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REVIEW

COMMUNITY-ACQUIRED PNEUMONIA – CURRENT ISSUES

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Abstract. Acute pneumonia was and still is one of the most important causes of morbidity and mortality. A patient with typical CAP presents sudden onset with chill, fever, pleural pain, cough, expectoration, dyspnea. Elderly patients may present an atypical clinical presentation: confusion, decompensation of underlying diseases. Chest radiography is recommended to patients suspected of having CAP. It is important to perform a severity assessment of CAP in order to decide whether to treat the patient with CAP as outpatient or as inpatient, in the ward or in the ICU. A lot of patients with CAP could be correctly treated with oral antimicrobial drugs.
Keywords: community-acquired pneumonia, etiology, susceptibility, resistance, severity, hospitalization

Introduction

Sir William Osler noted in the fourth edition of his book, "The Principles and Practice of Medicine", that pneumonia is the most important cause of morbidity and mortality of all acute diseases. More than a century later, the prominence of pneumonia did not change. Pneumonia is one of the most important causes of morbidity and mortality worldwide. The incidence of lower respiratory in-fections worldwide is 429.2 million cases, most cases being recorded in Africa and South-East Asia (~60% cases), and only 5% of the cases in Europe[1]. Lower respiratory infections are the third cause of death worldwide, accounting for 4.2 million of deaths (7.1% of all deaths), About 67% of deaths occur in Africa and South-East Asia, and only 6% of deaths occur in Europe[1]. Acute respiratory infections – mainly pneumonia – and diarrhoeal diseases are the first causes of death among children aged under five years (each accounting for 17% of all deaths)[1]. The leading causes of burden diseases in the world are lower respiratory diseases with 94.5 million years DALYs (6.2% of total DALYs); DALYs-Disability-Adjusted Life Year – they are calculated for each disease, as the sum of the years lost in a lifetime due to premature mortality (YLL) in the population, and the years lost due to disability (YLD) for incident cases of the disease[1].

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Community-Acquired Pneumonia (CAP)

According to the British Thoracic Society (BTS), pneumonia is defined as the presence of "symptoms and signs consistent with an acute lower respiratory tract infection associated with new radiographic shadowing for which there is no other explanation"[2].

CAP–etiology and antimicrobial drug resistance

CAP is caused by a wide variety of pathogens. Some pathogens, especially viral pathogens exhibit some seasonality (see Figure no. 1).

In a meta-analysis of 41 studies, published in 2002, the etiology of CAP in patients managed as outpatients in Europe was: *Streptococcus*

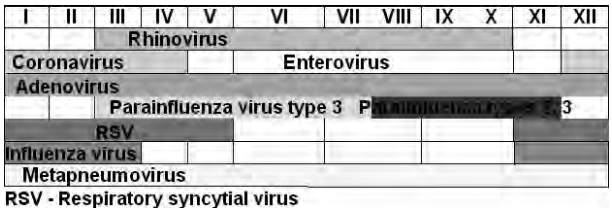

Figure 1. The seasonality of some viral etiologies of respiratory tract infections

pneumoniae, viruses, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Legionella spp.*[3] (see. Table no. I).

Europe recorded different resistance levels in the participating countries. (see Figure no. 2)

Resistance to macrolide antibiotics develops either by target modification (methylation of the ribosomal target site, encoded by the **ermB** gene, the so-called MLSB phenotype), conferring resistance to macrolides, lincosamides and streptogramins, or by active drug efflux (encoded by **mefE** gene in North America and **mefA** gene in Europe, M phenotype) conferring resistance only to macrolides[6]. The major risk factor for macrolide resistance is previous antibiotic use[6]. In a study carried out in 15

