Antibiotic Stewardship in Neonatal Intensive Care Unit

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Disclosures

None
Objectives

1. What is Antimicrobial Stewardship?
2. Pitfalls of antimicrobial use in NICU and the implications of their use/misuse.
3. How antimicrobials can be used most effectively?
4. Infection prevention as a NICU culture is key stewardship activity.
Definition and milestones of Antibiotic Stewardship

• “Interventions targeted towards improving and monitoring appropriate antimicrobial use: select most optimal drug regimen, including type of drug, dose, duration and route of therapy”
  — Infectious Disease Society of America (IDSA).

• CDC and IDSA promoted more judicious use of Antibiotics
  CDC: 1995 - National campaign for appropriate antibiotics use in community;
  2003 – “Get Smart: Know when antibiotics work program”;
  2007 IDSA - Guidelines for development & maintenance of formal ASP program (inpatient);
Antibiotic Resistance threat

- 1. Prevent infections and its spread
- 2. Tracking resistance patterns (antibiogram)
- 3. Improving use of antibiotics (stewardship)
- 4. Developing new antibiotics and diagnostic tests

Antibiotic resistance—when bacteria no longer respond to the drugs designed to kill them—is happening right now across the world.

ANTIBIOTIC RESISTANCE: THE GLOBAL THREAT

Super-Resistant Bacteria: Problem Today, Crisis Tomorrow

- In India, 58,000+ babies died in one year from super-resistant bacterial infections, which are usually passed on from their mothers.
- In the European Union, antibiotic resistance causes 25,000 deaths per year and 2.5m extra hospital days.
- In Thailand, antibiotic resistance causes 38,000+ deaths per year and 3.2m hospital days.
- In the United States, antibiotic resistance causes 23,000+ deaths per year and more than 2m illnesses.

[Website Link: www.cdc.gov/getsmart]
In the last 20 years, it has become recognized that decreasing unnecessary use of antibiotics is important.

2015: Executive Order 13676 (PCAST by combating antibiotic resistance): NAP
Action plan goals

- Collaborative partnership of US and foreign governments to strengthen healthcare, public health, veterinary medicine, agriculture, food safety, research and manufacture:
  1. Slow emergence of resistant bacteria, prevent spread of resistant bacteria;
  2. Strengthen national one-health surveillance efforts- combat resistance;
  3. Advance development and use of rapid diagnostic tests;
  4. Accelerate basic and applied research and development of new antibiotics, vaccines;
  5. Improve international collaboration to decrease antibiotic resistance, prevention, surveillance, control, R and D.

- By 2020: reduce inappropriate antibiotic use by 50% in outpatients, 20% in inpatients.
New Antimicrobial Stewardship Standard

Effective January 1, 2017

Applicable to Hospitals and Critical Access Hospitals

Medication Management (MM)

Standard MM.09.01.01
The [critical access] hospital has an antimicrobial stewardship program based on current scientific literature.

Elements of Performance for MM.09.01.01

1. Leaders establish antimicrobial stewardship as an organizational priority. (See also LD.01.03.01, EP 5)

   Note: Examples of leadership commitment to an antimicrobial stewardship program are as follows:
   - Accountability documents
   - Budget plans
   - Infection prevention plans
   - Performance improvement plans
   - Strategic plans
   - Using the electronic health record to collect antimicrobial stewardship data

2. The [critical access] hospital educates staff and licensed independent practitioners involved in antimicrobial ordering, dispensing, administration, and monitoring about

   Note: An example of an educational tool that can be used for patients and families includes the Centers for Disease Control and Prevention's Get Smart document, “Viruses or Bacteria—What's got you sick? at http://www.cdc.gov/getsmart/community/downloads/getspritchart.pdf.

4. The [critical access] hospital has an antimicrobial stewardship multidisciplinary team that includes the following members, when available in the setting:
   - Infectious disease physician
   - Infection preventionist(s)
   - Pharmacist(s)
   - Practitioner

   Note 1: Part-time or consultant staff are acceptable as members of the antimicrobial stewardship multidisciplinary team.

   Note 2: Telehealth staff are acceptable as members of the antimicrobial stewardship multidisciplinary team.

5. The [critical access] hospital's antimicrobial stewardship program includes the following core elements:
   - Leadership commitment: Dedicating necessary human, financial, and information technology resources.
   - Accountability: Appointing a single leader responsible for program outcomes. Experience with successful programs shows that a physician leader is effective.
Practice Improvement in NICU

- Highly vulnerable patient population, with staff dedicated to strategies to protect them.
- Controlled environment
- Well-defined leadership structure
Infection control and Prevention

- **Hand Hygiene practices:** soap or hand gel *before* and *after* patient contact; NO artificial nails, rings or nail polish; audit of hand hygiene with feedback.

