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# Guidelines for the management of Community-Acquired Pneumonia in Saudi Arabia: a model for the Middle East region

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**Abstract**

Worldwide, community-acquired pneumonia (CAP) is a common respiratory tract infection and is now a growing public health concern in Saudi Arabia. In an effort to simplify treatment regimens to aid the practitioner, empirical treatment guidelines for CAP have evolved across the international medical community, reducing the number of antibiotics used and improving outcomes. Saudi Arabia and the surrounding region have no such consensus guidelines and this document aims to redress this lack. The potential impacts of developing and implementing CAP treatment guidelines in Saudi Arabia, which are new to the Kingdom, will be examined. Widespread adoption of these SACAP guidelines could lead to nationwide reductions of antibiotic resistance and improvement of clinical outcomes. Ultimately, Kingdomwide uniformity of treatment algorithms provides a foundation for both database generation and valuable outcomes of research in the future.



*Keywords:* Community-acquired pneumonia; Saudi Arabia; Antibiotic resistance; Treatment guidelines

## 1. Saudi Arabian Community Acquired Pneumonia Working Group: guideline development

Practice guidelines are derived statements that lead to informed clinical decision making. Even though clinical practice guidelines in many fields are now widespread, their utility is still unclear and thus currently subject to intense scrutiny. Guidelines can only truly be as useful as their implementation: many practitioners refer to guideline statements daily, others balk at such an imposition on their practice. Successful implementation depends on clarity of the document, as well as its translation to real-time medicine. Guidelines can facilitate nationwide and worldwide comparisons of practice and lead to valuable derived databases. Significant resources have been reserved for guideline development, though their return on investment remains widely uncertain in all medical communities. Guidelines therefore are indeed a 'technology in need of assessment' [1]. Implementing guidelines in Saudi Arabia, a rapidly developing, forward thinking society, with already one of the most sophisticated health care systems in the world, is liable to lead to considerable changes in practice and it is hoped, improved health care delivery. Additionally, as the Saudi Arabian medical workforce is unusually diverse, with a major expatriate component, the management of community-acquired pneumonia (CAP) can be reasonably expected to be more disparate than normal. The need for standardization of CAP therapy is hence further magnified.

In 2000, a series of consensus meetings with regional representatives was held in Riyadh, Saudi Arabia. The Saudi Arabian CAP Working Group (SACAPWG) was thus formed. The SACAPWG is a multidisciplinary group of pulmonologists, infectious disease specialists and internists in the Kingdom, who support the concept of empirical CAP treatment guidelines specific to the

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region. After several consensus meetings, SACAPWG developed this document through current opinion on CAP management, coupled with the knowledge of endemic pathogens, local susceptibility patterns and regional antibiotic resistance. This report represents the final consensus document. These SACAP guidelines aim to standardize the future management of CAP in Saudi Arabia.

## 2. Introduction

The Kingdom of Saudi Arabia is located in the Middle East, bordering the Persian Gulf and the Red Sea, north of Yemen. It is the largest and most populated of the six Gulf Co-Operation Council (GCC) states, occupying four-fifth of the Arabian Peninsula. Saudi Arabia covers an area of about 2,000,000 $km^2$ (900,000 $m^2$) and has an estimated population of 22 million, including 5.3 million non-nationals. Seventy-five percent of the population lives in urban developments while the remaining 25% live rurally. Approximately 7% of rural dwellers are nomadic Bedouins [2].

The Kingdom still enjoys free health care, in contrast to North American systems, where health insurance or third party reimbursement is common and management organizations overwhelmingly drive cost and service control. In Saudi Arabia, free health care provision has lifted the usual constraints known to Western practitioners. Now, well beyond the petrochemical boom years, the duration of free health care in Saudi Arabia may well be limited. As the realities of a restricted economy set in, streamlining clinical management of commonly occurring conditions not only makes clinical sense but also has important economic value. Early moves towards privatization of the health care sector are in hand in Saudi Arabia. The sophisticated Saudi consumer is looking for advanced health care, in the past often journeying overseas. Of late, state-of-the-art medicine is increasingly available at 'home'. These developments are indicators underlining an impending cap on free health care later this century; standardization of therapy is now a pressing need.

Despite major advances in antimicrobial therapeutics, CAP is still associated with substantial morbidity and mortality. No incidence data have been generated in Saudi Arabia at present, though CAP is a major admitting diagnosis at regional hospitals throughout the Kingdom.

In the United States, over 5.6 million people are diagnosed with CAP annually; of these, 1.7 million are over 65 years of age. Most, 4.5 million, are managed as outpatients but the majority of inpatients with CAP are elderly. As Saudi Arabia enjoys decreased infant mortality rates and rapid urbanization, life expectancy is increasing and a rising incidence of CAP can be expected as the population ages.

The costs associated with CAP are enormous. In the United States, Niederman et al. [3] have estimated the annual costs to approach $8.4 billion for the 1.1 million CAP patients hospitalized. People of age 65 and above utilize a staggering $4.8 billion of the total. As is expected, a sharp rise in cost results when hospitalization is required. The average hospital stay for an elderly person with CAP was 7.8 days, costing $7166, compared with a younger CAP patient staying 5.8 days and costing $6042 [3]. Though currently no similar data exist in the Kingdom, these findings are likely to be mirrored in Saudi Arabia. Standardizing guidelines will enable similar economic assessment and database development for CAP costs in this region.

