Treatment options for severe pneumonia: Focus on Pseudomonas Pneumonia

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Abstract

Pneumonia due to Pseudomonas aeruginosa occurs in several distinct syndromes: 1/ Community Acquired Pneumonia (CAP) usually in patients with chronic lung disease e.g.: COPD / Cystic Fibrosis / bronchiectasis. Rather uncommon : 0.9%-1.9% of patients with CAP requiring hospitalization. 2/ Hospital Acquired Pneumonia (HAP), usually occurring in the ICU after day 4 or VAP. Much more common : 18%. 3/ bacteremic , usually in the neutropenic host e.g. hematologic malignancy, HIV (Pre HAART : 8-25%; HAART era: 5-6.7%)

P.aeruginosa. is a gram negative rod that is ubiquitous in nature and is an opportunistic pathogen in humans. It is a particularly virulent pathogen that produces many virulent factors, including exotoxins, enzymes and biofilms that protects it from host antibodies and phagocytes.

Pseudomonas pneumonia carries a notably higher mortality rate than other pneumonia pathogens. Therapy has always been challenging magnified in recent years by the emergence of MDR (multi drug resistant) and PDR (Pan drug resistant) pathogen, compounded further by the diagnostic problem of differentiating between colonization and infection, as blood cultures are rarely positive and gram stains have not proven useful.

Anti Pseudomonal antibiotics : Aminoglycosides; .β Lactam congeners; Monobactam; Extended spectrum penicillins e,g, piperacillin-tazobactam, Carbapenems; anti pseudomonal fluoroquinoles; Colistin. Combination antibiotic therapy may potentially broaden the antimicrobial spectrum, provide synergistic interaction, decrease emergence of antimicrobial resistance and minimize superinfection.

Incombination antibiotic therapy the greatest synergy is obtained by combining an aminoglycoside(A) + antipseudomonal penicillin (~90%), followed in decreasing order A + cephalosporin (~ 80%) then A + carbapenem (~50%), while the interaction of a fluoroquinolone + A or βlactam is usually indifferent or autonomous.

Given the nephrotoxicity of aminoglycosides the following algorithm is proposed : Combination of an anti-pseudomonal penicillin + an aminoglycoside for 3-5 days, then replace the aminoglycoside with an anti-pseudomonal fluoroquinolone for a total of 8-15 days.

Key Word : *Pseudomonal Pneumonia is treatable and potentially curable*

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INTRODUCTION:

To my unpleasant surprise SEVERE PNEUMONIA is not well defined in the literature, so for this paper it will be defined as pneumonia with a CPIS (clinical pulmonologic infection score) of ≥ 6 or CURB-65 of ≥ 3.(table 1-4)

Pseudomonas aeruginosa is a gram negative rod, ubiquitous in nature and opportunistic in humans. It is a particularly virulent pathogen that produces many virulent factors, including exotoxins and enzymes

Table 1

CPIS Used for the Diagnosis of RTI

		Points
1.	**Temperature °C**	
–	≥ 36.5 and ≤ 38.4	0
–	≥ 38.5 and ≤ 38.9	1
–	≥ 39.0 or ≤ 36.0	2
2.	**Blood leukocytes, mm^{-3}**	
–	≥ 4,000 and ≤ 11,000	0
–	< 4,000 or > 11,000	1
–	+ band forms 500	1
3.	**Tracheal secretions**	
–	Absence of tracheal secretions	0
–	Presence of tracheal secretions	1
–	Purulent secretions	1

*CPIS score > 6 Sensitivity: 93% Specificity: 100%

bandung 2010

(Pugin J et al. Am Rev Respir Dis 1991;143:1121-1129)

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Table 2

CPIS Used for the Diagnosis of RTI(cont'd)

4.	**Oxygenation: PaO_2/FiO_2, mm Hg**	
–	> 240 or ARDS	0
–	≥ 240 and no evidence ARDS	2
5.	**Pulmonary radiography**	
–	No infiltrate	0
–	Diffuse or patchy infiltrate	1
–	Localized infiltrate	2
6.	**Culture of tracheal aspirate** (semiquantitative 0-1-2-3 +)	
–	Pathogenic bacteria cultured ≤ 1+ or no growth	0
–	Pathogenic bacteria cultured > 1+	1
–	Same pathogenic bacteria on Gram Stain > 1+	1