- **Environment control:** bed space cleaning with audit and feedback, environment cleaning, minimize overcrowding.

- **Antibiotic stewardship:** Limit empirical therapy to *narrowest-spectrum agents* that cover likely pathogens in the unit; *avoid prolonged & unnecessary antibiotic Rx* for suspected or proven infections; *surveillance* of antibiotic use, with feedback and interventions.

- **Multidisciplinary approach:** Involve neonatologist, infection control, nurses, unit managers, RTs, environment services and microbiology. –Outbreaks: proven benefit and routine prevention. Hospital administrators and health department can expedite.
Why is Antibiotic Stewardship important?

- Increase in drug resistance
- Increase in Necrotizing enterocolitis, fungal infections
- Increase in Asthma, atopy, and obesity
- Increase in morbidity and mortality
- Increase in duration of hospital stay
- Increase in Cost

Antibiotic Resistance is Rising in NICUs

Overuse of Antibiotics in NICUs

- Retrospective observational study of 323 antibiotic courses for a total of 3344 antibiotic days.

- 35% of neonates received at least one inappropriate dose due to continuation of antibiotics versus initiation of therapy (39 versus 4% respectively, $p < 0.001$).

- **Vancomycin** was most commonly used: 895 antibiotic days, of which 284 days were considered inappropriate.

### Patient-Level Impact of Potentially Inappropriate Antibiotic Use in NICUs

<table>
<thead>
<tr>
<th>Study</th>
<th>Population Description</th>
<th>Clinical Outcomes</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotton et al 2007¹</td>
<td>5693 ELBW infants in 19 centers NICHD- NRN</td>
<td>&gt; 5 days initial empiric therapy despite sterile cultures NEC or Death NEC Death</td>
<td>1.50 (1.22-1.83)</td>
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<td></td>
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<td></td>
<td>1.34 (1.04-1.73)</td>
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<td></td>
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<td></td>
<td>1.86 (1.45-2.39)</td>
</tr>
<tr>
<td>Kuppala et al 2011²</td>
<td>365 VLBW infants, 3 centers</td>
<td>&gt; 5 days initial empiric Rx despite sterile cultures NEC, LOS or Death LOS</td>
<td>2.66 (1.12-6.3)</td>
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<td></td>
<td></td>
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<td>2.45 (1.28-4.67)</td>
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</tbody>
</table>

Neonatal Intensive Care Unit Antibiotic use

Interquartile 1.5 times the median AUR (total # of patients exposed to antibiotics/antifungals)

CPQCC/CCS: Septic workups done in 127 California NICUs (n=52,061):
Similar burden of proven infection, NEC, surgical volume, and mortality, yet
40-fold variation (2.4% - 97%) in antibiotic prescribing practice.

Conclusion: Because antibiotic stewardship principles dictate that antibiotic use should correlate with burden of infection, some NICUS overuse antibiotics

Schulman et al, Pediatrics 135:826, 2015
Association of **Antibiotic Use** and **Neonatal M/M in LBW Infants** Without Culture-Proven Sepsis or NEC

**14703** Birthweight <1500 g

**965** Major congenital anomalies or unknown discharge date

**13738** Total eligible infants

**2069** Never received any antibiotics

**11669** Received antibiotics during hospitalization (objective 1)

**2845** Infants diagnosed as having EOS, LOS, or stage ≥2 NEC

**8824** Infants without EOS, LOS, or stage ≥2 NEC (objective 2)

*Ting et al., JAMA Pediatrics, Oct 2016*
## Odds Ratio for 10% Increase in Antibiotic Usage Rate

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted Odds Ratio (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite primary outcome&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.18 (1.13-1.23)</td>
</tr>
<tr>
<td>Mortality</td>
<td>2.04 (1.87-2.21)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>1.04 (1.00-1.10)</td>
</tr>
<tr>
<td>Persistent echogenicity or echolucency on neuroimaging</td>
<td>1.01 (0.96-1.05)</td>
</tr>
<tr>
<td>≥3 Stage retinopathy of prematurity</td>
<td>1.18 (1.06-1.32)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ting et al., JAMA Pediatrics, Oct 2016
Risk of missed infection or delayed treatment