Organism	CAP managed in community	CAP managed in general wards	Cap managed in ICU
Studies (no)	9	23	13
Streptococcus pneumoniae	19.3	25.9	21.7
Haemophilus influenzae	3.3	4.0	5.1
Legionella spp.	1.9	4.9	7.9
Staphylococcus aureus	0.2	1.4	7.6
Moraxella catarrhalis	0.5	2.5	
Gram-negative enteric bacteria	0.4	2.7	7.5
Mycoplasma pneumoniae	11.1	7.5	2
Chlamydia pneumoniae	8	7	
Chlamydia psittaci	1.5	1.9	1.3
Coxiella burnetii	0.9	0.8	0.2
Viruses	11.7	10.9	5.1
Other	1.6	2.2	7.4
Unidentified etiology	49.8	43.8	41.5

Table I. Frequency of etiologic agents of CAP

Globally, *S. pneumoniae* is the most frequent and important cause of CAP regardless of severity. Pneumococci are human commensals that colonize the nasopharynxes of 10-50% of healthy adults, and this reservoir represents a source for all pneumococcal infections[4,5]. Before 1967, there was no pneumococcal isolate resistant to penicillin; afterward, resistance to β-lactam antimicrobials, macrolides and fluoroquinolones was documented worldwide.

Resistance to β-lactam antimicrobials is due to structural changes in penicillin-binding proteins (PBP); alteration in PBP reduces binding to the target site and is responsible for resistance to all β-lactam antimicrobials, though variably. Some risk factors were identified for pneumococcal infections caused by penicillin-resistant strains such as: young age, previous hospitalization, underlying disease, previous antibiotic therapy, immunosuppression, nosocomial pneumonia or previous episodes of pneumonia, infection with a certain serotype (i.e. 19A)[5-7]. Studies carried out in the USA reported that 23-44% of pneumococci were penicillin-nonsusceptible. A study carried out in European states between 2004-2005, the prevalence of macrolide-nonsusceptible *S. pneumoniae* was 24,6%[10]. According to the European Antimicrobial Resistance Surveillance System (EARSS), the global proportion of macrolide-nonsusceptible *S. pneumoniae* is 16%. (see Figure no. 3)

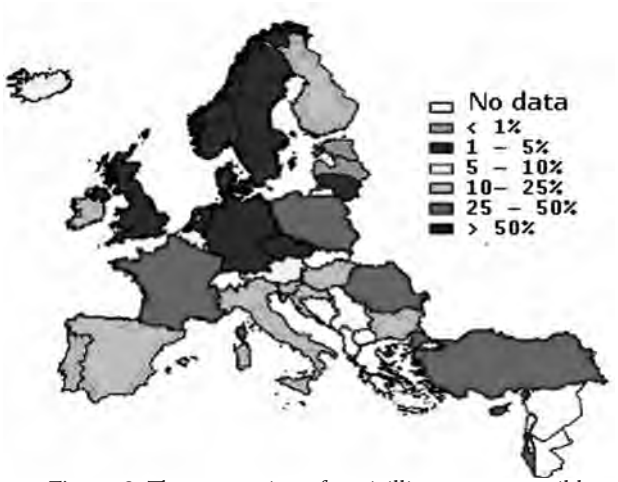

Figure 2. The proportion of penicillin-non-susceptible *S. pneumoniae* in Europe (2007) source: EARSS

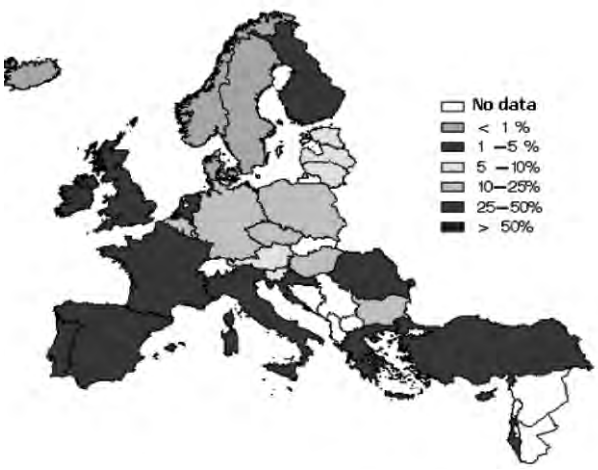

Figure 3. The proportion of macrolide-non-susceptible *S. pneumoniae* in Europe (2007) source: EARSS

