Epidemiology, pathogenesis, microbiology, and diagnosis of hospital-acquired, ventilator-associated, and healthcare-associated pneumonia in adults

INTRODUCTION — Hospital-acquired (or nosocomial) pneumonia (HAP), ventilator-associated pneumonia (VAP), and healthcare-associated pneumonia (HCAP) are important causes of morbidity and mortality despite improved antimicrobial therapy, supportive care, and prevention [1].

The epidemiology, pathogenesis, and microbiology of HAP, VAP, and HCAP will be reviewed here. The diagnosis, risk factors, prevention, and treatment of HAP, VAP, and HCAP are discussed separately. (See "Clinical presentation and diagnosis of ventilator-associated pneumonia" and "Risk factors and prevention of hospital-acquired, ventilator-associated, and healthcare-associated pneumonia in adults" and "Treatment of hospital-acquired, ventilator-associated, and healthcare-associated pneumonia in adults".)

DEFINITIONS

Pneumonia types — The 2005 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines on the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia used the following definitions [2]:

- Hospital-acquired (or nosocomial) pneumonia (HAP) is pneumonia that occurs 48 hours or more after admission and did not appear to be incubating at the time of admission.
- Ventilator-associated pneumonia (VAP) is a type of HAP that develops more than 48 to 72 hours after endotracheal intubation.
- Healthcare-associated pneumonia (HCAP) is defined as pneumonia that occurs in a non-hospitalized patient with extensive healthcare contact, as defined by one or more of the following:

- Intravenous therapy, wound care, or intravenous chemotherapy within the prior 30 days

- Residence in a nursing home or other long-term care facility

- Hospitalization in an acute care hospital for two or more days within the prior 90 days

- Attendance at a hospital or hemodialysis clinic within the prior 30 days

The guidelines can be accessed through the ATS web site at www.thoracic.org/sections/publications/statements/index.html.

Multidrug resistance — The definition of multidrug resistance (MDR) in gram-negative bacilli, which are an important cause of HAP, VAP, and HCAP, is variably defined as resistance to at least two, three, four, or eight of the antibiotics typically used to treat infections with these organisms [3].

Panresistance refers to those gram-negative organisms with diminished susceptibility to all of the antibiotics recommended for the empiric treatment of VAP, including, cefepime, ceftazidime, imipenem, meropenem, piperacillin-tazobactam, ciprofloxacin, and levofloxacin. (See "Treatment of hospital-acquired, ventilator-associated, and healthcare-associated pneumonia in adults", section on 'Empiric treatment'.)

EPIDEMIOLOGY — HAP is the leading cause of death among hospital-acquired infections, with estimates of HAP-associated mortality ranging from 20 to 50 percent [1,2,4,5]. In contrast, data on HAP-attributable mortality conflict. While some studies indicate an attributable mortality of 33 percent [6,7], another suggests that pneumonia is not a significant risk factor for death after adjusting for other predictors of mortality [8].

Most cases of HAP occur outside of intensive care units. However, the highest risk for HAP is in patients on mechanical ventilation (ie, VAP), in whom the entity has been best studied. Estimates of incidence range from four to seven episodes per 1000 hospitalizations, accounting for 13 to 18 percent of all nosocomial infections.

PATHOGENESIS — The pathogenesis of HAP, VAP, and HCAP is related to the number and virulence of microorganisms entering the lower respiratory tract and the response of the host (eg, mechanical, humoral, and cellular host defenses). The primary route of infection of the lungs is through microaspiration of organisms that have colonized the oropharyngeal tract (or, to lesser extent, the gastrointestinal tract). Approximately 45 percent of healthy subjects aspirate during sleep, and an even higher proportion of severely ill patients aspirate routinely [5]. Although frequently regarded as partially protective, the presence of an endotracheal tube permits the aspiration of oropharyngeal material or bacteria of gastrointestinal origin. Depending upon the number and virulence of the organisms reaching the lung, pneumonia may ensue.

Hospitalized patients often become colonized with microorganisms acquired from the hospital environment, and as many as 75 percent of severely ill patients will be colonized within 48 hours [5,9,10]. The most common mechanism of infection in

mechanically ventilated patients is direct contact with environmental reservoirs, including respiratory devices and contaminated water reservoirs [11,12]. Such contamination frequently occurs despite rigorous cleaning of ventilator equipment because disposable tubing used in respiratory circuits or tracheostomy or endotracheal tubes may become contaminated in the process of routine nursing care or via the (contaminated) hands of hospital personnel.

