être difficile à traiter par les maladies associées qui peuvent se développer à tout moment et être délicates à diagnostiquer à leur début.

**REFERENCES**


1. CHANEZ P & al. Les asthmes difficiles à traiter. Rev Mal Resp 1999; 16: 3848-3850.
2. ULRIK CS. Outcome of asthma: longitudinal changes in lung function. Eur Respir J 1999; 13: 904-918.
3. CHUNG KF, GODARD P, ADELROTH E & al Difficult/therapy-resistant asthma: the need for an integred approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task Force on difficult/therapy-resistant asthma Eur Respir J 1999; 13: 1198-1208.
4. TOGIAS A. Mechanisms of nose-lung interaction. 1999; Allergy; 54; suppl. 57: 94-105.
5. BONFILS P. Le traitement médical de la polypose naso-sinusienne. Etude prospective sur une série de 181 patients. 1998; 115: 202-214.
6. BRUCE A. Eight key questions to ask when your patient with asthma does not get better. American Family Physician. 1997; 55: 183-189.


# What to do when they occur


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What to do when the Hospital Acquired Pneumonia (HAP) or Nosocomial Pneumonia (N P) occurs? This a difficult question for the intesivists when they are infront to this major problem. Despite the advances in antimicrobial chemotherapy, successful treatment of patients with HAP or NP remains a difficult and complex issue. The intensivist has obligation to his patients (ought to suggest the newest and strongest antibiotic because it is necessary to be treated immediately, especially when the HAP is life threatening), and to the community (ought to protect the emergence of antibiotic resistance with the avoidance of unnecessary use of antibiotics) as well. It is well known, that the Ventilator Associated Pneumonia (VAP) is included among the Hospital Acquired Pneumonias or Nosocomial Pneumonia types.

Therefore, the early identification of the HAP and the accurate selection of antimicrobials agents for the initial treatment represent important clinical goals , since it appears that appropriate treatment of the infection might have a major role in reducing HAP associated mortality and morbidity[1]. So the infection guided directed antimicrobial chemotherapy (IDAC) must be started as soon as possible. The term IDAC defines the administration of antimicrobials for a specific clinically localized source of infection (e.g. pneumonia, urinary tract, wound, blood stream). But before the IDAC is started, the following questions have to be answered by the physician in order to establish criteria to guide restricting IDAC without causing patient harm.

## QUESTION 1

What is the patient past medical history? Because there is a direct connection among the patients past medical history and the microorganisms involved.

It is known that in the presence of acute or chronic alcoholism pneumococcus, S. aureus, H. influenzae, K. pneumonia are implicated.

Tuberculosis, Chronic Obstructive Pulmonary Disease (COPD): Pneumococcus H. influenzae, M. Catarrhalis.

Recent viral infection: Pneumonococcus, S. aureus H. influenzae, gram negative bacilli.

Nursing home, age > 75 year: Gram negative bacilli, Pneumococus, H. Influenzae, aspiration (anaerobes).

AIDS (risk group: IV drug abuser, hemophilia, hommosexual): Pneumococcus, Salmonella, cytomegavirus, H. Influeanzae, Cryptococcus, Pneumocystis carinii.

High risk for aspiration: Anaerobes, gram negative bacilli.

Underlying cardiac disease: Pneumococcus, gram negative bacilli.

Neutropenia: P. aeruginosa, Aspergillus, gram negative bacilli[2].

## QUESTION 2

It is very crusial to identify the onset of the HAP. Early or late onset due to different microbial strains involved.

Community – acquired pathogens, such as H. Influeanzae, Pneumococcus of methicillin susceptible, S. aureus often are responsible for the early onset of HAP occurring in the first four days of hospitalization. In these cases pathogens with strong intrinsic or acquired antimicrobial resistance are rarely causative.