Resistance to fluoroquinolones develops either by target modification: topoisomerase IV enzyme (target for ciprofloxacin, mutations of **parC, parE** genes) and/ or DNA gyrase (target for moxifloxacin, mutations of **gyrA, gyrB** genes) or by efflux-mediated resistance (it seems to affect only the susceptibility to ciprofloxacin). Mutation of **parC** confers ciprofloxacin resistance, but

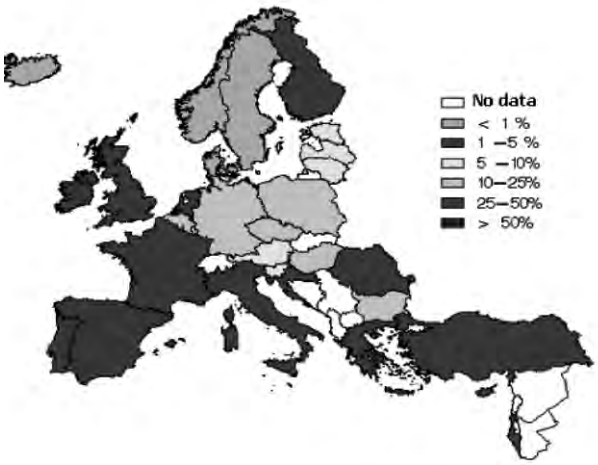

Figure 4. The proportion of methicillin-resistant *S. aureus* in Europe (2007) source: EARSS

the isolates remain susceptible to recent fluoroquinolones. Dual mutations affecting both **parC** and **gyrA** confer resistance to all fluoroquinolones. Globally, the rates of fluoroquinolones resistance remain low (<2%)[6,10,11].

Other common etiologies of CAP consist of: *Mycoplasma pneumoniae, Chlamydia pneumoniae, Haemophilus influenzae, Legionella spp.* and viruses[2]. These atypical pathogens are rarely identified in clinical practice because of the lack of specific, rapid, standardized diagnostic tests. The major viral cause of CAP in adults is influenza; there may be other viral etiologies such as: respiratory syncytial virus, parainfluenza virus and less common viruses: adenovirus, metapneumovirus, coronavirus, herpes simplex, varicella, measles virus.

Staphylococcus aureus is a less common cause of CAP; this etiology occurs more frequently as flu complication or in intravenous drug users. Methicillin-resistant *Staphylococcus aureus* (MRSA), more likely to cause skin and soft tissue infections, could be a redoubtable flu complication. The resistance levels of *S. aureus* in Europe are illustrated in figure no. 4.

Risk factors for certain CAP-causing pathogens have been described[4, 13]. (see table no. II)

CAP – clinical issues

Usually, the patient with CAP presents: fever (65-90% of cases) and respiratory symptoms such as cough (90% of cases), expectoration (66% of cases), dyspnea (66% of cases), pleuretic pain (50% of cases) and hemoptysis (15% of cases)[4,14]. The pulse usually increases with temperature, so tachycardia is a common sign. Bradycardia may be found in PDC due to viral, mycoplasmal, chlamydial infection, or infection with *Legionella spp*. Herpes labialis is present in up to 40% of patients with pneumococcal pneumonia[4]. *Legionella* pneumonia may present with extrapulmonary manifestations such as: diarrhea, myalgia, confusion, headache; the cases of *Mycoplasma* pneumonia may manifest: myringitis, encephalitis, uveitis, iritis, myocarditis, erythema multiforme, erythema nodosum. In elderly patients, the clinical manifestation of CAP may be atypical: asthenia, decreased appetite, altered mental status, decompensation of underlying diseases, tachycardia, tachypnea. Evidence of consolidation at physical examination is highly suggestive of bacterial infection. A constellation of cough, fever, tachypnea, tachycardia and pulmonary crackles raises the possibility of pneumonia, which is present in 20% to 50% of cases[4,15].

