Antibiotic Stewardship in the ICU: An Official American Thoracic Society Workshop Report in Collaboration with the AACN, CHEST, CDC, and SCCM

Richard G. Wunderink, Arjun Srinivasan, Philip S. Barie, Jean Chastre, Charles S. Dela Cruz, Ivor S. Douglas, Margaret Ecklund, Scott E. Evans, Scott R. Evans, Anthony T. Gerlach, Lauri A. Hicks, Michael Howell, Melissa L. Hutchinson, Robert C. Hyzy, Sandra L. Kane-Gill, Erika D. Lease, Mark L. Metersky, Nancy Munro, Michael S. Niederman, Marcos I. Restrepo, Curtis N. Sessler, Steven Q. Simpson, Sandra M. Swoboda, Christina Vazquez Guillamet, Grant W. Waterer, and Curtis H. Weiss; on behalf of the American Thoracic Society, Centers for Disease Control and Prevention, American Association of Critical-Care Nurses, American College of Chest Physicians, and Society of Critical Care Medicine

ONLINE DATA SUPPLEMENT
ADDITIONAL METHODOLOGY DETAILS:

The proposal for a Workshop on Antimicrobial Stewardship in the ICU was initiated by the Acute Pneumonia Working Group of the Microbiology Tuberculosis and Pulmonary Infections (MTPI) Assembly of the ATS in response to an ATS Board of Directors Request for Proposals independent of the Assembly process. Discussions with CDC leadership on collaboration occurred early in the process. Topics for discussion in the Workshop and discussion leaders were chosen by the Acute Pneumonia Working Group. In response to ATS Board approval of the proposal, other members of the Critical Care Societies Collaborative were invited and accepted participation. After negotiating a memorandum of understanding, each society designated representatives to participate in the Workshop.

Prior to the Workshop, a questionnaire (see below) was sent to all participants in order to stimulate thoughts and optimize discussions. Results of this questionnaire were tabulated and sent to participants prior to the workshop meeting (see below). A brief synthesis of the results was also presented at the Workshop Introduction.

The ATS Workshop on Antimicrobial Stewardship in the ICU was held on May 13, 2016 in conjunction with the American Thoracic Society International Conference in San Francisco. Twenty-six people participated, including representatives from the Centers for Disease Control and Prevention (CDC), Society of Critical Care Medicine (SCCM), American College of Chest Physicians (ACCP), and the American Association of Critical Care Nurses (AACN). The group was multidisciplinary with Pulmonary, Critical Care, Surgery, Infectious Diseases, Nursing, and Critical Care Pharmacist participants.

The one-day meeting format was broken down into three focus areas after introductory statements – community-acquired pneumonia, hospital-acquired pneumonia (including ventilator-associated pneumonia), and sepsis. These three topics were chosen as most pertinent and common to general critical care practitioners. The primary focus of the workshop was to point out issues, identify opportunities, and define problems in antibiotic stewardship in the ICU. While unable to offer independent recommendations, workshop participants were encouraged to point to recommendations consistent with guidelines already approved by ATS and the other critical care societies. Two opening talks designed to focus on current status and challenges in current management, followed by breakout sessions moderated by two participants each, was the format for each topic area. Breakout Session Moderators and scribes then presented discussion conclusions and themes to all Workshop participants. Discussions of the all Workshop participants confirmed major general themes and disease-specific recommendations. The Workshop concluded with a general discussion regarding common themes and plans for implementation.

Subsequently, a face-to-face/videoconference meeting was held for 90 minutes at the 2017 ATS International Conference in Washington DC. A working draft of the Workshop was discussed at
this meeting and issues for emphasis in the document were verified. The initial draft was submitted to the ATS Documents Editor on The Workshop report was submitted to the ATS guidelines committee in November 2019 and reviews by all involved Societies were received in February 2019. A revised document and response to reviewers was submitted 2019 ATS Board approval on _. Other participating societies endorsed over the next _ months
Antibiotic Stewardship Workshop - Questionnaire

As critical care clinicians, we are frequently faced with acutely ill patients with a variety of infections. The tendency in the past has been to assume that broader antibiotic therapy is better. More recent data has questioned this assumption. The epidemic of multidrug-resistant gram-negative pathogens forces us to reevaluate our use of broad-spectrum antibiotics for prolonged periods of time. This workshop is designed to address antibiotic stewardship with the competing pressures of appropriate empirical antibiotics for severely ill patients with overuse of antibiotics, particularly broad-spectrum.

