
- Retrospective: 3/08-8/08 & 3/09-8/09
- 1062 NB evals (14.7%)-70% d/t maternal fever; majority rest for inadq maternal tx
- 8% tx abs for sepsis r/o (vs 25% & 11%)
- 6 cases EO sepsis: only 1/6 w/ initial abn WBC; 3 w/ sx; 1 not initially started on abs at time of eval
- At WMH: 2 year review, all deliveries ≥ 35 wks: sepsis eval & tx = 3.9%
# Clinical factors/WBC

<table>
<thead>
<tr>
<th>Comps</th>
<th>Neuts</th>
<th>Bands</th>
<th>I/T</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>4+</td>
<td>0</td>
<td>+</td>
<td>72</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>2+</td>
<td>3+</td>
<td>24</td>
</tr>
<tr>
<td>Pitocin</td>
<td>0</td>
<td>2+</td>
<td>2+</td>
<td>120</td>
</tr>
<tr>
<td>Gluc</td>
<td>0</td>
<td>2+</td>
<td>3+</td>
<td>24</td>
</tr>
<tr>
<td>Crying</td>
<td>0</td>
<td>4+</td>
<td>4+</td>
<td>1</td>
</tr>
<tr>
<td>Hem Dx</td>
<td>2+</td>
<td>2+</td>
<td>3+</td>
<td>7-28 d</td>
</tr>
<tr>
<td>PTX</td>
<td>0</td>
<td>4+</td>
<td>4+</td>
<td>24</td>
</tr>
</tbody>
</table>
Current U Mass Study

- Current guidelines begun April, 2012
- Data analyzed every 6 months
- All newborns admitted to NICU & started on antibiotics tracked throughout hospital course
Data

- Total 833 newborns admitted w/ sepsis r/o
  - Abs d/c’d at 24 hrs = 495 (59.4%)
  - Abs continued min 48-72 hrs = 338 (40.6%)
- Documented early-onset sepsis
  - 8 (E coli (2), Strep viridans (2), GBS (1), others (3))
- Presumed sepsis
  - 9 (persistent abn WBC &/or abn CRP at ~72 hrs)
Antibiotic doses:
- 24 hour r/o = 3
- 48-72 hr r/o = 5.9

Antibiotic days:
- Average pts/day: 6.7% (range 2.4-12.8%)
- Earlier study: 45.8% (range 15.2-85.7%)
<table>
<thead>
<tr>
<th>Weight Range</th>
<th>&lt; 24 hrs</th>
<th>48+ hrs</th>
<th>% &lt; 24 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 750 gms</td>
<td>5</td>
<td>30</td>
<td>14.2%</td>
</tr>
<tr>
<td>751-1000</td>
<td>16</td>
<td>30</td>
<td>35%</td>
</tr>
<tr>
<td>1001-1250</td>
<td>25</td>
<td>41</td>
<td>38%</td>
</tr>
<tr>
<td>1251-1500</td>
<td>44</td>
<td>30</td>
<td>60%</td>
</tr>
<tr>
<td>&gt; 1500</td>
<td>405</td>
<td>207</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>&lt; 24 hrs</td>
<td>48+ hrs</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
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<td>---------</td>
<td></td>
</tr>
<tr>
<td>NEC: &gt; 2A</td>
<td>9 = 8.2%</td>
<td>11 = 8.4%</td>
<td></td>
</tr>
<tr>
<td>NEC: All</td>
<td>16 = 14.5%</td>
<td>13 = 9.9%</td>
<td></td>
</tr>
<tr>
<td>&lt; 1001 &amp; &gt; 5 days abs</td>
<td>9/21 = 43%</td>
<td>26/60 = 43%</td>
<td></td>
</tr>
<tr>
<td>1001-1500 gms &amp; &gt; 5 days abs</td>
<td>10/69 = 14.5%</td>
<td>11/71 = 15.5%</td>
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</tr>
</tbody>
</table>
## Late-Onset Sepsis

<table>
<thead>
<tr>
<th></th>
<th>&lt; 24 hours</th>
<th>48-72 hours</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1500 gms</td>
<td>4/89 = 4.3%</td>
<td>5/127 = 3.9%</td>
<td>9/216 = 4.2%</td>
</tr>
<tr>
<td>&lt; 32 wks</td>
<td>4/108 = 3.7%</td>
<td>5/133 = 3.8%</td>
<td>9/241 = 3.7%</td>
</tr>
<tr>
<td>Birth Wt</td>
<td>NICHD</td>
<td>WMH</td>
<td></td>
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<tr>
<td>----------</td>
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<td>-------------</td>
<td></td>
</tr>
<tr>
<td>&lt; 500 gms</td>
<td>185/284 = 65.1%</td>
<td>1/3 = 33%</td>
<td></td>
</tr>
<tr>
<td>501-750</td>
<td>1779/3434 = 52%</td>
<td>3/32 = 9.4%</td>
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</tr>
<tr>
<td>751-1000</td>
<td>1693/5258 = 32%</td>
<td>3/46 = 6.5%</td>
<td></td>
</tr>
<tr>
<td>1001-1250</td>
<td>874/5463 = 16%</td>
<td>1/66 = 1.5%</td>
<td></td>
</tr>
<tr>
<td>1251-1500</td>
<td>462/6033 = 7.7%</td>
<td>1/74 = 1.4%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4993/20472 = 24.4%</td>
<td>9/221 = 4.1%</td>
<td></td>
</tr>
<tr>
<td>Gestational Age</td>
<td>NICHD</td>
<td>WMH</td>
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<td>-----------------</td>
<td>-------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>&lt; 25 wks</td>
<td>1255/2008 = 63%</td>
<td>4/28 = 14.3%</td>
<td></td>
</tr>
<tr>
<td>25-28</td>
<td>2907/9489 = 31%</td>
<td>3/76 = 3.9%</td>
<td></td>
</tr>
<tr>
<td>29-32</td>
<td>783/7796 = 10%</td>
<td>2/88 = 2.3%</td>
<td></td>
</tr>
<tr>
<td>≥ 32</td>
<td>48/1175 = 4.1%</td>
<td>0/29 = 0%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4993/20468 = 24.4%</td>
<td>9/221 = 4.1%</td>
<td></td>
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</tbody>
</table>
Conclusions

- Evaluating own data essential
- Considerations of practice changes:
  - LOS > 10-15% in ELBW/VLBW
  - Fungal infections > 1-2/year or use Fluconazole prophylaxis routinely
  - Recurrent MRSA/other resistant organism infections
  - Frequent use broad-spectrum abs
  - High % antibiotic use days (> 10-20% pts/d)
  - > 5 total days ab exposure (> 50% ELBW/> 20% VLBW)
If not satisfied w/ own data:
- Evaluate ways to change antibiotic usage
- Review sepsis r/o approaches
- Review use antibiotics especially in ≤ 1.5 kg

If own data acceptable:
- Consideration of early discontinuation of abs in selected infants
Selected Bibliography