CAP – classification, severity assessment

Classically, pneumonia has been classified as typical and atypical pneumonia.

Clinical characteristics of typical pneumonia are: sudden onset with chill followed by fever, pleuretic chest pain and cough that produces mucopurulent sputum; physical examination may reveal signs of consolidation. Chest films

Etiology of CAP	Risk factors
Hantavirus	Exposure to rodent
SARS	Travel to area of outbreaks
Legionella spp	Smoking
	Pulmonary comorbidity
	Exposure to air-conditioning
	Recent travel to Mediterranean area
Enterobacteriaceae	Prior antimicrobial therapy
	Pulmonary comorbidity
	Residence in a nursing home
	Multiple comorbidities
	Aspiration
	Recent hospitalization
P aeruginosa	COPD
	Bronchiectasis
	Cystic fibrosis
	Corticotherapy
	Aspiration
	Recent hospitalization
H influenzae	Chronic obstructive pulmonary disease
	Bronchiectasis
S aureus	Intravenous drug users
	Postinfluenza
	Cystic fibrosis
C psittaci	Exposure to birds
C burnetti	Exposure to goats, cattle, sheep

Table II. Risk factors for certain etiologies of CAP

show lobar or segmental infiltrate and sometimes pleural effusion. The patient with typical CAP classically presents leukocytosis with neutrophilia and an increased number of juvenile forms. Sputum cultures may be positive. The etiology of typical CAP is represented by: *S. pneumoniae* (20-60%), *H. Influenzae (5-15%), M. catarrhalis,* less frequently *K. pneumoniae* or other Gram-negative bacilli (7-18%), *S. aureus* (2-10%).

In contrast, atypical pneumonia is considered in patients with gradual onset with symptoms more frequently systemic than respiratory (headache, myalgia, asthenia, arthralgia), cough with or without sputum production and no abnormalities on physical examination of the thorax. Chest radiography reveals an interstitial involvement. White blood cell count may be normal or decreased. The etiology of atypical CAP is represented by: viruses (influenza, adenovirus, respiratory syncytial virus, coronavirus and others), *Ch. psittaci, Ch. pneumoniae, C. burnetii, M. pneumoniae, L. pneumophila.*

Severe CAP should be urgently recognized, because these patients require prompt initiation of therapy in the ICU. The mortality rates in patients with severe CAP are high – 20-50%[16,17].

Prognostic scoring systems, such as: Pneumonia Severity Index Score (used in the US), CURB-65 (preferred in Europe), CRB-65, were developed in order to provide support for severity assessement[2].

CURB-65 is easy to perform and offers a therapeutic orientation[2]. It is a 5-point score, one point for any feature present out of four: **C**onfusion (defined as a Mental Test Score of 8 or less, or new disorientation in person, place or time), **U**reea >7 mmol/l, **R**espiratory rate ≥ 30/min, low systolic (<90 mm Hg), or diastolic (≤ 60 mm Hg) **B**lood pressure, age > 65 years. Severity assessment using CURB-65 in order to determine the management of CAP is illustrated in figure no. 5.

CRB-65 is another prognostic score system, that can be used for clinical assessment when only clinical parameters can be considered, giving a 4-point score (see figure no. 6).