*CPIS score>6 Sensitivity: 93% Specificity: 100%

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(Pugin J, et al. Am Rev Respir Dis 1991; 143:1121-1129)

Table 3

CURB-65

Assessment of pneumonia severity

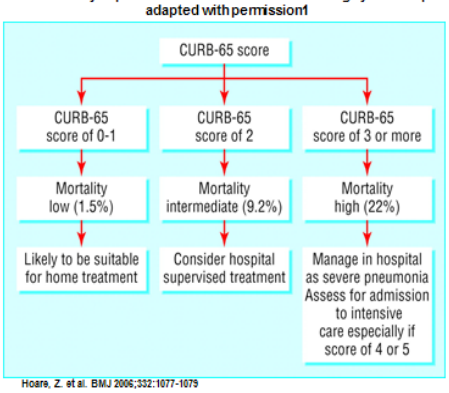
- **C** onfusion of new onset (< 8) :10
- **U** rea > 7 mmol (~ BUN > 19) :20
- **R** esp. rate > 30 / min :30
- **B** lood Pressure :
  - Diast < 60 mmHg :60
  - Syst < 90 mmHg :90
- > **65** yrs :65

(Recommended by British Thoracic Society)

PNEUMONIA: CAP, HAP, VAP, HCAP, 2011 5

Table 4

Assessment of severity of pneumonia with the CURB-65 scoring system. Reproduced and adapted with permission1



Hoare, Z. et al. BMJ 2006;332:1077-1079

PNEUMONIA: CAP, HAP, VAP, HCAP, 2011

BMJ

and also biofilm that protects it from environmental elements, host antibodies and phagocytes. Among the anatomic sites of P.aeruginosa infection, the lung is associated with the highest mortality rate

PSEUDOMONAS PNEUMONIA:

Several distinct syndromes of P.aeruginosa respiratory tract infection exists:

1. Community acquired pneumonia (CAP):
   - P.aeruginosa as the etiologic pathogen in CAP is quit rare : 0.9-1.9% of patient with CAP requiring hospitalization, but crude mortality is high : 61.1%
   - Risk factors for CAP caused by P.aeruginosa are:

i. Chronic ling disease, especially COPD
ii. Colonization is an important antecedentary event , previous hospitalization (HCAP), intubation, enteral tube feeding.
iii. Smoking, HIV infection
iv. Structural lung disease e.g. bronchiectasis

2. Hospital acquired pneumonia (HAP)
   - In the US there is a gradual increase in the incidence of Pseudomonal HAP from 9.6% in 1975 to 18.1% in 2003
   - P.aeruginosa is the most frequently isolated gram negative aerobic bacteria from the respiratory tract (31.6%)
   - In Ventilator associated pneumonia (VAP) : P.aeruginosa was the most frequent pathogen (9.3%) in patients with VAP, where pneumonia occurred after > 4 days after mechanical ventilation
3. P.aeruginosa bacteremia in the immunocompromised host.

   P.aeruginosa in HIV patients:
   - Trimethoprim sulfamethoxazole prophylaxis for pneumocystic pneumonia is associated significant protection against Toxoplasmosis, Salmonella, Haemophilus and Staphyloccus aureus, but NOT against S.pneumonia, non pneumococcal streptococcus and P.aeruginosa.
   - In the HAART era the most common cause of HAP in HIV is P.aeruginosa, with a crude mortality of 23%. The median CD4 count at presentation ranged from 27 t0 42 cell/µL.
   - But for CAP in the HAART era the most common cause is still S.pneumonia(30%-35.7%)

DIAGNOSIS

The most consistent finding radiologic findings was bilateral distribution of infiltrates, present in 48 - 91 % of cases.

Diagnosis of P.aeruginosa pneumonia is challenging because of relative ease of colonization of the upper and lower respiratory tract, giving rise to a colonization v/s infection problem. P. aeruginosa is a colonizer and pulmonary infiltrates does not necessarily represent infection

Because P.aeruginosa bacteremia is very rare in HAP, definitive confirmation of the etiologic role of P.aeruginosa is difficult. Prior antibiotic use is a risk factor for P.aeruginosa colonization. P.aeruginosa is the dominant species colonizing endotracheal aspirates. P.aeruginosa enhances mucous secretion, disrupts ciliary activity and causes airway epithelial injury, thereby impairing pulmonary clearance

Invasive procedures : protected brush bronchoscopy + quantitative cultures :

Colonization : bacteria counts < 10^3 cfu / mL

Infection : bacteria counts > 10^3 cfu / mL could be the procedure of choice

Anti pseudomonal antibiotic therapy based on respiratory tract culture may therefore lead to overtreatment. Quantitative cultures have proven to be effective in selecting patients who would benefit from antimicrobial therapy

Limiting antibiotics in the ICU with pulmonary infiltrates with CPIS ≤ 6, did NOT lead to higher mortality.