CAP is the sixth leading cause of death in the United States [4]. CAP is not a reportable disease, either in the United States or in Saudi Arabia and therefore exact rates of incidence are difficult to quantify. The elderly account for the vast majority of CAP-related deaths.

CAP related antibiotic related costs constitute a major component of the sum total of expenditure on antibiotics. Despite popular misconception, Saudi Arabia is as cost conscious as any other advanced society. Streamlining and encouraging judicious antibiotic choices through guideline-driven therapy is a natural curb to this mounting cost. Appropriate empirical therapy selection without guideline documents remains difficult. Physicians today rely on guidance from consensus panels and national guidelines in an effort to provide rational and standard care treatment for patients.

Regarding CAP management, four major guidelines are important: the American Thoracic Society (ATS) guidelines [4], the CDC guidelines [5], the Infectious Disease Society of America (IDSA) guidelines [6] and the British Thoracic Society (BTS) guidelines [7]. Combined these guidelines drive much of the standards of pneumonia care in Saudi Arabia reflecting the diverse backgrounds of the expatriate workforce throughout the Kingdom. This diversity in training and guideline preference probably accounts for some lack of standardization of therapy of CAP within this region.

With myriad groups developing guidelines, it is interesting to examine who utilizes them in practice. Dean and colleagues looked at which physicians treated CAP patients in a study of 16,420 episodes of pneumonia [8], only 11.7% of all pneumonia episodes were attended to by subspecialists. Of all CAP patients, a mere 10.6% were seen by chest physicians and 0.9% by an infectious disease specialist. Greater frequency of specialty consultation was seen in those patients who needed hospitalization (20.0% vs. 8.6%) or who died (20.5% vs. 11.2%).

Dean demonstrated even though the primary care physician treats most patients with CAP without seeking the advice of a respiratory or infectious disease specialist, he has the lowest case volume and rarely sees many patients with this illness, in stark contrast to the specialists. Overall, 41.7% of primary care physicians saw less than one case of CAP per month. These guidelines therefore have been written specifically for the primary care physician practicing in Saudi Arabia.

## 3. Presentation

CAP is diagnosed on the basis of a suggestive history, compatible physical findings and new infiltrates on a chest radiograph. No criteria or combination of criteria based on history and physical examination have been found to be gold standard [4–6].

As an important observation, TB remains highly prevalent in the Middle East region and in fact is endemic to Saudi Arabia, with a reported incidence of 17 per 100,000 population (Saudi MOH, personal communication, 2001). Any patient presenting with CAP could potentially be a case of primary pulmonary TB. The diagnosis and management of TB are beyond the scope of this paper and will not be discussed here, though appropriate diagnostic tests for *Mycobacterium tuberculosis* may be indicated if the patient fails to respond to therapy for bacterial CAP. Any suspicion of acute TB warrants subspecialist opinion.

## 4. Risk factors for CAP

Risk factors identify likelihood of disease onset and may allow prognostication. Prognostic factors can focus resources and efforts on those who may need special observation. Hospitalization rates rise with increasing age. Age alone may not be an isolated factor contributing to an increased risk; rather it is the companions of age that increase risk. As the Saudi population ages, more elderly will present with CAP, rates of hospitalisation for CAP can be reasonably expected to rise.

Risk associated with tobacco consumption is an important modifiable risk factor and warrants mention. Cigarette smoking in Saudi Arabia is prevalent, though no published statistical data exist. Cigarette smoking alone is the most important risk factor for morbidity and mortality in developed countries today. Tobacco smoking is recognized as a risk factor in chronic obstructive pulmonary disease (COPD) genesis and is a recognized risk for respiratory infections including bronchitis and other respiratory infections. Smoking alters host defenses through oxidative stress and altered responsiveness of inflammatory cells, effects that are directly mediated by chemicals in cigarette smoke. The relationship between CAP and cigarette smoking has been examined in a few studies and smoking is accepted as a risk factor for CAP.

Almirall et al. [9] investigated the relationship of smoking to CAP in a population-based study of adults. The study was sited in a residential area of 74,620 Spanish residents in an urban area of Barcelona, Spain, between 1993 and 1995. Over the 2-year observational period, 205 patients with CAP aged between 15 and 74 were identified [9]. Of all CAP patients, 64.9% were either current or ex-smokers. Amongst the control group, 56.2% were current or ex-smokers. A positive trend for CAP was seen in smokers vs. non-smokers, increasing with duration of habit and increasing quantities smoked and cumulative cigarette consumption. The proportion of CAP cases attributable to any tobacco consumption ever was found to be 32.4%. Thus, cigarette smoking is one of the few modifiable factors when any patient presents with pneumonia. Extolling the benefits of smoking cessation is still worthwhile. It may reduce the likelihood of a second pneumonia.