Late onset HAP defined as lower respiratory tract infection occurring after 5$^{th}$ day of hospitalization is caused often by aerobic gram – negative bacilli: Pseudomonas Aeruginosa, Enterobacteriaceae or Acinetobacter or Methicillin Resistance Staph. Aureus (MRSA).

Late onset pneumonia is due to P. aeruginosa Acinetobacter, MRSA in 30% – 71% of cases and Enterobacteriaceae[3].

## QUESTION 3

What is the hospital's predominant microbial flora as well as the local antibiotic susceptibility patterns of pathogens, it has be taken into account, before the antimicrobial chemotherapy is initiated. The reason is that microbial flora and antibiotics susceptibility patterns are different depending on the hospital and the general policy. (how the antibiotics have been administered, what kind are the patients admitted to the ICU etc.). For these reasons it would be prudent to collect and study these data just before the initiation of antimicrobial chemotherapy.

## QUESTION 4

Pharmacokinetics. Adequate drug levels have to be achieved in the lung, which it is possible with the use antibiotics like Cephalosporins or Carbapenems or Piperacillin/Tozabactam or Fluoroquinolones.

The aminoglycosides problem: Despite the extensive clinical use, aminoglycosaids are not used as a monotherapy but in combination with a ²-actam antibiotic (this combination theoretically reduces the emergence of resistance and extends the spectrum of activity). However the benefit of aminoglycosides use in H.A.P remains controversial. Aminoglycosides penetrate poorly into bronchopulmonary secretions and the lung, are inactivated under conditions of low pH and have serious potential toxicities (particularly nephrotoxicity)[4].

There are not enough data supporting the extend use of aminoglycosides for the treatment of HAP. In one series of 78 patients with HAP caused by Gram-negative bacteria, clinical response to therapy was more rapid when target ratios of maximal concentration of aminoglycide in serum to the minmal inhibitory concentration were achieved[5]. In another controlled, multicenter, randomized study, clinical response rates were highest with ceftazidime plus long-course (9 days) amikacin treatment. The benefit of the aminoglycoside was more pronounced when P. aeroginosa was implicated[6].

It seems, that the optimization of anminoglycosides dosing may be critical for theto successful treatment of severe H.A.P. caused by Gram-negative bacteria, but it needs a lot of caution due to the toxicity particularly the nephrotoxicity, specially in case of septic shock.

## QUESTION 5

Is there any organ failure? What is the organ failure? When the organ failure or organ dysfunction happened? It is very important for the intensivist to be aware for the time that organ failure appeared (before or after ICU admission). And if it took place after the admission, what is the causative reason? However the doses have to be adjusted in case of renal of liver failure. The doses of antibiotics must be reviewed daily according to the patient's general condition and the results of antibiotics plasma levels.

## QUESTION 6

Should any precaution be taken? Special care must be taken in patients with a reduction in lean body mass and an increase in fat (is it happen in the elderly). The drug levels may rise if chosen on a per kilogram basis.

In those with reduced serum albumin, free drug concentration rise if the antibiotic is normally highly bound to proteins. The sodium content of many drugs especially the penicillin or Primaxin (imipenem/silastatin sodium) may be important in patients with renal or heart failure.

## QUESTION 7

Are the anaerobic responsible for the HAP? There are not clinical data supporting the administration of antibiotics against anaerobes in patients with suspected HAP or VAP. Marik and Careau describe their experience in 185 cases of suspected aspiration pneumonia in 143 patients. Despite the use of specific methods to isolate anaerobic bacteria – anaerobia were isolated just in one case of 75 episodes that were classified as aspiration pneumonia. These results differ somewhat from those of Dore and coworkers, that examined 130 patients with microbiologically documented VAP using protected specimen brush (PSB) cultures and rigorous anaerobic culturing techniques. In 30(23%) patients PSB cultures resulted in anaerobic strains. In 26 patients aerobic plus anaerobic agents where isolated whereas just only anaerobic strains were isolated in 4 patients from PSB cultures.