CRB-65 = Confusion, Respiration, Blood (pressure), 65 years

CAP-management

CAP is a common disorder that is potentially life-threatening, especially in elderly and in persons with comorbidities. A first decision that the clinician is faced with is whether to hospitalize the patient with CAP. The decision to admit the patient with CAP depends on many issues: severity

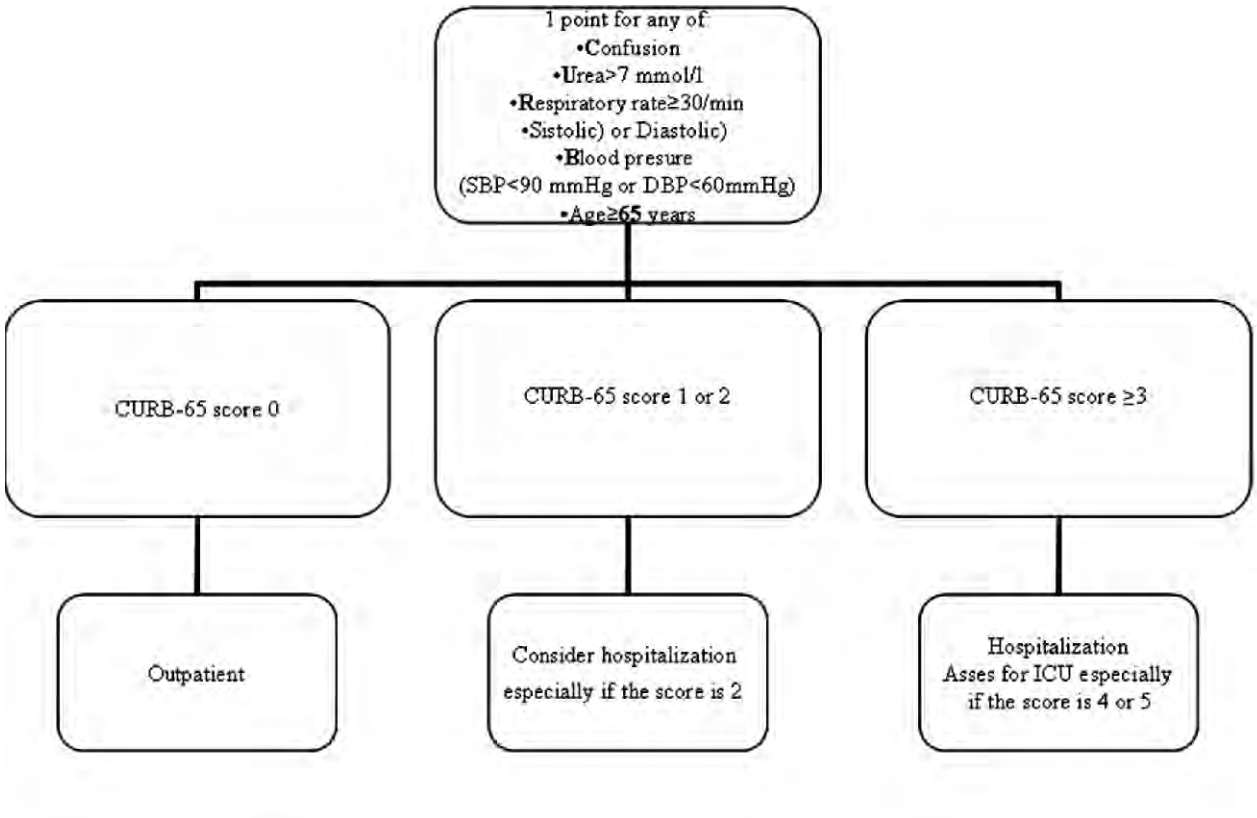

Figure 5. CURB-65 score use to determine the management of CAP (apud 12)
CURB-65 = Confusion, Urea, Respiration, Blood (pressure), 65 years