## 5. Epidemiology

The optimal management of CAP is controversial. Differential etiological diagnosis of CAP demands a focus on etiology. An understanding of local epidemiology is paramount and leads to focused and successful empiric therapy.

In spite of advances in microbiological and serological investigations over the last two decades, etiological attribution remains difficult in CAP. Even using careful and exhaustive investigations, the etiology of CAP remains unknown in up to 50% of patients with CAP [3–5]. It is fair to predict that in less than optimal but real-life ambulatory practices, the likelihood that microbiological investigations would aid in the therapeutic decision process is small. However, knowledge of likely pathogens is imperative. Even when a pathogen is identified, empirical therapy is usually acceptable for providing adequate coverage to the extent that alteration in therapy is only performed in less than 10% of those cases [10].

Most patients diagnosed with CAP grow pneumococci, if any etiological agent is recovered. Other organisms are also important in the etiology of CAP. They include *Haemophilus influenzae* and *Chlamydia pneumoniae* as well as *Legionella pneumophila*, *Staphylococcus aureus* and *Branhamella catarrhalis*. Note that 30–60% of all cases of CAP do not yield positive microbiology.

Internationally, 'atypical' pathogens such as *Mycoplasma pneumoniae*, *C. pneumoniae* and *L. pneumophila* are common and important pathogens in CAP [11–13].

'Atypical' pathogens can cause varying severity of disease even resulting in hospitalization [14,15]. Recent data suggest that atypical organisms, such as *C. pneumoniae*, may serve as important co-pathogens with more 'typical' pathogens such as *S. pneumoniae* [16].

The pneumococcus is the most commonly isolated bacterial pathogen causing CAP in Saudi Arabia, just as in the United States. Even in this era of improved antimicrobial therapy, mortality rates for CAP can be as high as 20% for the bacteraemic elderly patient. Antibiotic resistance is now of particular concern in Saudi Arabia, as elsewhere in the world.

### 5.1. Antibiotic resistance patterns in Saudi Arabia

Antibiotic resistance is a multifactorial problem driven by a number of vectors. Looking through the lens of the Saudi experience, a number of common circumstances are conducive to antibiotic resistance. Over the counter, availability of antibiotics is widely seen throughout the Kingdom, even though MOH mandates a prescription to be issued prior to any sale to an individual. Enforcing this requirement is not always easy. Private, office-based practices are particularly guilty of over-prescription and contribute to resistance. Often these physicians have financial incentives for medicating the patient [17]. A second factor driving increased antibiotic resistance is the limited availability of both infectious disease specialists and infection control personnel. This lack may be another barrier to intelligent antibiotic practice patterns. Instituting a nationally standardized document or even having access to a national statement on CAP therapy will be one tool towards reducing this uncontrolled, indiscriminate use of antibiotics.

Rates of antibiotic resistance may vary widely across institutions within the Kingdom. Knowledge of local rates of resistance is important. Organisms can show resistance to one agent or to multiple agents; unfortunately cross-resistance is becoming more common.

Within the Kingdom, susceptibility profiles of antibiotics against intracellular pathogens such as *C. pneumoniae* and *M. pneumoniae* are not routinely performed. Animal and clinical data indicate that macrolides, tetracyclines and fluoroquinolones remain effective against these organisms but penicillins and cephalosporins are inactive [16,18]. At the time of writing, no regional antibiotic susceptibility data are available for atypical pathogens, and thus only antibiotic susceptibility data with typical pathogens will be discussed.

The prevalence of antibiotic resistance in typical respiratory pathogens such as *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* obtained from Saudi Arabia has been reported previously [19–21].

The National Committee for Clinical Laboratory Standards classifies pneumococcal resistance as susceptible if MIC (minimum inhibitory concentration) is less than 0.06 mg/l, intermediate if MIC is 0.1–1.0 mg/l and resistant if MIC is greater than 2.0 mg/l [22]. These categories were initially selected based on the treatment of meningitis and otitis media; they are probably inappropriate for treating CAP. There is now a move towards reclassifying levels of resistance with an upshift, as laboratory resistance may not always be indicative of clinical response.

Nevertheless, using these imperfect definitions, in Saudi Arabia, penicillin–intermediate-resistant (MIC, 0.12–1.0 mg/l) pneumococci and penicillin–resistant (MIC > 2.0 mg/l) pneumococci account for 40.7–51.2 and 6.2–14.8% of strains, respectively. These rates are very high when compared with North America and Europe.

However, pneumococcus resistance rates to amoxycillin and third-generation cephalosporins remain low at 3.5 and 4.5%, respectively. *S. pneumoniae* resistance rates are moderate with second-generation cephalosporins and doxycycline (14.9 and 11.1%, respectively) and should be kept in mind when initializing therapy. Macrolide resistance in *S. pneumoniae* in the Kingdom varies from 3.7 to as much as 10.8%, while trimethoprim/sulphamethoxazole resistance is very high at 22.2%.

Its is worth noting that although high rates of in vitro macrolide resistance can coexist with penicillin resistance, there are few reports of macrolide failures in CAP due to drug-resistant pneumococci. This may be the result of the high degree of drug penetration by the macrolides in respiratory tissue and is an example of the disparity between in vitro findings and in vivo response.