To date, no convincing clinical data are available supporting the hypothesis that routine treatment for anaerobic bacteria strains will improve the outcome of patients with suspected HAP[7,8].

## QUESTION 8

Was there any previous antibiotic therapy? Prior antibiotic use, particularly the use of broad spectrum antibiotics implicates the risk for colonization or infection with P aeruginosa or Acinetobacter. Two different studies support the aforementioned remark. Fagon and al[9] found that prior antimicrobial chemotherapy markedly increased the rate of VAP caused by P aeruginosa or Acinetobacter.

These two pathogens accounted for 65% of VAP cases among partients who had previously received antibiotics, compared to 19% of VAP cases among antibiotics-naïve patients. The second one by Rello J et al[10]; in their study of 129 concecutive ICU patients with VAP, P aeruginosa was the causative agent in 40% of patients who had previously received antibiotics (within the preceding 10 days) but in only 5% of those who had not received antibiotics.

A numerous of studies demonstrated that prior antibiotic use is the most common risk factor for colonization and infection with MRSA. Other risk factors for pneumonia due to MRSA include use of corticosteroids, prolonged mechanical ventilation (> 6 days) and COPD. Drug resistant pathogens are uncommon in the absence of previous antibiotic therapy.

## QUESTION 9

Is it a life threatening infection? If so, an antibiotic or a combination treatment should be utilized if a combination of antibiotics is used, which is the most appropriate?

Combination of antimicrobial agents theoretically acting at different sites of the bacterial cell, may limit resistance. The advantage of adding a second agent has not been yet clarified in clinical trials

Better designed studies are necessary , in order to prove, what usually takes place in the every day practice, which is the use of combination treatment.

### Combination of Aminoglycoside and ²-Lactam antibiotics

Data supporting incremental benefit of aminoglycosides for the treatment of HAP are sparse. There is proof from the existing studies, that there is benefit by using this combination especially if the microorganism involved for the HAP is P aeruginosa.

### Combination therapy with ²-Lactam and Fluoroquinolones

Clinical data employing such combination are limited. Ciprofloxacin is the most active fluoroquinolone in vitro against P. aeruginosa. There are limited data evaluating levofloxacin for HAP.

## WHAT ANTIBIOTIC MUST I SUGGEST?

After answering the critical questions, the antimicrobial chemotherapy has to be initiated. The suggested antimicrobial chemotherapy is the following and depend upon the patients general condition and the causative microorganisms

### Non life threatening infection

Ceftazidime or Cefepime or Piperacillin/Ta-zobactan or Carbapenems or Fluoroquinolones.

### Pneumonia possibly caused by P. aeruginosa

Ceftazedime or Cefemime or Piperacillin/Tazobactam or Carbapenems plus aminoglycoside or fluoroquinolone.

### Life threatening pneumonia

Ceftazedime or Cefepime or Piperacilline/Tazobactam or Carbapenemes, plus Aminoglycoside or Fluoroquinolones. (It is difficult for the clinician to define exactly the life threatening pneumonia. According to my opinion this must be based on the patient general condition and the every hour evaluation).

**Pneumonia that Gram+cocci and Gram-bacilli may be involved**

Ceftazedime or Cefepime or Piperacillin/Ta-zobactam or carbapenems or fluoroquinolones plus teicoplanin or vancomycin

**Life threatening pneumonia that Cram+cocci and Gram-bacilli may be involved**

Ceftazedime or Cefepime or Piperacillin/Taobactem or carbapenems plus aminoglycoside or fluoroquinolones plus teicoplanin or vancomyc.

**High suspicon that a fungus is involved**

Ceftazedime or Cefepinne or Piperacillin/Taobactam or Carbapenems or fluoroquinolones plus amphotericin.

