Hospital-Acquired Pneumonia Educational Module
Developed by: Linda Dresser, BScPhm ACPR PharmD FCSHP with contributions from the CAHO ASP Project Team

Antimicrobial Stewardship Program (ASP) in Intensive Care Units (ICU) ARTIC Project
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“Getting patients the right antibiotics, when they need them”

SCENARIO

AH is a 77 year old woman admitted to your ICU following a stroke. In the ED vital signs are stable; BP 140/90 mm Hg, RR 18 breaths per minute, T 37.5 °C, and regular pulse with a HR of 79 beats per minute; she was intubated to protect her airway. The patient’s past medical history is significant for COPD and CAD. She did not receive an influenza vaccine this year. She has no known allergies. She is extubated within 48h of admission, however her right-sided hemiplegia and aphasia persist and a swallowing assessment indicates a need for aspiration precautions; she currently has an NG tube for feeds.

On hospital day 6 the patient has increased cough with purulent sputum, decreased air entry bilaterally and decreased level of consciousness. Her SpO₂ is 87% on 15 L by non-rebreather mask. On exam her temperature is 38.7°C, RR 26, BP 110/55. A CXR reveals a new right lower lobe opacity. Her laboratory investigations are below (Table 1). Sputum and blood are sent for culture and sensitivity testing. What would be your advice to the team with respect to antimicrobial therapy? AH has no known allergies and her admission MRSA and VRE screens were negative.

Table 1. Laboratory results day 6

<table>
<thead>
<tr>
<th>WBC</th>
<th>17.3 x 10e9/L</th>
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<tr>
<td>Creatinine</td>
<td>140 mmol/L (baseline 66mmol/L)</td>
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KEY MESSAGES

- Appropriate and prompt initial antimicrobial therapy is important for optimal clinical outcomes.
- Empiric antimicrobial therapy should be tailored based on culture and sensitivity results; if cultures are negative at 48-72 h and the patient has improved, antibiotics can be de-escalated or stopped.
- Monotherapy has similar efficacy to combination therapy.
- For most patients 7 days of therapy is sufficient.

BACKGROUND

Hospital-acquired pneumonia (HAP) is the second most common nosocomial infection next to urinary tract infection. The estimated crude overall rate is 6.1 per 1000 discharges. HAP may occur anywhere in the hospital, from general medicine or surgical wards to the ICU. Similar to ventilator-associated pneumonia (VAP) HAP is associated with increased morbidity and mortality, as well as increased lengths of stay and cost. Clinical practice guidelines have been published to aid in the diagnosis and management of HAP but the clinician must be aware of the limitations of the guidelines. Developing an approach to patient care that utilizes knowledge of local microbiology susceptibility patterns, patient risk factors in conjunction with the guidelines will improve antimicrobial prescribing and hopefully patient outcomes.

CLINICAL PRESENTATION

Hospital-acquired pneumonia (HAP): pneumonia that occurs 48 hours or more after admission and that was not incubating at the time of admission.

Ventilator-associated pneumonia (VAP) is a subset of HAP and is defined as pneumonia which occurs in patients receiving invasive mechanical ventilation for > 48 hours.

Health-Care Associated Pneumonia (HCAP) is defined as pneumonia occurring in patients who are hospitalized for > 48 hours within 90 days of the diagnosis of pneumonia; those who reside in a long-term care facility; those who received recent parenteral antimicrobial therapy, chemotherapy or wound care within 30 days of pneumonia; or those who received treatment in a hemodialysis unit or other hospital clinic.
There is considerable overlap in the presentation, diagnosis and management of all these pneumonia syndromes.\(^3\)

The clinical manifestations are nonspecific and generally comprise a constellation of fever, dyspnea, chest pain, cough, sputum production, hypoxia and leukocytosis. Many of these may be mimicked by other clinical entities such as congestive heart failure, acute respiratory distress syndrome (ARDS) or pulmonary embolism.

The guidelines suggest the following diagnostic criteria for HAP.

**Two** or more of the following clinical features:

- a. Temperature > 38 °C or < 36 °C
- b. Leukopenia or leukocytosis
- c. Purulent tracheal secretions
- d. Decreased PaO\(_2\)

**PLUS** a CXR compatible with pneumonia, showing:

- a. Alveolar infiltrates, or
- b. Air bronchograms, or
- c. New or worsened infiltrates

**PLUS** a Clinical pulmonary infection score (CPIS) > 6

A comment about CPIS:

The CPIS score was originally proposed in 1991 as a diagnostic tool for VAP.\(^4\) It was suggested that a CPIS > 6 out of 12 correlated with high bacterial counts isolated from the lower respiratory tract. A more recent study found that adding a gram stain of respiratory tract secretions to the CPIS increased the diagnostic accuracy for VAP but the authors cautioned that further refinement of the clinical scoring approach was necessary to improve the utility of the tool.\(^5\) In 2000, a trial using the CPIS in the diagnosis of HAP or VAP was published; almost 60% of the patients in either the intervention (use of CPIS) or control arm were mechanically ventilated.\(^6\) Therefore, the evidence validating the use of the CPIS in HAP is limited and inclusion of a CPIS score in the diagnosis of HAP is not widely endorsed.
ETIOLOGY