The prevalence of β-lactamase-producing *H. influenzae* in Saudi Arabia is also high at 27.9%. Other than high levels of resistance to trimethoprim/sulphamethoxazole, *H. influenzae* is susceptible to the majority of antibiotics.

The prevalence of β-lactamase-producing *M. catarrhalis* is greater than 90%. Low levels of resistance to trimethoprim/sulphamethoxazole aside, *M. catarrhalis* is also susceptible to almost all antibiotics used for CAP treatment.

The extraordinarily high penicillin resistance in Saudi Arabia warrants closer scrutiny. Penicillin-resistant pneumococci (PRSP) can show resistance to multiple agents and hence the term drug-resistant *Streptococcus pneumoniae* (DRSP). Primary care physicians working in the Kingdom need to have a good understanding of DRSP today and how it impacts therapy.

The prevalence of DRSP is rising worldwide. Living in areas with high geographical rates of DRSP need not confer additional risk for DRSP but it does warrant an increased awareness if effective empirical therapy is to

be initiated. The risk factors for DRSP infection include extremes of ages, alcoholism, recent β-lactam therapy (within 3 months), comorbidities, immunodeficiency, child day care attendance, recent or current hospitalization, institutionalization (prison or nursing home) and military personnel.

As a reflection of this growing concern, recent CDC guidelines were developed to resolve several aspects of DRSP in the setting of CAP in the immunocompetent host. The DRSP Therapeutic Working Group (DRSPTWG) came to a number of important conclusions in this area [5].

How important is in vitro drug resistance in DRSP and how do the laboratory findings of varying susceptibility translate at the bedside? DRSP is found to exert significant impact on outcome. Pallares et al. [23] conducted a 10-year study in Barcelona on culture-proven pneumococcal pneumonia. Of the 504 patients, 145 had resistance at MICs more than 0.12 mg/l (intermediate). Pallares found predictors of mortality to be patient factors and not levels of resistance measured. Key patient factors included the presence of shock, multilobar infiltrates and leukopenia, which are direct correlates of disease severity. Unadjusted mortality was indeed seen to be higher with resistance however (38% vs. 24%).

Plouffe et al. [24] studied 590 patients from one Ohio county in United States from 1991 to 1994. Over this period, penicillin resistance increased from 4 to 14%. The mortality rates were unaffected by resistance, though length of stay did increase with isolation of resistant strains.

Metlay et al. [25] looked at DRSP and medical outcomes in a series of 192 adults with bacteraemic pneumococcal pneumonia (without meningitis). Resistance was seen in those from nursing homes or of older age; 44 had non-susceptible organisms and 36 were intermediately resistant. Those with non-susceptible organisms had more severe disease (as measured by formal pneumonia severity scoring tools) and greater suppurative complications. Empyema was seen fourfold more often in those with highly resistant isolates.

Feikin et al. [26] found resistance (in very high penicillin MICs of greater than 4.0 mg/l) not to be a risk for death, but for death after day 4 of hospitalization. Older age and underlying comorbidities were the most important factors influencing death from pneumococcal pneumonia. Once deaths in the early days of hospitalization were excluded, DRSP became an independent risk factor—mortality earlier on is a reflection of severity and not treatment failure.

In summary, DRSP contributes to greater length of stay, and if resistance is high level, greater morbidity in terms of suppurative illness and disease severity. Mortality rates are increased later in the course. As DRSP prevalence rises in Saudi Arabia, patients with CAP may face longer hospitalizations due to more complex courses and an attendant higher mortality. Although atypical agents are thought to be a major cause of CAP either alone or mixed with other pathogens, no solid data from the Middle East on the incidence or prevalence of these pathogens exist.

#### *5.1.1. Assessment of disease severity: the decision to hospitalize*

The decision to hospitalize a patient with CAP is probably the most important factor in determining outcome and often the most difficult decision to make. The ATS observes that disposition of the CAP patient is an 'art of medicine' decision [4]. The considerable variation between different practitioners in the assessment of disease severity influences rates of hospitalization for CAP. Fine et al. [27] looked at this problem in their recent work. By stratifying patients according to severity of illness at presentation, simplified algorithms have been developed.

Fine et al. proposed a prognostic index for CAP-related mortality in 1997 called the pneumonia severity index (PSI). They studied 14,199 inpatients with CAP to derive a prediction rule classifying patients into one of five classes, reflecting 30-day mortality rates of each class. The prediction rule was later validated in a second study on 38,039 CAP inpatients and also on 2287 inpatients and outpatients in the Pneumonia Patients Outcomes Research Team (PORT) cohort study.

PSI is a cumulative score of 20 variables derived from the history, physical examination, laboratory tests and chest X-ray of the CAP patient. The PSI score has been validated in various settings and has been shown to risk stratify CAP patients at risk of dying [28–31].

PSI, which resulted from this group, is now widely used to predict mortality in CAP patients and help in the decision to admit. Though undoubtedly a new and useful tool, certain limitations must be noted and practitioners evaluating the CAP patient need to be aware of these caveats.