P.aeruginosa carries a notably higher mortality rate than other pneumonia pathogens. Therapy has always been challenging, because of its multiple mechanism 0f resistance

Mechanism of antibiotic resistance are summarized in table 5

Table 2—*Mechanisms of Antibiotic Resistance to* P aeruginosa

Mechanism	Resistance for
β-Lactamase	
AmpC	Penicillins, cephalosporins
ESBLs	Penicillins, cephalosporins
Metallo-β-lactamases	Penicillins, cephalosporins, carbapenems
Efflux pumps	Cephalosporins, ureidopenicillins, carbapenems, aminoglycosides, quinolones
Mutational gyrases	Quinolones
Inactivating enzymes	Aminoglycosides
Outer membrane impermeability	Carbapenems, aminoglycosides, quinolones

ESBL = Extended-spectrum β-lactamases

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Antibiotics that exhibit activity ≥ 70% against P.aeruginosa may be regarded as drug of choice (Table 6)

Table 6 : DRUG of CHOICE

Aminoglycosides (amikacin, tobramycin, gentamicin)
β-Lactam congeners
Cephalosporins, third-generation (cefoperazone, cefsulodin, ceftazidime)
Cephalosporins, fourth-generation (cefepime, cefpirome, cefclidin)
Monobactam (aztreonam)
Extended-spectrum penicillins (ticarcillin and/or ticarcillin-clavulanate, piperacillin and/or piperacillin–tazobactam, azlocillin)
Carbapenems (imipenem, meropenem, doripenem)
Fluoroquinolones (ciprofloxacin, levofloxacin)
Colistin/polymyxin B

Based on pharmacokinetics and pharmacodynamics (PK/PD) in time-dependent antibiotics eg. β-lactams, using continuous infusion or slowing the infusion from 1 to 4 hrs will increase the the time above MIC and result in higher bacterial kill. While the anti-pseudomonal quinolones : Ciprofloxacin and Levofloxacin, as concentration dependent antibiotics the AUC / MIC ratio defines the bacteria kill. Ciprofloxacin has a lower MIC (0.5µg/ml) than Levoflocaxin (MIC 1.0µg/ml), but this advantage is offset by cipro's lower serum and tissue concentration as compared to levo, resulting in similar potency against P.aeruginosa.

Of the carbapenems, doripenem is the most active against P.aeruginosa.

ANTIBIOTIC THERAPY

Mortality was 3.6 – 40.2 % in patients with appropriate empirical antibiotic therapy and increased to 17.6-81.6% in inappropriate empirical antibiotic therapy.

Combination antibiotic therapy can broaden the antimicrobial spectrum, synergistic interaction, decrease emergence of antimicrobial resistance and minimize superinfection. However demonstrated

improvement in outcome for combination therapy has been elusive.

The greatest likelihood of synergy is :

AGENT	+	AGENT	SYNERGY
AMINOGLYCOSIDE		ANTI-PSEUDOMONAL PENICILLIN	~90%
AMINOGLYCOSIDE		CEPHALOSPORIN	~80%
AMINOGLYCOSIDE		CARBAPENEM	~50%
FLUORO-QUINOLONE		AMINOGLYCOSIDE	Additive/indifferent
FLUORO-QUINOLONE		β-LACTAM	Additive/indifferent

Mono-therapy of Fluoro-quinolone is NOT recommended, given the high likelihood of bacterial resistance (38%) and failure to achieve bacterial eradication (67%)

Likewise, using an aminoglycoside carries the risk nephrotoxicity. It is proposed that to minimize nephrotoxicity the use of an aminoglycoside should be limited to≤ 5 days, then replace by a fluoro-quinolone.

RECOMMENDATION:

Based on PK/PD and synergy empirical antibiotic therapy in pseudomonas pneumonia is recommended to be a combination regiment of :

> Anti – pseudomonal penicillin PLUS Aminoglycoside ≤ 5 days , then replace by an antipseudomonal fluoro-quinolone (8-14 days)

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