Risk of overtreatment
Neonatal Sepsis
Severe Bacterial Infection

Seale, Pediatric Research 2014;74:73-85
Causes of death in the NICU

- EP/ELBW, 14%
- NEC, 10%
- Lung hypoplasia, 10%
- RDS, 8%
- IVH/ICH, 9%
- BPD, 3%
- Severe intrauterine growth restriction, 2%
- Major heart defects, 3%
- Lethal anomaly, 8%
- Neonatal encephalopathy, 6%
- Sepsis ≤7 days, 5%
- Sepsis >7 days, 7%
- Renal failure, 9%
- Shock/anemia, 9%
- Other, 1%
- CDH, 7%
- Pulmonary hypertension, 5%
- Genetic syndrome, 5%
- HIE, 6%
- Major structural heart defect, 3%
- Sickle cell disease, 2%
- Renal failure, 4%
- CDH, 1.1%
- Pulmonary hypertension, 8%
- Other, 14%

Antibiotic Stewardship in NICU: Specific Opportunities and Challenges

• **Opportunity**
  - Alternative approaches to prevention of early onset sepsis, which is the cause of most of empiric antibiotic use in NICUs.

• **Challenge**
  - Convince neonatologists (who are trained to be very sensitive to risk of missed infection) to alter their practice.
Clinical Signs of Neonatal Sepsis: Too Late

- Respiratory distress (90%)
- Apnea
- Temperature instability
- Gastrointestinal: vomiting, diarrhea, abdominal distension, ileus, poor feeding
- Neurologic: decreased activity, lethargy, irritability, tremor, seizure, hyporeflexia, hypotonia
- Cardiovascular: hypotension, metabolic acidosis, tachycardia
- Skin: pallor, mottling, petechiae, cyanosis
### Early-Onset Neonatal Sepsis: Still a Serious Problem

3300 early-onset sepsis cases and 390 deaths in the United states each year

<table>
<thead>
<tr>
<th></th>
<th>Rate (/1000 live births)</th>
<th>Case fatality ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black preterm</td>
<td>5.14</td>
<td>24.4%</td>
</tr>
<tr>
<td>Non-black preterm</td>
<td>2.17</td>
<td>21.5%</td>
</tr>
<tr>
<td>Black term</td>
<td>0.89</td>
<td>1.7%</td>
</tr>
<tr>
<td>Non-black term</td>
<td>0.40</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

Most Common Bacteria in Early-Onset Sepsis

- Group B β-hemolytic streptococcus
- Escherichia coli
- Listeria monocytogenes

In Developing countries:
- Staphylococcus aureus
- Klebsiella
Causes of serious bacterial infections in babies aged 0–3 days in hospitals of developing countries (1990–2004)

Sources: *Includes 23% Klebsiella spp, 7% Pseudomonas spp, 4% Acinetobacter spp, ...*


Percentage of selected potential pathogens in WHO regions. Numbers in parentheses indicate the total numbers of pathogens isolated for each region.

Group B Beta Strep: **Mother to Infant Transmission**

- GBS colonized mother (20-50%)
- Non-colonized newborn (50%)
- Colonized newborn (50%)
- Asymptomatic (98%)
- Early-onset sepsis, pneumonia, meningitis (2%)
Algorithm for secondary prevention of early-onset GBS among newborns (Centers for Disease Control and Prevention, 2010)

- Signs of neonatal sepsis? Yes → Full diagnostic evaluation* Antibiotic therapy†
  No → Maternal chorioamnionitis?§
    Yes → Limited evaluation§ Antibiotic therapy†
    No → GBS prophylaxis indicated for mother??
      Yes → Mother received intravenous penicillin, ampicillin, or cefazolin for ≥4 hours before delivery?
        Yes → Observation for ≥48 hours++§§
        No → ≤37 weeks and duration of membrane rupture <18 hours?
          No → Either <37 weeks or duration of membrane rupture ≥18 hours?
            Yes → Limited evaluation§ Observation for ≥48 hours++
          Yes → Observation for ≥48 hours++
        Yes → Observation for ≥48 hours++
      No → Routine clinical care++

Evaluation of **asymptomatic infants ≥37 weeks’ gestation** with risk factors for sepsis