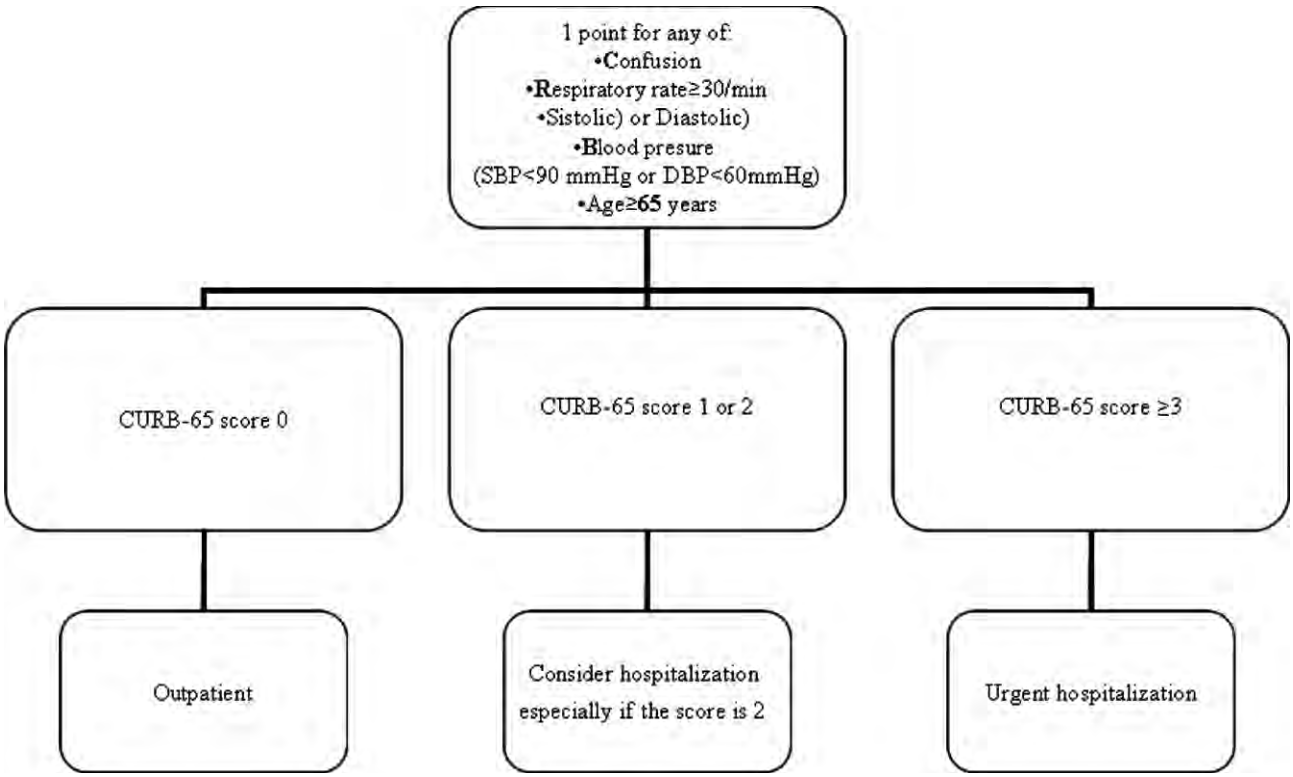

Figure 6. CRB-65 score used to determine the management of CAP when only clinical parameters could be assessed (apud 12)

Preferred treatment	Alternative treatment
British Thoracic Society Guidelines (12)	
Oral amoxicillin	Oral doxycycline or clarithromycin
American Thoracic Society Guidelines (16)	
No comorbidities and without antimicrobial therapy within the previous 3 months	
Oral macrolide (azithromycin, clarithromycin, erythromycin)	Oral doxycycline
Presence of comorbidities or the use of antimicrobials within the previous 3 months	
Oral respiratory fluoroquinolone (moxifloxacin, gemifloxacin, levofloxacin)	Oral βlactam (amoxicillin / amoxicillin-clavulanate) plus a macrolide