Severity of illness and risk factors for resistant pathogens should be used to guide choice of empiric coverage and potentially less emphasis on time of onset (early, < 96 h after admission versus late, ≥96 h after admission). Daneman and colleagues recently studied the likelihood of isolating P. aeruginosa as a function of time from hospital admission. This was a hospital wide study (not just ICU) which showed the likelihood of a positive culture yielding P. aeruginosa increased linearly throughout the first 10 weeks of hospital stay. There was not a significant spike in positive cultures, for example on day 5.

Although the study was limited by being microbiology-culture based (many of the positive cultures may represent colonization) and culture negative infections were not included, the results may point away from splitting VAP into early versus late as a means to decide which patients need initial antipseudomonal coverage. Table 2 lists the core organisms which should be considered with either early or late onset illness. Table 3 identifies potential pathogens that warrant empiric coverage in the presence of specific risk factors and may be more prevalent in late onset infection. The Canadian guidelines for the management of HAP further subdivide these groups. The clinician is encouraged to assess the guidelines for applicability to their practice site.

Table 2. Core Pathogens

<table>
<thead>
<tr>
<th>Early Onset (&lt; 96 h) or Late Onset (≥ 96 h)</th>
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<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
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<tr>
<td>Streptococcus sp</td>
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<tr>
<td>Haemophilus influenzae</td>
</tr>
<tr>
<td>Enterobacter sp</td>
</tr>
<tr>
<td>Escherichia coli</td>
</tr>
<tr>
<td>Klebsiella sp</td>
</tr>
<tr>
<td>Proteus sp</td>
</tr>
<tr>
<td>Serratia marcescens</td>
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<td>Staphylococcus aureus</td>
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Table 3. Extended Etiology with Risk Factors

<table>
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<th>Core pathogens (from Table 2) PLUS</th>
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<tr>
<td>Pseudomonas aeruginosa</td>
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<tr>
<td>Methicillin-resistant Staphylococcus aureus (MRSA)</td>
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<tr>
<td>ESBL-enterobacteriaceae</td>
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Risk factors for extended etiology, other than duration of hospitalization, that should be considered:

+ recent hospital admission
+ prior broad-spectrum antimicrobial exposure:
  - during the current hospital admission
  - within preceding 90 days for any reason
+ prior isolation of, or known colonization with multi-drug resistant organisms (e.g. ESBL-enterobacteriaceae, MRSA)
+ immunosuppression

**PHARMACOTHERAPY**

**EMPIRIC**

The Canadian HAP guidelines state that greater severity of illness at presentation with organ dysfunction, whether early or late onset, may imply the presence of more resistant, harder to treat pathogens, and for this group combination therapy which includes coverage for *P. aeruginosa* is preferred to attain better outcomes. There is a paucity of evidence to support this statement.²

Evidence validating an improved mortality benefit with early antimicrobial (within 1 hour of diagnosis) administration does not exist for HAP. However, patients who develop HAP within the ICU or are transferred to the ICU and who require mechanical ventilation or other life-sustaining support (e.g. pressors) may also benefit from early appropriate antimicrobial administration similarly to patients with VAP, which may include broad-spectrum agents.

**Early Onset Options:**

+ Non-antipseudomonal third generation cephalosporin (i.e. cefotaxime, ceftriaxone)
Late Onset or Presence of Risk Factors Options:

- Antipseudomonal cephalosporin (i.e. ceftazidime) OR
- Antipseudomonal beta-lactam/beta-lactamase inhibitor (i.e. piperacillin/tazobactam) OR
- Antipseudomonal carbapenem (i.e. imipenem, meropenem, doripenem)

PLUS / MINUS (depending on local risk of pseudomonal resistance)

- Aminoglycoside (i.e. gentamicin, tobramycin)

PLUS / MINUS (depending on patient risk and local risk of MRSA acquisition)

- Vancomycin; OR
- Linezolid

It should be noted that the IDSA/ATS guidelines recommend respiratory fluoroquinolones or carbapenems as empiric treatment options in HAP. From an antimicrobial stewardship perspective, carbapenems are reserved for patients known to be colonized with extended spectrum beta-lactamases (ESBL), treatment of MDR pathogens, and instances of drug allergy. Fluoroquinolone use is not encouraged as empiric therapy because they are generally over utilized in ICUs and are strongly associated with the emergence of the NAP1 strain of Clostridium difficile.