**WHEN THE ANTIBIOTIC TREATMENT SHOULD BE CHANGED?**

The evaluation of the response of pneumonia to the initial antibiotic treatment should be performed early, at 72 hours from diagnosis and should be based on the assessment of the initial criteria of diagnosis and on additional scores of organ function. Lack of response to the antibiotic treatment must be suspected in the following circumstances: persistence of fever, purulent tracheal secretion, leukocytosis, progression of the radiographic pulmonary infiltrate, lack of improvement of further impairment of gas exchange.

Other parameters of organ dysfunction must be assessed (creatine, bilirubin, platelets) in order to rule out concomitant disorders that may contribute to the failure to improve.

The first approach in case of non-response consists of revising the antibiotic treatment based on bacteriological results and adjusting the combination and dosage if necessary. Some microorganisms that are not covered by the empirical treatment (MRSA, fungi, Legionella spp, CMV) must be considered when risk factors are present (head trauma for MRSA, immunocompromised condition for fungi and viruses).

Other frequent causes of fever in critically ill patients concomitant to pneumonia could be catheter related sepsis, sinusitis or urinary tract infection. The radiographic pulmonary infiltrate in critically ill patients could be related to ARDS, atelectasis, pulmonary embolism or pulmonary oedema after lung resection.

**Causes of non response of pneumonia to empirical antibiotics treatment**

Inappropriate election/combination of antibiotics, low dosage/serum level of antibiotics. Resistance to antibiotics. Microorganisms not covered by the initial treatment, superinfection. Infection other than pneumonia like sinusitis, vascular catheter-related sepsis, abdominal sepsis, pulmonary abscess, pleural effusion/empyema, urinary sepsis. Non infections conditions, like ARDS, Atelectasis, BOOP, Pulmonary embolism, Congestive heart failure, Pulmonary oedema after lung recection, Drug related fever[11].

**ANTIBIOTICS BY CONTINUOUS INFUSION**

There are ongoing studies where the antibiotics have been given by continuous infusion. Vancomycin is one of them. The results are promising. Theoretical benefits of antibiotics infusion include greater efficacy, reduction of drug expenditure, and the possibility of shorter courses resulting in less risk of the emergence of resistant bacteria[12].

## NOVEL ROUTES OF ADMINISTRATION

Under evaluation is the administration of a nebulized antibiotic in serious respiratory tract infections via endotracheals tubes. This method ensures high antibiotic concentration at the site of infection, minimizing systemic concentrations and their resultant risk of toxicity[13], but it is not clear yet, if this route of administration increases the possibility of resistance from microorganisms involved.

## DURATION OF ANTIMICROBIAL CHEMOTHERAPY

Duration of treatment of HAP should be individualized, depending on the severity of illness, time of onset, rapidity of clinical response and responsible pathogens.

To date, recommended duration of treatment of HAP is based on multilobar involvement, cavitation of necrotizing pneumonia or presence of P. aeruginosa or Acinetobacter spp as responsible pathogen.

Clinical response (lower of temperature, radiological score, leukocytosis, $PaO_2/FiO_2$ ratio, organ failure, evolution of markers of inflammation) merits to be evaluated. In the absence of factors identified as strong arguments for deciding to stop antimicrobial therapy, clinical trials are required to evaluate the prognostic value of clinical, bacteriological, of inflammatory parameters[14].

## RECOMMENDATIONS FOR THE AVOIDANCE OF INADEQUATE ANTIMICROBIAL CHEMOTHERAPY ADMINISTRATION

It appears that antimicrobial therapy should be administered early in the course of the infection, to be most effective, especially prior to the development of severe sepsis and septic shock

This will require a high index of suspicion on the part of practitioners, caring for critically ill patients in order to consider the diagnosis of infection in a timely manner.

Due to the greater mortality associated with delays in treatment, starting empiric antimicrobial treatment at the first suspicion of infection in critically ill patients seems prudent in most instances.

In order to avoid increasing problems with drug-resistant infections, the antimicrobial regimen should subsequently be narrowed of discontinued altogether, based on the patient's clinical course and culture results.