Age is heavily weighted in PSI, particularly in males. In fact high risk of mortality is identified as a score of more than 90 points and males are ascribed one point for each year of age (women are allowed some compensation by allowing age minus 10 as the points ascribed for chronological age). Hence, any elderly male with a chronic illness, of any kind, will automatically have enough points to meet criteria for the high risk group and be admitted without any assessment of the severity of the pneumonic; probably a crude overestimate of true risk. Like all prediction tools or guidelines, their value exists only in the context of, and as an adjunct to, good clinical acumen.

Most practitioners find it difficult to remember the score assigned to each variable, which ranges from 10 to 30 [27]. In order to make PSI more user-friendly and

Table 1
The modified pneumonia severity scoring index system (adapted from [27])

| Three key questions: assessing risk of mortality in (CAP) |
|---|
| Age > 50 years |
| One or more of the following comorbidities? |
| Cancer |
| Congestive heart failure |
| Cerebral vascular disease |
| Liver disease |
| Renal disease |
| Unstable vital signs or altered level of consciousness |
| Altered level of consciousness |
| Heart rate > 125 $min^{-1}$ |
| Respiratory rate > 30 $min^{-1}$ |
| Systolic blood pressure < 90 mmHg |
| Temperature < 35 °C or > 40 °C |

*Group I*. 'No' to all three questions. Low mortality risk: eligible for outpatient management of CAP. *Group II*. 'Yes' to 1–2 of the three questions. Intermediate mortality risk: close monitoring or hospitalization, for up to 48 h, while initial therapy is initiated. *Group III*. 'Yes' to all three questions. Moderate to high mortality risk: proceed to hospitalization.

therefore more implemented throughout the Kingdom, SACAPWG modified the original PSI scoring system (Table 1).

The modified PSI scoring system classifies patients into three groups only. Group I consists of patients more than 50 years of age with no significant medical comorbidity and stable vital signs. According to Fine's PSI score, this group is at low risk for death and is therefore safely managed as outpatients.

Group III includes patients who are more than 50 years of age with one or more medical comorbidities and have altered level of consciousness or unstable vital signs. This group would be at least class III or more likely class IV or V in Fine's PSI scoring scheme. As such, they carry moderate to high mortality rates and must be managed in the hospital setting.

SACAPWG identified Group II as those who fall in between Groups I and III; these are patients with intermediate risk. One can either apply the full PSI score to further risk stratify this group or keep these patients under close monitoring while initial therapy is instituted.

The modified PSI scoring system is designed to identify rapidly those patients who can safely be managed as outpatients and hence immediately streamline those patients away from admission. Additionally, it allows those patients who need immediate hospitalization to be admitted post-haste. Using this modified approach, one may overhospitalize patients as there is no detailed substratification of the intermediate group, whether they have five comorbidities or merely one but for a society new to guidelines this will prove a useful initial tool to standardize admission criteria. Once practitioners in the region become familiar with thinking about CAP in this systematic way, applying the full PSI criteria becomes more feasible. The teaching institutions of the Kingdom region will need to lead the way for the entire region in changing practitioner's habits and ultimately changing therapeutic decision making.

Irrespective of the site of care, prompt initiation of empirical CAP therapy is critical to achieve favorable outcomes. Timely therapy can only be given when the disease is recognized and when severity is appropriately assessed. The key to remember is that CAP is an evolving process and patients may well shift between risk groups; the physician needs to be aware and responsive to these changes—and can only do so if the patient is managed in the appropriate setting. Ideally, the first dose of antibiotic must be administered within 6 h of initial medical assessment to improve the outcome [8].

## 6. Principles of empirical therapy

As described earlier, despite local Ministry of Health regulations stipulating prescriptions prior to selling antibiotics, antibiotics are freely available over the counter in Saudi Arabia, often at a fraction of their usual market price. Many of these drugs are within the means of the average Saudi. The market cost of drugs in the Kingdom is determined by a centrally controlled committee at the Saudi Ministry of Health. These prices are based on a wide analysis of manufacturers' prices from well over 40 countries. The Ministry of Health makes the most cost-effective choice and hence many drugs are available at low cost. No health insurance or prescription plans exist in the Kingdom and so the patient self-pays for outpatient treatments. Thus, though it is necessary for these drugs to be affordable until third party payment becomes the reality, the affordability of these drugs opens the gates to antibiotic abuse, both by patient and practitioners alike. The need for education and guideline-driven therapy becomes apparent. Of note, drug costs in the Kingdom are some of the lowest in the region, though extensive comparative studies are needed to see if there are significant differences in over the counter purchasing habits.

Treating CAP depends on age and comorbidities, as well as local epidemiology and disease severity. Table 2 shows the current guidelines for managing CAP in the healthy outpatient, the outpatient with modifying factors or comorbidities and the inpatient with CAP. SACAPWG took into account regional bacteriology, antibiotic resistance data and available antibiotics to formulate these recommendations.