1. Do you think there is a real conflict between stewardship and aggressive management of serious infections?
2. If no, do you think there is a perceived conflict between stewardship and aggressive management of serious infections?
3. How can we overcome the real or perceived conflict between stewardship and aggressive management of serious infections?

We will focus on three clinical syndromes-community-acquired pneumonia, hospital-acquired pneumonia, and sepsis that are most pertinent to critical care clinicians in the workshop. In order to facilitate thinking and discussions regarding these topics, please consider and evaluate the following questions in each clinical syndrome.

Community-acquired pneumonia

1. Where the primary areas of opportunity for better antibiotic stewardship for CAP?
   a. 
   b. 
   c. 
   d. 

2. What are the major barriers to improved antibiotic stewardship for CAP?
   a. 
   b. 
   c. 
   d. 
   e. 

Hospital-acquired pneumonia/ventilator associated pneumonia
1. Where the primary areas of opportunity for better antibiotic stewardship for HAP/VAP?
   a.
   b.
   c.
   d.
   e.

2. What are the major barriers to improved antibiotic stewardship for HAP/VAP?
   a.
   b.
   c.
   d.
   e.

Severe sepsis/septic shock

1. Where the primary areas of opportunity for better antibiotic stewardship for sepsis?
   a.
   b.
   c.
   d.
   e.

2. What are the major barriers to improved antibiotic stewardship for sepsis?
   a.
   b.
   c.
   d.
   e.

Name:__________________________________________________________
Antibiotic Stewardship Workshop – Questionnaire Results

The following are tabulated results of the questionnaire answers. Comments reflect individual Workshop participant’s experiences and may not reflect the views of the group as a whole. Many critical issues were not fully developed but summarized as single words or short phrases. All answers were not necessarily discussed or elaborated upon in the Workshop.

These tabulated results were made available before and at the Workshop with the intent of stimulating discussion and clarifying areas for greater emphasis.

4. Do you think there is a real conflict between stewardship and aggressive management of serious infections?
   a. It depends on who does the stewardship. Yes, if a stewardship team not involved in patient care does it, no if the ICU team does it
   b. Yes
   c. Occasional discrepancies between severity of the disease and the need to de-escalate or reduce the duration.
   d. Conflict between appropriate dosing in patients critically ill with renal or liver dysfunction.
   e. Conflict between clinical resolution or clinical failure and decision regarding appropriate duration of antibiotics.

5. If no, do you think there is a perceived conflict between stewardship and aggressive management of serious infections?
   a. Sometimes, when it limits access to agents when the patient is acutely ill
   b. 

6. How can we overcome the real or perceived conflict between stewardship and aggressive management of serious infections?”
   a. Have the management team be part of the process and not the target of stewardship
   b. Better diagnostics, prediction models and team science
   c. Generate more evidence based information that will inform implementation programs to actually treat aggressively serious infections, rather than extrapolation from other groups of patients less sick and with different risks factors.