For patients with suspected infection who have received prior antimicrobial therapy directed at Gram-negative bacteria, subsequent empiric antimicrobial treatment should include coverage of pathogens that may be potentially resistant to the earlier administered antibiotics.

Although the routine use of combination antimicrobial therapy with dual agents directed against Gram-negative bacteria is controversial, the administration of such therapy seems reasonable when attempting to avoid the occurrence of inadequate antimicrobial therapy due to antibiotic resistant Gram-negative bacteria.

Similar recommendations for the empiric treatment of Gram-positive bacteria cannot be made since the number of available agents for antibiotic resistant Gram-positive cocci is limited. The initial empiric treatment with teicoplanin or vancomycin, it seems sufficient in patient at risk for infection with this specific pathogen[15].

## REFERENCES

1) CHASTRE J, TROUILET J-L. Nosocomial pneumonia: uidelines for initial management and empirical treatment, 101-117 In: European Respiratory Monograph, Vol 2, monograph 3. Edited by Torres A, Woodhead M 1997.

2) NIEDERMAN M, FEIN A. Acute Infectious Pneumonia, p: 903-922. In: Intensive Care Medicine 3th ed. Rippe J,

Irwin R, Fink M, Cerra F. Little, Brown and Company 1996.

3) EWIG S, TORRES A, EL-EBIARY M. Bacterial colonization patterns in mechanically ventilated patients with traumatic and medical head injury incidence, risk factors, and association with ventilator-associated pneumonia. Am J Respir Crit Care Med 2001; 159:188-198.

4) EDSON RS, TERRELL CL. The aminoglycosides.Mayo Clin Proc 1999; 74: 519-528.

5) KASHUBA AD, NAFZIGER AN, DRUSANO GL et al. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by Gram-negative bacteria.Antimicrob Agents Chemother 1999; 43: 623-629.

6) EORTC International Antimicrobial Therapy Cooperative Group. Ceftazedime combined with a short or long course of amikacin for empirical therapy of Gram-negative bacteremia in cancer patients with granulopenia. N Engl J Med 1987; 317: 1692-1698.

7) DORE P, ROBERT R, GROLLIER G et al. Incidence of anaerobes in ventilator-associated pneumonia with use of a protected specimen brush. Am J Respir Crit Care Med 1996; 153: 1292-1298.

8) KOLLEF M. Antimicrobial Therapy of Ventilator- Associated Pneumonia. Chest 1999; 115: 8-11.

9) FAGON J-Y, CHASTRE J, DOMART Y et al. Nosocomial pneumonia in patients receiving continuous mechanical ventilation: prospective analysis of 52 episodes with use of a protected specimen brush and quantitative culture techniques. Am Rev Respir Dis 1989; 139: 877-884.

10) CELLO J, ASIAN V, RICER M et al. Impact of previous ant microbial therapy on the etiology and outcome of ventilator-associated pneumonia. Chest 1993; 104: 123-1235.

11) FERRER M, IOANAS M, TORRES A. Evaluation of Non-responding Patients with Ventilator-associated Pneumonia. p:365-375.In:2002 Yearbook of Intensive Care and Emergency Medicine. Edited by Vincent J-L 2002.

12) WYNCOLL D, BOWRY R, GILES L. Antibiotics by Continuous Infusion: Time for Re-evaluation? p:399-406. In: 2002 Yearbook of Intencive Care and Emergency Medicine. Edited by Vincent J-L 2002.

13) COLE PJ. The role of Nebulized Antibiotics in Treating Serious Respiratory Infections.Journal of Chemotherapy 2001; 13 Nº4: 354-362.

14) FAGON J-Y. Nosocomial Pneumonia: Duration of Antimicrobial Therapy In: Proceedings of International Symposium on Infections in the Critically Ill Patient, Barcelona 2000.

15) KOLLEF M, SHERMAN G, WARD S, FRASER V. Inadequate Antimicrobial Treatment of Infections. Chest 1999; 115: 462-474.