**Risk Factors**
- PPROM ≥18 h or IAP indicated, but inadequate

**Diagnostic Tests**
- WBC/Diff ± CRP at age 6–12 h

**Antibiotics**
- No antibiotics needed observation

**Risk Factors**
- Chorioamnionitis

**Diagnostic Tests**
- Blood culture at birth WBC/Diff ± CRP at age 6–12 h

**Antibiotics**
- Broad-spectrum antibiotics

**Management**
- Lab data abnormal
  - Blood Culture
    - Blood culture negative Infant remains well, discharge by 48 h
  - Blood culture positive
    - Continue antibiotics if mother received antibiotics during labor and delivery

**Management**
- Lab data normal Infant remains well, discharge by 48 h
  - Blood culture positive
    - Continue antibiotics Lumbar puncture
  - Blood culture negative Infant remains well Lab data abnormal
    - Continue antibiotics if mother received antibiotics during labor and delivery
  - Blood culture negative Infant remains well Lab data normal
    - Discontinue antibiotics and discharge by 48 hours

**AAP's COFN:** Polin R A, Pediatrics 2012;129: 1006-1015
All-cause E coli and GBS early-onset invasive disease, 2005 to 2014
Preterm infants can mount C-Reactive Protein (CRP) response to early onset sepsis

CRP levels of infants in GA ≤32 weeks and GA > 32 weeks at 0, 12, 24, 48, 72, and 96 hours of septic work-up. Values are least square means. Both groups showed significant changes over time (p < 0.0001). Response and the change in the response rate over time was similar in both the groups, p = 0.59 and 0.74.

CRP, C-reactive protein; GA, gestational age.

Am J Perinatology 2015;32:1281-1286
Low PPV of Maternal Fever for Early Onset Sepsis

Table III. Neonatal outcome in the study and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 159)</th>
<th>Study group (n = 159)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean gestational age (weeks)</td>
<td>39.3 ± 1.2</td>
<td>39.5 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean birth weight (g)</td>
<td>3321 ± 390</td>
<td>3313 ± 400</td>
<td>NS</td>
</tr>
<tr>
<td>Mean 5-min Apgar score</td>
<td>9.9 ± 0.5</td>
<td>9.9 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender</td>
<td>85 (53.5%)</td>
<td>84 (52.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Resuscitation</td>
<td>3 (1.9%)</td>
<td>2 (1.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Full sepsis work up</td>
<td>6 (3.8%)</td>
<td>28 (17.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Partial sepsis workup</td>
<td>14 (8.9%)</td>
<td>131 (82.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neonatal leukocytosis</td>
<td>0 (0%)</td>
<td>8 (5.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neonatal thrombocytopenia</td>
<td>0 (0%)</td>
<td>6 (3.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C reactive protein&gt;1.0</td>
<td>1 (0.6%)</td>
<td>6 (3.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Neurological insult*</td>
<td>1 (0.6%)</td>
<td>3 (1.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Abnormal hearing test</td>
<td>1 (0.6%)</td>
<td>5 (3.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>3.7 ± 1.1</td>
<td>4.2 ± 1.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Early re-hospitalization†</td>
<td>5 (3.2%)</td>
<td>8 (1.5%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Hypoxic ischemic encephalopathy, convulsions or hypotonia; †Defined as re-hospitalization during the first month of life.
Data are presented as mean ± SD or N (%).

Full Term infants
Study group: >37.8°C
IV antibiotics given to 17.6% of infants in the fever group

Linder et al., J Mat-Fet and Neonat Med, 2013
**Table 2**  Attack rate for CPEOI and antibiotic treatment for neonatal infection based on CAM ICD-9

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>CPEOI</th>
<th>Antibiotic treatment with negative cultures&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n (%)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>No IPF&lt;sup&gt;b&lt;/sup&gt;</td>
<td>28,162</td>
<td>13 (0.05)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>IPF-not CAM&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1,707</td>
<td>1 (0.06)</td>
<td>1.3 (0.2, 9.7)</td>
</tr>
<tr>
<td>CAM&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1,243</td>
<td>5 (0.4)</td>
<td>8.7 (3.1, 24.6)</td>
</tr>
</tbody>
</table>

Abbreviations: CAM, chorioamnionitis; CI, confidence interval; CPEOI, culture-positive early-onset bacterial neonatal infection; ICD-9-CM, International Classification of Disease-Ninth Revision-Clinical Modification; IPF, intrapartum fever; RR, relative risk.

<sup>a</sup>Received antibiotic treatment in the first 96 hours after birth with negative cultures.

<sup>b</sup>No IPF maternal temperature measurement <100.4°F within 24 hours before to 4 hours after delivery and no ICD-9-CM diagnosis.

<sup>c</sup>IPF-not CAM maternal temperature measurement ≥100.4°F within 24 hours before to 4 hours after delivery and no ICD-9-CM diagnosis.