Community-acquired pneumonia

3. Where the primary areas of opportunity for better antibiotic stewardship for CAP?
   a. Narrowing after 2-3 days
   b. Narrowing when on oral therapy
   c. More focused empiric therapy, if we have better diagnostics x 2
   d. Early de-escalation based on culture data and/or clinical response
   e. Treating as CAP not HCAP x 2
   f. Microbiology
i. Point of care testing in ED, urgent care clinics with multiplex PCR arrays (multiple viruses and some bacteria) and also Strep pneumo realtime PCR
ii. Optimal POC assays for rapid differentiation of viral from bacterial CAP
iii. Differentiation from viral disease x 3
iv. More rapid rule-out atypicals
g. Rapid POC identification and Abx sensitivity testing for CAP pathogens
h. Inpatients: clinical pathways to include inflammatory markers
i. Utilization of risk stratification to inform choice of drug
j. switch therapy: iv-po after 48-72 hrs even in severe cases after clinical stability x 2
k. much shorter courses x 4
l. Appropriate empiric and directed antibiotic therapy
m. Use of biomarkers to determine the duration of antibiotics and de-escalation x 2
n. Appropriate duration of antibiotics and discharge from the hospital
o. Development and validation of novel, non-antibiotic immune and inflammatory regulators to shorten time to cure
p. Not treating bronchitis as CAP
q. Randomized trials demonstrating the less is more
r. Medication histories with focus on antibiotic use in previous 90 days
s. Desensitization for allergies
t. Availability of antibiograms from other hospitals/region/ER; drug combinations
u. Variations in prescribing regimens

4. **What are the major barriers to improved antibiotic stewardship for CAP?**
   a. Delay in therapy with prescribing approval
   b. Limited etiologic diagnoses with current testing
   c. Too long a duration of therapy
   d. No local antibiograms x 2
   e. Slavish application of treatment protocols with no local modification on etiology
   f. Reliance on 19th century microbiological tests to determine etiology x 4
      i. Lack of highly precise and rapid POC biomarkers for diagnosis
      ii. Lack of reliability of rapid micro assays for respiratory secretions
g. Outpatient pressure
h. Lack of high quality data
i. Associating severity of presentation with need for broad spectrum abx
j. USA clinical practice culture which would rather over treat than under treat
k. Do we need two antibiotics or one antibiotic is enough
l. The unclear value of HCAP in communities and the uncertainty about the antibiotic therapy x 2
m. Lack of data for the duration management of antibiotics in patients with Severe CAP
n. The risks associated with certain medications, such as macrolides and fluoroquinolones
o. Lack of system integrated information between guidelines, available medications and the actual prescription
p. Overly broad guidelines
q. Lack of successful evidence based implementation programs
r. Concerning immunosuppressed community of patients with respiratory infections
s. Wide-spread inappropriate and broad spectrum empiric antibiotic treatment for CAP
   i. Widespread use, particularly in developing healthcare environments of broad spectrum antimicrobials including quinolones and 3rd gen cephs.
t. Expansion of resistance into community-acquired pathogens (e.g. MRSA for skin/soft tissue) x 2
u. Sometimes hyper-acute presentation in CAP
v. Issues related to entanglement with sepsis
w. Performance measure which is concerned with timely antibiotic administration and not over use
x. Allergy documentation – reaction
y. Possible knowledge gaps in appropriate therapies and guidelines

Hospital-acquired pneumonia/ventilator associated pneumonia

3. Where the primary areas of opportunity for better antibiotic stewardship for HAP/VAP?
   a. Narrower spectrum therapy
   b. Not treating anaerobes where none exist
   c. Early de-escalation based on negative culture data and procalcitonin
   d. Shorter duration of therapy x 4
      i. Microbiology correlation and duration of antibiotics
   e. More aggressive de-escalation x 4
   f. Not treating in the first place because it is futile (end of life care)
   g. Better diagnosis and not starting abx just for temperature x 2
   h. Increase use of invasive diagnosis
   i. Communication especially Patient history
   j. Medication histories with focus on antibiotic use in previous 90 days
   k. Newer microbiology methods x 3
      i. Most feasible MRSA PCR on lower tract specimens. Also other molecular methods, automated microscopy, VOCs
      ii. Widespread validation and deployment of rapid, highly precise microbiological diagnostics for respiratory samples including BAL
      iii. Rapid identification of MDR pathogens
iv. Tracheal aspirate surveillance
l. Timely notification of results with alerts
m. Desensitization for allergies
n. Locally derived prediction / mathematical models, de-escalation scores (estimate risk for Pseudomonas, Acinetobacter, ESBLs etc)
   i. Wide implementation of automated decision support technology
   ii. Development of apps to help guide practice or computerized programs
o. PK/PD monitoring
p. Appropriate dosing balancing risks and benefits of antibiotics
q. inhaled abx
r. IV to PO
s. ideally: species- specific antibiotics
t. in-line monitoring of VOC: diagnostics, therapeutic monitoring
u. Following gram stain and culture reports, especially in the ongoing ventilator dependent patient population x 2
v. Teaching resident teams to look at the patient and all the data
w. Possible knowledge gaps in appropriate therapies and guidelines
x. IDT rounding with active pharmacist input
y. Current availability of outcome data supporting stewardship
z. Feedback to providers on usage patterns and resistance
aa. Biomarkers and duration of antibiotics
bb. Reliable and well calibrated biomarkers for disease diagnosis, treatment response monitoring and de-escalation – including plasma, BAL and exhaled breath biomarkers.
cc. Novel antimicrobial peptides as antibiotic sparing therapies
dd. Care bundles that are easy to use/understand; built in limits to length of therapy