Table 2
Empirical treatment of CAP:[a] therapeutic guidelines

| | First line | Alternative |
|---|---|---|
| *Outpatients* | | |
| Young and otherwise healthy | Macrolide[b] | Doxycycline |
| Comorbid illness[c] or risk factors[d] | Second ceph[e] ± macrolide | Macrolide + β-lactam/β-lactamase inhibitor[f] or respiratory quinolones[g] |
| *Hospitalized patients* | | |
| Ordinary cases | Second or third ceph[h] + macrolide | Respiratory quinolones |
| With suspected aspiration | β-Lactam/β-lactamase inhibitor ± macrolide | Clindamycin ∓ macrolide |
| With bronchiectasis | Anti-pseudomonal third/fourth ceph[i] ± macrolide | Respiratory quinolones ± macrolide |
| *Severe pneumonia* | | |
| No pseudomonas risk[j] | Third ceph + macrolide | Carbapenem[k] + macrolide |
| Pseudomonas risk | Anti-pseudomonas third ceph + aminoglycoside[l] ± macrolide | Carbapenem + aminoglycoside ± macrolide |
| | | Anti-pseudomonas penicillin[m] + aminoglycoside ± macrolide |

[a] Regimen should be tailored upon the results of microbiological testing.
[b] For example, clarithromycin, azithromycin, roxythromycin.
[c] For example, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), cancer, diabetes mellitus (DM), hepatic or renal disease.
[d] Risk factors: recent antibiotics within 3 months, age > 50 years, hospitalization or immunosuppressive therapy within 3 months, DRSP = drug-resistant *S. pneumoniae*.
[e] Second ceph = second-generation cephalosporins (e.g. cefuroxime, cefaclor, cefprozil).
[f] Amoxycillin/clavulanate, ampicillin/sulbactam.
[g] For example, moxifloxacin, levofloxacin, gatefloxacin, gemifloxacin.
[h] Third ceph = third-generation cephalosporins (cefotaxime, ceftriaxone).
[i] For example, anti-pseudomonal third cephalosporin: ceftazidime, fourth cephalosporins: cefipime.
[j] Structural lung disease, prior hospitalization, immunosuppressive therapy.
[k] For example, imipenem, meropenem.
[l] For example, gentamicin, tobramycin, amikacin.
[m] For example, piperacillin-tazobactam, ticarcillin-clavulonic acid.

Initial treatment of CAP has to be given empirically without the help of culture data. Valid cultures are difficult to obtain and results rely greatly on interpretation—even highly trained individuals such as infectious disease personnel and respiratory physicians can have a discrepancy of up to 30% in interpretation. Delaying therapy by 'waiting for cultures' contributes to mortality and morbidity underlining the need for timely appropriate therapy.

DRSP is unlikely in the outpatient unless one or more of the aforementioned risk factors are present and therefore usual therapy needs no modification if risks are not identified. Cardiopulmonary disease, risk factors for DRSP or risk factors for Gram-negatives results in greater likelihood of DRSP to be present. Once hospitalization occurs, DRSP risks must always be considered, both in the ward patient and in the intensive care unit (ICU). The diagnostic work-up remains unchanged, and no evidence exists that the suspicion of DRSP should require additional testing.

Outpatient therapy is considered in two groups: those with and without comorbidities and/or modifying factors. Comorbidities include cardiopulmonary disease, renal failure, and other medical problems. Modifying factors include age over 65, recent β-lactam treatment, immunosuppressive therapy, aspiration risks, alcoholism and structural lung disease such as bronchiectasis.

The patient with no modifying risks of comorbidities can be treated as an outpatient with a single advanced generation macrolide, which would include azithromycin and clarithromycin. These newer drugs are preferred due to their greater activity against *H. influenzae* [31]. Often these agents are once daily, and so compliance is good. If the patient is intolerant of macrolides or macrolide-allergic, doxycycline is a second choice, as its anti-pneumococcal activity ranks lower. Erythromycin would be also acceptable but it is a four times daily drug and gastrointestinal intolerance is common. Additionally, advanced generation macrolides are also good coverage for *H. influenzae*, which is a problem in smokers. Doxycycline remains an alternative to macrolides and is preferred in patients with concomitant brucellosis, which is endemic to Saudi Arabia, though rarely exhibits any pulmonary manifestations.

The outpatient with modifying factors receives a β-lactam added to the above regimen; an alternative would be anti-pneumococcal fluoroquinolone monotherapy. The oral β-lactam needs to be effective against

DRSP, as outlined in Table 2. This regimen provides excellent coverage of both typical (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*) and atypical pathogens (*M. pneumoniae*, *C. pneumoniae*, *L. pneumophila*) including β-lactamase-producing *H. influenzae*, *M. catarrhalis* and penicillin–intermediate-resistant (MIC, 0.12–1 mg/l) pneumococci. Alternative therapy would be a macrolide in combination with one of the respiratory quinolones.

In fact, for certain compliant patients who have access to the office, intravenous (IV) ceftriaxone may be an option and can be switched to oral cefpodoxime after 24–48 h. Any aspiration risks or nursing home residence should be addressed by adding anaerobic coverage.