In addition, the near sterility of the stomach and upper gastrointestinal tract may be disrupted by alterations in gastric pH due to illness, medications, or enteric feedings. For this reason, much attention has been paid to the possible adverse effect of ulcer prophylaxis regimens that raise the gastric pH. Less frequently, pneumonia results from inhalation of infectious aerosols or from bacteremia originating in a distant focus. (See "Risk factors and prevention of hospital-acquired, ventilator-associated, and healthcare-associated pneumonia in adults", section on 'Role of gastric pH'.)

MICROBIOLOGY — HAP, VAP, and HCAP may be caused by a wide variety of pathogens and can be polymicrobial. Common pathogens include aerobic gram-negative bacilli (eg, Escherichia coli, Klebsiella pneumoniae, Enterobacter spp, Pseudomonas aeruginosa, Acinetobacter spp) and gram-positive cocci (eg, Staphylococcus aureus, including methicillin-resistant S. aureus [MRSA], Streptococcus spp). Nosocomial pneumonia due to viruses or fungi is significantly less common, except in the immunocompromised patient.

Ventilator-associated and hospital-acquired pneumonia (VAP and HAP) — There is a paucity of data regarding whether the pathogens that cause VAP differ from those that cause HAP in patients who are not mechanically ventilated. One prospective observational study evaluated 158,519 patients admitted to a single center over a four year period [13]. A total of 327 episodes of VAP and 261 episodes of HAP in non-ventilated patients were identified:

- The infecting flora in patients with VAP included MSSA (nine percent), MRSA (18 percent), P. aeruginosa (18 percent), Stenotrophomonas maltophilia (7 percent), Acinetobacter spp (8 percent), and other spp (9 percent).
- The infecting flora in non-ventilated patients with HAP was similar, except non-Enterobacteriaciae gram-negative bacilli (P. aeruginosa, Acinetobacter, and S. maltophilia) were less likely. Specifically, it included MSSA (13 percent), MRSA (20 percent), P. aeruginosa (9 percent), S. maltophilia (1 percent), Acinetobacter spp (3 percent), and other spp (18 percent).

These findings are supported by a prospective, multicenter, observational study of 398 ICU patients with suspected VAP [14]. In this study, there was a similar distribution of

pathogens — MRSA (14.8 percent), P. aeruginosa (14.3 percent), and other Staphylococcus species (8.8 percent) (table 1) [14].

A frequent criticism of such studies is that they may underestimate the prevalence of certain pathogens (eg, anaerobes) because special culturing techniques are required to identify them. However, a study performed anaerobic cultures using protective brush specimens and bronchoalveolar lavage fluid from 185 patients with possible VAP identified only one anaerobic organism, nonpathogenic Veillonella spp [15]. This suggests that the practice of including anaerobic coverage in the treatment of VAP is unnecessary.

Differences in host factors and in the hospital flora of an institution also influence the patterns of pathogens seen.

Healthcare-associated pneumonia (HCAP) — The clinical and microbiologic features of HCAP are more similar to HAP and VAP than to CAP but the incidence of specific pathogens varies with the population studied [16-19]. Most patients included in these studies were recently hospitalized or had been transferred from nursing homes. Principles from these studies are illustrated by the following observations:

- A retrospective cohort study of 4543 patients with pneumonia occurring within the first five days of admission to United States hospitals between January 2002 and December 2003 examined the distribution of pathogens responsible for HCAP compared to HAP or CAP [17]. The incidence of S. aureus in the HCAP and HAP groups were comparable (47 percent) and significantly higher than in the CAP group (26 percent). The rate of MRSA infection was also higher in HCAP and HAP patients compared to CAP (27 and 23 versus 9 percent for CAP). Besides S. aureus, P. aeruginosa was the only other pathogen with a significant occurrence (25 percent) in HCAP patients.
- A prospective observational analysis of 727 cases of pneumonia from Spain compared the etiology of 126 cases of HCAP and 601 cases of CAP [18]. The most common organism in both groups was S. pneumoniae; however, drug-resistant strains were more common in patients with HCAP. Legionella was more common in CAP, but aspiration, H. influenzae, and gram-negative bacilli were more common in HCAP. S. aureus was also more common in patients with HCAP, but the incidence was substantially lower than in the previous study (2.4 percent for HCAP versus 0 percent for CAP).
- In a multicenter, prospective observational study from 55 hospitals in Italy, 362 patients were hospitalized during two one-week periods [19]. Among these, 62 percent of patients had CAP, 25 percent had HCAP, and 14 percent had HAP. Patients with HCAP had higher mortality (18 versus 7 percent) and longer length

of hospitalization (19 versus 15) compared with CAP patients. However, the great majority of patients classified as having HCAP were those who had been hospitalized within 180 days (a longer period than the 90 days included in the definition of HCAP in the ATS/IDSA Guidelines) [19].