4. What are the major barriers to improved antibiotic stewardship for HAP/VAP?
   a. Inappropriate empiric treatment
   b. Limited access to antibiotics
   c. Non-specific diagnostic testing x 6
   d. Oncologists/ Hematologists
   e. Intensivists who can't/won’t have end of life discussions
   f. Poor diagnostic criteria x 3
   g. Cultures not obtained around fever, instead after antibiotic initiated
   h. Underutilization of invasive diagnosis
   i. VAP mimics
   j. PK/PD parameters x 2
   k. More susceptibilities at a more detailed level
   l. vague risk factors for MDR pathogens
   m. Knowledge of resistance patterns
   n. Healthcare professional knowing the difference between HAP and CAP
o. Adherence to guidelines or knowledge of current recommendations needs multimodal approach
p. Patience & wisdom
q. complacency
r. Cost concerns
s. Do we need so many (three) empiric antibiotics or a more limited approach will preserve the antibiotics
t. Overly broad spectrum of regimens recommended by guidelines, often not evidence based
u. The risks associated with certain medications, such as aminoglycosides
v. Lack of system integrated information between guidelines, available medications and the actual prescription
w. The need to obtain microbiology samples in order to implement de-escalation strategies
x. Lack of successful evidence based implementation programs
y. Lack of compelling prospective literature to withhold antibiotics in low risk situations
z. High pneumonia failure rates with certain pathogens as MRSA or Pseudomonas
aa. High rates of antimicrobial resistance
bb. Lack of integrated decision analysis tools at bedside to practice point-of-care antibiotic stewardship programs
cc. Patients with tracheobronchitis or persistent MDR colonization
dd. Difficult to manage cohorts of patients such as immunosuppressed or chronic ventilated
ee. De-escalation
ff. Getting exact MIC
gg. The definition of VAP has so much inter-observer variability that it is nearly impossible to sort out what is meaningful in the literature
hh. The downsides of not covering early for potential pathogens in VAP are so high that it feels mandatory to do so (Iregui 2002)
ii. The quantification of harms from antibiotics needs to be more robust: there is little perceived downside
jj. When is it safe to de-escalate VAP ABX when cultures are obtained already on antibiotics? Respiratory cultures are often not obtained (or not possible to be obtained) prior to initiation of antibiotics – meaning that de-escalation is really challenging. I do NOT think that we will fix this problem with exhorting providers to get cultures earlier
kk. Lack of structure of an “antibiotic time out” for VAP (e.g. on day 3)