Inpatient therapy is also stratified by comorbidities and severity. Data now exist that for the admitted CAP patient without comorbidities or modifying factors, monotherapy with intravenous azithromycin is as effective as traditional β-lactam/macrolide combinations. The use of intravenous azithromycin monotherapy is an attractive idea but there are likely to be few patients with CAP in this population who require admission. Intravenous azithromycin is still not registered in the Ministry of Health in the Kingdom. If the patient is macrolide-allergic, anti-pneumococcal fluoroquinolone monotherapy is again appropriate.

For the admitted patient with CAP, empirical treatment is with a second- or third-generation cephalosporin with a macrolide. This regimen provides broad-spectrum activity against both typical and atypical respiratory pathogens as well as *S. aureus*, many Gram-negative bacilli and penicillin–intermediate-resistant *S. pneumoniae*. Alternatives include a macrolide with clindamycin, β-lactam/β-lactamase inhibitor or respiratory quinolone. It should be mentioned that the above treatment guidelines are empiric in nature. Once the causative pathogen is isolated and antibiotic susceptibility testing results are known, the antibiotic regimen should be tailored accordingly.

When DRSP risks and enteric Gram-negative (EGN) risks are present, empirical therapy should be with β-lactam (suitable for DRSP) with a macrolide either oral or intravenous, depending on the severity of CAP. Again, doxycycline is an alternative for those with macrolide allergies. Risks for anaerobic infection should be covered with appropriate agents. Lung abscess if documented should be treated with clindamycin or metronidazole.

The severely ill hospitalized CAP patient needs empirical therapy for pneumococci, Legionella, *H. influenzae* but risk of pseudomonal infection must also be considered. Pseudomonas CAPs can be seen in select patients. Those with no risks for pseudomonas can be treated intravenously, again with an anti-DRSP β-lactam and a macrolide combination though erythromycin in this group is not indicated, as it is frequently not tolerated. A fluoroquinolone can be substituted for the macrolide in those with allergies to cover atypical agents. Anti-pneumococcal fluoroquinolone monotherapy is not recommended as efficacy data in this population is lacking; most of the trials were not conducted in the critically ill CAP patient. When pseudomonal risk factors exist such as structural lung disease or recent hospitalization, two anti-pseudomonal agents should be used, as outlined in Table 3 and coverage for DRSP also becomes necessary. These two requirements can be met with the selected β-lactams as listed.

For inpatients with CAP who are hospitalized to ICU, the recommended antimicrobial treatment is a combination of a macrolide and anti-pseudomonal antibiotics. Aggressive critical care is essential with early mechanical ventilation when appropriate. An aminoglycoside is added if *P. aeruginosa* is suspected. Alternative treatment with a macrolide along with respiratory quinolones is also recommended. As above, an aminoglycoside is added if *P. aeruginosa* is suspected, such as in patients who are immunocompromised (e.g. malignancy, long-term steroid therapy) or have structural lung disease (e.g. bronchiectasis) or had recent hospitalization.

### 6.1. Oral switch therapy in CAP management

Oral antibiotics with good bioavailability have been introduced worldwide for the treatment of systemic infections including CAP. Most new agents are now better tolerated than their earlier counterparts and can be taken once or twice a day, enhancing patient compliance [9]. Recent comparative studies evaluating the pharmacokinetic properties of new oral antibiotics suggest that with a fully functioning gastrointestinal tract, sick patients with CAP can be managed effectively with oral agents starting from the first dose or be switched over from an intravenous formulation to an oral (PO) agent within a few days [10,29,31].

Oral agents should be considered whenever appropriate, even in patients who require hospitalization for CAP. If intravenous treatment is used as initial therapy, sequential switch to an oral agent is recommended as soon as the patient is able to tolerate the drug and has shown clinical stabilization.

Table 3
Oral therapy: patient selection (adapted from references [10,29–32])

| |
|---|
| Exclude critically ill patients |
| Fully functional gastrointestinal tract |
| No history of prior intolerance |
| Monitor tolerance after the switch |
| Clinical response to prior therapy (in a switch patient) |
| Otherwise medically stable |

Table 3 outlines criteria for making the switch to sequential or step-down oral therapy [29,30]. Earlier studies reported IV-PO switch after 3–4 days [10] but more recent data suggest that the switch can be performed after 1–3 days of intravenous therapy [31]. A limited number of studies also support the notion that, in the carefully selected patient, oral therapy can be initiated even as first line treatment in the hospitalized CAP patient [10,29,32].

## 7. Prevention

Prevention of morbidity and mortality due to DRSP and other resistant organisms is imperative and can be considered in three separate areas: improved surveillance, judicious prescription habits, and implementation of the pneumococcal vaccine. Surveillance for *S. pneumoniae* reveals locally prevalent serotypes and can follow progress of the disease within the community. Empirical therapy can be based on knowledge gained by effective surveillance. Additionally, serotype prevalence can change rapidly allowing the antibiotic therapy to be appropriately tailored.

The rapidly increasing incidence of antibiotic resistance in Saudi Arabia demands rigorous application of new treatment regimens and programmes. Such programmes must address three primary needs: to prevent the new emergence of resistant pneumococcal strains (through responsible prescribing, formation of local expert committees to control antibiotic use and development of new agents); to limit the spread of resistant strains (through infection control procedures); and to protect those with DRSP risk factors (through widespread pneumococcal vaccination programmes).