<sup>d</sup>CAM based on discharge diagnosis ICD-9-CM codes 762.7 or 658.4x.

American Journal of Perinatology Vol. 33 No. 2/2016
New Terminology for Chorioamnionitis

• NICHD Expert Panel:
  • Abandon “chorioamnionitis”
  • Alternative: “intrauterine inflammation or infection or both”, or “Triple I”

Eunice Kennedy Shriver National Institute of Child Health and Human Development
Health research throughout the lifespan

What’s in a name? “**Triple I**” or **Chorioamnionitis**

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Features and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated maternal fever</td>
<td>Maternal oral temperature 39.0°C or greater (102.2°F) on any one occasion is documented fever. If the oral temperature is between 38.0°C (100.4°F) and 39.0°C (102.2°F), repeat the measurement in 30 minutes; if the repeat value remains at least 38.0°C (100.4°F), it is documented fever</td>
</tr>
<tr>
<td>Suspected Triple I</td>
<td>Fever without a clear source plus any of the following: 1) baseline fetal tachycardia (greater than 160 beats per min for 10 min or longer, excluding accelerations, decelerations, and periods of marked variability) 2) maternal white blood cell count greater than 15,000 per mm³ in the absence of corticosteroids 3) definite purulent fluid from the cervical os</td>
</tr>
<tr>
<td>Confirmed Triple I</td>
<td>All of the above plus: 1) amniocentesis-proven infection through a positive Gram stain 2) low glucose or positive amniotic fluid culture 3) placental pathology revealing diagnostic features of infection</td>
</tr>
</tbody>
</table>
Reconsidering current PPROM antibiotic prophylaxis

Chorioamnionitis - Placental & amniotic membrane cultures at delivery [740/1,133 (65% Gm -ve)]. 27 NB had EOS-BC+

Antibiotic sensitivity profile of E.coli and Klebsiella

Am J Perinatology 2015;32:1247-50
Decreasing vancomycin utilization in a NICU (LOS)

• Evaluate **efficacy** of **education** vs **audit and feedback** in decreasing vancomycin utilization.

• Data collected prospectively in 3 periods
  1. Baseline,
  2. After education and introduction of a late-onset sepsis treatment guideline, and
  3. After prospective audit-feedback to physicians.

• **Guideline**: Obtain 2 blood culture → Nafcillin and Gentamycin (MRSA colonization: Vancomycin and Gentamycin); after 48 hrs.→ cultures negative: Discontinue antibiotics. *If clinical improvement* Nafcillin and Gentamycin x 7-10 d. If 2/2 blood culture positive for CNS→ repeat BCx 2 → **Nafcillin to Vancomycin and D/C Gentamycin.** If ½ positive CNS→ repeat BC, If negative: DC antibiotics because contaminant. If any other organism→ CSF and treatment. **Suspect NEC:** If no pneumatosis→ Ampicillin and Gentamycin; if Pnematosis→ Ampicillin, Gentamycin and Metronidazole.

• **Vancomycin utilization and administration >3 days significantly decreased with education and guideline use,** but it was **not affected** by audit and feedback.

*Am Jr. of Infection control. 2015;43:1253-7*
• Infection control and prevention.
• Indications for late-onset sepsis work-ups versus observation.
• Interpretation of meningitis versus IVH or ‘bloody’ tap; urine cultures – analysis; TA cultures – colonization versus pneumonia.
• Diagnosis- specific duration of treatment (e.g. ?sepsis, meningitis versus IVH, NEC versus feeding intolerance).
• Standards for perioperative prophylaxis.
Summary and Take Home Message

- **Antibiotic Stewardship team**: MD, Pharmacy, infection control nurse, micro.
- **Monitor**: antibiotic use versus organisms cultured, duration, antibiogram, trends & pattern, education of all staff/patients, involve administration.
- Guidelines for- Early onset Sepsis;
  - Septic work-up, Late onset Sepsis, prophylactic Antibiotics
  - Monitor drug resistance
- **If problem**: conduct QI and follow-up.
- **CDC**: <www.CDC.Gov.getsmart>.
Thank you for providing Compassionate Care

“...There are no feet too small that it cannot leave an imprint on the world.”
“Learn from yesterday, live today. Hope for tomorrow. The important thing is **NOT to stop questioning**”.  ---- *Albert Einstein*

“The Art and Science of **asking questions** is the source of all knowledge”.  ---- *Thomas Berger.*