Severe sepsis/septic shock

3. Where the primary areas of opportunity for better antibiotic stewardship for sepsis?
a. Less broad spectrum therapy
b. My main concern is that we will use broad-spectrum antibiotics widely in response to SEP-1, which depends largely on SIRS (>50% prevalence on the wards outside the ICU!). I am unconvinced the qSOFA is better.
c. Initial broad-spectrum antibiotics when there is clear evidence in favor of tailored therapy from the beginning (e.g. true community-dweller with urinary pneumococcal ag (+)).
d. Observation of patients in whom infection seems unlikely (this is a bit off topic, because by definition patients with severe sepsis/septic shock have a confirmed or suspected infection, but clinicians often “cover” anyway even when there is another cause to account for the hemodynamic findings)
e. Broad spectrum antibiotics to cover most of highly resistant pathogens
f. Consideration of combination therapy in patients with septic shock
g. Not treating in the first place because it is futile (end of life care)
h. Better microbiological testing to improve de-escalation x 2
   i. Non Culture diagnostic methods
   ii. Use of the many molecular arrays available for blood culture
i. Shorter duration once source control achieved x 5
j. Prolonged broad-spectrum antibiotics with evidence in favor of tailoring
k. De-escalation at 48-72 hours when pathogens such as MRSA or Pseudomonas have not been identified
l. Discontinuation of antibiotics when cultures are negative
m. Locally derived prediction models for abx changing pathogens: VRE, Candida etc
   i. Computerized antibiotic selection and dosing.
   ii. Use of Big Data on antibiotic use at all levels, mathematical models for hospital specific total use and mix of classes of abx
   iii. Antibiograms for drug combinations, source, ICU
   iv. Feedback to staff about trends in infections, usage
n. Non antibiotic anti-infectives
o. Clinical outcomes to base decisions during unstable period
p. Early administration of antibiotics
q. Source control in addition to antibiotic stewardship
r. Early and definitive diagnostic and prognostic biomarkers for bacterial sepsis
s. Use of procalcitonin as an aid to de-escalation
t. Novel treatment response and host immune biomarkers validated for guiding deescalation
u. Reliable direct from blood rapid ID/AST microbiological diagnostics for POC application
v. Reliable and well calibrated biomarkers for disease diagnosis, treatment response monitoring and de-escalation – including plasma, BAL and exhaled breath biomarkers.
w. Validated and widely implemented automated clinical decision support tools for empiric broad spectrum antibiotic treatment
x. Not one regimen for all patients
4. **What are the major barriers to improved antibiotic stewardship for sepsis?**
   a. Lack of identifying a site of infection/culture negative sepsis x 3
   b. Using antibiotics when patients are sick, even without a documented or likely infection.
   c. Poor microbiological platforms in current use x 2
   d. Failure of clinicians to engage in end of life care discussions
   e. Knowledge: limited choices in empirical regimens
   f. Associating severity of presentation with need for broad spectrum abx
   g. Results available but still want broad coverage because patient got better
   h. Cultures not obtained around fever, instead after antibiotic initiated
   i. Failure to believe or rely on or obtain microbiologic data
   j. Caregiver expertise in antibiotic selection
   k. Pressure to assure all possible sources are covered
   l. The lack of sepsis rather than other disease specific antibiotic therapies
   m. Awaiting for culture results to define direct therapy
   n. Lack of consistency in available biomarkers to determine infection and need for antibiotic agents
   o. Lack of implementation programs that might improve cost, morbidity and mortality
   p. Practice culture in US which favors unnecessary treatment
   q. Dearth of sufficient high level evidence de-escalation studies
   r. Lack of reliable biomarkers (Troponin for sepsis)
   s. Fear of litigation
   t. Desire to cover everything out of fear
   u. “Vanco-syn” and “Vanco-pime” (Shooting from the hip empiric combination therapies – esp for community acquired sepsis)
   v. Perceived impact of non-human inappropriate use of antibiotics on resistance profiles (particularly agricultural/veterinary)
   w. Optimizing PK/PD
   x. Front-loading antibiotics
   y. De-escalation
   z. Getting Exact MIC
   aa. Drug cost
   bb. SEP-1 as a publicly reported measure
   cc. Lack of clarity in underlying definition of sepsis x 2
   dd. Implementation of bundles and provider adherence
   ee. Changing guidelines and recommendations
   ff. Cost and availability of new diagnostic testing: resources
   gg. Lack of structure of an “antibiotic time out” for sepsis (e.g. on day 3)