MDR risk factors — The etiology of HAP, VAP, and HCAP depends upon whether the patient has risk factors for multidrug resistant (MDR) pathogens [2]. The frequency of specific MDR pathogens varies among hospitals, specific hospital units, and patient populations including those with recent exposure to antibiotics. An awareness of the susceptibility patterns of the nosocomial pathogens within a given healthcare setting is important for appropriate empiric antimicrobial therapy. The frequency of MDR bacteria as etiologic agents of HAP is increasing, especially among patients in ICUs.

Host risk factors for infection with MDR pathogens include [2]:

- Receipt of antibiotics within the preceding 90 days
- Current hospitalization of ≥5 days
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Immunosuppressive disease and/or therapy
- Patients with HCAP are at variable risk for infection due to MDR pathogens. In a recent review of studies of HCAP published since the development of the ATS/IDSA guidelines, specific risk factors for MDR pathogens associated with HCAP included hospitalization for ≥2 days during the preceding 90 days, severe illness, antibiotic therapy in the past 6 months, poor functional status as defined by activities of daily living score, and immune suppression [20]. The risk factor of long-term care facility (LTCF) residence applies specifically to those who have more severe illness, prior antibiotic therapy in the preceding six months, or poor functional status as defined by activities of daily living score [16,21].

DIAGNOSIS — The clinical diagnosis of HAP, VAP, and HCAP is difficult in part because the clinical findings are nonspecific. The 2005 ATS/IDSA guidelines on the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia did not provide specific criteria for the diagnosis of these disorders. The guidelines concluded that HAP, VAP, or HCAP should be suspected in patients with a new or progressive infiltrate on lung imaging as well as clinical characteristics such as [2]:

- Fever
- Purulent sputum
- Leukocytosis

- Decline in oxygenation

The presence of a new or progressive radiographic infiltrate plus at least two of the three clinical features (fever >38ºC, leukocytosis or leukopenia, and purulent secretions) represents a clinically relevant combination of criteria for starting empiric antimicrobial therapy. When findings at autopsy are used as a standard of reference, this combination of findings resulted in 69 percent sensitivity and 75 percent specificity for pneumonia [22].

The diagnostic approach to HAP, VAP, and HCAP is similar, and is discussed in detail separately. (See "Clinical presentation and diagnosis of ventilator-associated pneumonia", section on Recommended diagnostic approach.)

The use of sputum cultures is reviewed elsewhere. (See "Sputum cultures for the evaluation of bacterial pneumonia".)

SUMMARY

- The following types of nosocomial pneumonia have been defined:

- - Hospital-acquired pneumonia (HAP) is pneumonia that occurs 48 hours or more after admission, and did not appear to be incubating at the time of admission.
- - Ventilator-associated pneumonia (VAP) is a type of HAP that develops more than 48 to 72 hours after endotracheal intubation.
- - Healthcare-associated pneumonia (HCAP) includes pneumonia in any patient who was either hospitalized in an acute care hospital for two or more days within 90 days of the infection; or resided in a long term care facility; or received intravenous antimicrobial therapy, chemotherapy, or wound care within the 30 days prior to the current infection; or attends a hospital or hemodialysis clinic. (See 'Definitions' above.)

- Multidrug resistance (MDR) in gram-negative bacilli, which are an important cause of HAP, VAP, and HCAP is variably defined as resistance to at least two, three, four, or eight of the antibiotics typically used to treat infections with these organisms. (See 'Definitions' above.)

- HAP is the leading cause of death among hospital-acquired infections. (See 'Epidemiology' above.)

- The pathogenesis of HAP, VAP, and HCAP is related to the numbers and virulence of microorganisms entering the lower respiratory tract and the response of the host. The primary route of infection of the lungs is through microaspiration of organisms, which have colonized the oropharyngeal tract (or to lesser extent

the gastrointestinal tract). (See 'Pathogenesis' above.)

- HAP, VAP, and HCAP may be caused by a wide variety of pathogens, can be polymicrobial, and may be due to MDR pathogens. (See 'Microbiology' above.)
- The frequency of MDR bacteria as etiologic agents of HAP, VAP, and HCAP is increasing, especially among patients in intensive care units and/or patients with certain risk factors. (See 'MDR risk factors' above.)
- The diagnosis of HAP, VAP, and HCAP should be suspected in patients with a new or progressive infiltrate on lung imaging as well as clinical characteristics such as fever, purulent sputum, leukocytosis, and/or decline in oxygenation. (See 'Diagnosis' above.)