Linezolid

Similar to VAP, there remains debate amongst clinicians regarding the optimal antimicrobial choice for MRSA HAP. The ZEPHYR study was a Phase IV randomized, controlled, non-inferiority trial which compared linezolid with vancomycin for the treatment of MRSA HAP and VAP. Of the 1184 patients treated, only 448 (linezolid, n = 224; vancomycin, n = 224) were included in the modified intention to treat analysis. There was no difference in mortality at 60 days between the two groups (linezolid, 15.7%; vancomycin, 17.0% [p = ns]), although patients in the linezolid treatment group did have higher end of study clinical success (linezolid, 57.6%; vancomycin, 46.6% [p = 0.042]). The patients in the vancomycin arm were found to have higher rates of nephrotoxicity (linezolid, 8.4%; vancomycin 18.2%), however the clinical severity and relevance of the renal dysfunction is not quantified. The decision whether to consider linezolid or vancomycin as the first line option for MRSA HAP should be taken with thoughtful input from all institutional stakeholders as well as consideration of
local microbiology (i.e. MRSA rates and local MIC’s to vancomycin among S. aureus isolates). The UHN-MSH ASP program continues to encourage use of vancomycin as a first line treatment of MRSA pneumonia.

Monotherapy versus Combination Therapy

The guidelines acknowledge that the recommendation for combination therapy to manage infections due to P. aeruginosa is not substantiated in the literature. A meta-analysis which evaluated all prospective randomized trials of beta-lactam/aminoglycoside combination regimens, including a group of patients who had HAP or VAP, found no advantage for combination therapy compared with beta-lactam monotherapy for P aeruginosa infections. A second meta-analysis determined that there was no beneficial effect of beta-lactam/aminoglycoside combination therapy versus beta-lactam monotherapy in preventing the emergence of resistance.

The most compelling reason to use combination empiric beta-lactam/aminoglycoside therapy is to administer at least one active agent against P aeruginosa where local resistance rates support this concern.

TARGETED

If a pathogen is identified, therapy should be tailored and stream-lined to a single agent for the remainder of the course of therapy.

If a high-probability of HAP remains after 48h, despite lack of an identified pathogen, and the patient is responding, empiric therapy is continued. However if combination therapy was initiated empirically the need for continued multiple agents should be re-evaluated.

DE-ESCALATION

A formalized discontinuation strategy should be employed. The benefits of such an approach are discussed in the ventilator-associated (VAP) module.

The fluoroquinolone class of antibiotics is ideal for IV to PO switch in selected patients; i.e. patient is tolerating oral or NG nutrition or is receiving medication by mouth or NG tube; patient has a functional gastrointestinal tract; signs and symptoms of infection are improving, patient does not have an infection which precludes oral antibiotic use. An additional criteria for oral fluoroquinolone use is the absence of significant drug interactions that would decrease the amount of oral fluoroquinolone absorbed (i.e. bi/tri-valent cations).
Ciprofloxacin, moxifloxacin and levofloxacin have each been studied in HAP or HAP/VAP clinical trials administered as IV initially with an oral switch option however the results are not robust. In one study of ciprofloxacin IV/PO versus ceftazidime IV, patients in both arms received IV antimicrobials on average for 9 days with an additional few days of oral antibiotics in the ciprofloxacin arm. Based on these finding the authors concluded that clinicians were reluctant to use oral antibiotics for the treatment of hospitalized patients with pneumonia. In another study of levofloxacin IV/PO versus imipenem/cilastatin followed by oral ciprofloxacin, the clinical and microbiological response rates were similar between groups, however the paper does not describe the mean number of days of IV or oral therapy received by each treatment arm so it is not possible to draw any inferences with respect to the efficacy and safety of oral treatment. Regardless of the scant clinical trial data, switching to an oral fluoroquinolone may be considered in select patients.

DURATION OF THERAPY

Traditionally patients with HAP have received antibiotics for 10 – 14 days with little evidence to support this duration. There is evidence to indicate that patients who have received appropriate antimicrobial therapy demonstrate rapid microbiological eradication and improvement in clinical symptoms within 6 days of treatment of their VAP. This supports the rationale that 7 days of treatment will be adequate for most patients with VAP. Additionally this duration is supported by a randomized, controlled trial of patients assigned to 8 versus 15 days of antimicrobials for the treatment of VAP. The authors concluded that 8 days of therapy is non-inferior to 15 days for all cause mortality and microbiologically documented recurrence of infection. There was no significant difference in secondary endpoints including 60-day mortality, lengths of stay in ICU or hospital, or mechanical ventilation days. Treatment for 8 days resulted in significantly more antibiotic-free days. Finally, a Cochrane review of short-course versus prolonged course antibiotic therapy for critically ill patients with HAP, found no difference in mortality. All this represents evidence that is predominantly gleaned from patients with ventilator-associated hospital-acquired pneumonia and is extrapolated to the non-ventilated HAP patient.

REFERENCES