Table III. Initial empirical treatment of CAP treated in community

Preferred treatment	Alternative treatment
British Thoracic Society Guidelines (12)	
Non-severe CAP (CURB65 = 2)	
Oral amoxicillin **plus** clarithromycin *If oral administration not possible:* amoxicillin or benzylpenicillin **plus** clarithromycin iv	Oral doxycycline or antipneumococcal fluoroquinolone: oral levofloxacin or moxifloxacin
Severe CAP (CURB65 =3-5)	
Amoxicillin-clavulanate iv **plus** clarithromycin iv (if Legionella strongly suspected: ± levofloxacin)	Benzylpenicillin **plus** either levofloxacin iv or ciprofloxacin iv ***or*** cefuroxime iv or cefotaxime iv **plus** clarithromycin iv (if Legionella strongly suspected: ± levofloxacin)
American Thoracic Society Guidelines (16)	
In-patient, non-ICUI	
Respiratory fluoroquinolone (moxifloxacin, gemifloxacin or levofloxacin, iv or po)	βlactam (cefotaxime/ceftriaxone/ampicillin/ertapenem in selected patients) **plus** macrolide (erythromycin, clarithromycin), po or iv
In-patient ICU	
• βlactam (cefotaxime/ceftriaxone/ampicillin-sulbactam) **plus** azithromycin or respiratory fluoroquinolone (moxifloxacin, gemifloxacin or levofloxacin iv • For *P aeruginosa* infections: • antipseudomonal βlactam (piperacillin-tazobactam, cefepime, imipenem or meropenem) **plus** either ciprofloxacin or levofloxacin **or** • antipseudomonal βlactam **plus** aminoglycozide and azithromycin **or** • antipseudomonal βlactam **plus** aminoglycozide and respiratory fluoroquinolone iv • For CA-MRSA add vancomycin or linezolid iv	

Table IV. Initial empirical treatment of CAP treated in hospital

of illness, comorbidities, adequacy of home support, compliance.

The decision to hospitalize the patient with CAP remains a judgmental one: prognostic scoring systems have been developed only to provide support for this decision, not to replace the medical judgment.

Using the CURB-65 prognostic score, in study cohorts, the risk of 30-day mortality among patients with 0, 1 or 2 score was 0.7%, 2.1% and 9.2%[18]. The mortality was higher when the score was 3, 4 and 5 and the reported rates were: 14.5%, 40% and 57%. The authors suggested that patients with scores 0-1 be treated as outpatients, those with a score of

2 be admitted to the wards and that patients with score 3 or more often require ICU admision[2].

The CRB-65 score is a simplified version of the latter, used when only clinical parameters are available, admission to the hospital being recommended for 1 or more points.

The diagnostic tests used to determine the etiology of CAP may have a number of shortcomings such as: lack of rapid, easy to perform, accurate, cost-effective methods. In outpatients with CAP, if a patient has purulent sputum, a sample for Gram's stain and culture may be examined in order to manage the treatment if the patient is failing to respond to initial empirical therapy. In patients requiring admission, investigations include blood culture, sputum Gram's stain and culture, urinary antigen tests for *Legionella*, pneumococci, the examination of bronchoalveolar lavage in patients with severe CAP on ventilators.

Since the etiology of CAP is identified in less than 75% of cases and is time consuming, the initial antimicrobial treatment will be empirical[19,20]. The selection of specific antimicrobial regimens for empirical therapy is based on a number of principles such as: covering the most likely pathogens, the presence of comorbidities, pharmacokinetic and pharmacodynamic profile, the potential for inducing resistance, the efficacy, the safety profile, costs.

The BTS and ATS guidelines' treatment recommendation is illustrated in tables no. III and IV. According to ATS guidelines, the duration of therapy for CAP should be at least 5 days, and patients should be afebrile for 48-72 hours before discontinuation of therapy[6,21].

According to BTS guidelines, the duration of therapy should be 7 days for outpatients with CAP and 10 days for hospitalized patients with CAP[2,6].

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