Reduction in driving selection forces caused by inappropriate or ignorant antibiotic usage is the first line approach to reducing antibiotic resistance. This is also probably hardest to modify, as it requires changes in physician behaviors and attitudes. Ecological studies have shown the relationship between the use of particular antimicrobials and the appearance of resistant strains. Limiting unnecessary antibiotic usage is therefore a cornerstone of prevention. Antibiotics are often prescribed to placate the patient or because the physician has a degree of diagnostic uncertainty. Educating the outpatient, or the parent of the child-patient, is vital and CDC has worked to develop patient education materials that can be helpful to the clinician in practice.

Isolates intermediately resistant to penicillin can still be treated with penicillin or aminopenicillin or cephalosporins if given at appropriate doses. Infections due to highly resistant pneumococcus, however, must be treated with antibiotics to which they are susceptible. New antimicrobials are emerging, facilitating their treatment. Antibiotics with the lowest levels of resistance should be selected but they still need to be monitored for emerging resistance. Vancomycin is uniformly effective against all pneumococcal isolates but rigorous control on over-use must be imposed and any legislation respected. Local antibiotic selection committees have key roles to limit abuse of vancomycin and limit the emergence of 'vancomycin-tolerant' strains.

Long-term care facilities, which are yet to become part of the Saudi health care landscape, represent an important reservoir for DRSP, as do the region's institutions with higher levels of resistance in the Kingdom. Antibiotic usage is frequent here and it is estimated that 25–75% of the systemic antibiotics used here could be inappropriate [33]. Chronic antibiotic usage is common and telephoned orders without patient assessment is also widespread contributing to casual antibiotic usage. Rational and limited prescription of antibiotics is valuable. There is a real risk of resistant clones arising in these health care facilities subsequently escaping to the community. In these semi-closed environments, basic infection control policies become very important to limiting intra-institutional spread. The infection control team needs to alert all clinicians of current resistance patterns and aid in rational antibiotic prescribing.

Finally, the available pneumococcal vaccine is widely underutilized both internationally and in the Kingdom. It is a vital tool in eliminating the mortality and morbidity that accompanies DRSP infections, particularly in the elderly. The pneumococcal vaccine carries 23 of the 90 known pneumococcal serotypes and these 23 cause the vast majority of clinical infections seen in the United States, including 85% of all infections seen in the elderly due to pneumococci. Epidemiological data have shown the vaccine to be effective in preventing invasive pneumococcal infection in the elderly with certain chronic medical conditions. Overall efficacy in the immunocompetent over 65 years of age is 75%, but efficacy tails off with advancing age likely due to reduced antibody formation later in life. Data regarding noninvasive pneumococcal disease (bronchitis or pneumonia without bacteraemia) are unknown but vaccination in the elderly has been shown to be cost-effective. Compliance in even the most advanced health care systems remains poor; in the 1995 Behavioral Risk Factor Surveillance System, only 35% of elderly Americans ever reported receiving any dose of pneumococcal vaccine. Vaccination rates varied from 11.6% in New Jersey to 46.6% in Arizona [34]. Educational and vaccination programmes to combat this problem are actively in development in the Kingdom. They must be fully implemented for society to begin deriving the cumulative benefit. The CDC advisory committee on immunization practices recommends pneumococcal vaccine for all over the age of 65. The vaccine is also recommended for those under the age of 2 who have

chronic medical conditions, which predispose them to invasive pneumococcal disease. If the patient has been vaccinated at an age less than 65, then a repeat dose can be administered, provided that 5 years have elapsed since the initial dose.

Both the influenza vaccine and the 23-valent pneumococcal vaccines are currently available in Saudi Arabia but no national policies are yet in place. Recent national data on prevalence and pneumococcal serotypes for vaccine susceptibility both for the adult and children revealed that 58% of serotypes leading to blood and CSF diseases are included in the 7-valent vaccine. Furthermore, the 9-valent and the 11-valent vaccines included 62 and 74% of the invasive serotypes, respectively. The non-conjugated 23-valent vaccine would have covered 73% of invasive serotypes in our study [35]. National policy making in this area is soon to follow and certain institutional vaccination programmes are now held during the influenza season.

## 8. Future goals of SCAPWG

As the life expectancy rises in Saudi Arabia and infant mortality falls, more health care resources will be expended on an aging population. CAP incidence will inevitably rise. The economic and clinical burden exerted by CAP will only increase, underlining the need for a developed and efficient nationwide standardization of therapy. This document is the first step towards this new efficiency.

The SACAP guidelines represent the first consensus statement on management of CAP in Saudi Arabia today. The initial goals of SACAPWG include adoption of these guidelines nationally in the Kingdom, with parallel support from the neighboring states in the region. The Saudi Ministry of Health will play a leadership role in successful implementation as the Executive Office for Ministers of Health of GCC states is also based in Riyadh and the open communication lines enjoyed between the two will consolidate regional support.

Long-term goals include learning from both the development and implementation of these guidelines. The development of this document has already outlined how much work remains to be done. Once this document is applied in daily practice in Saudi Arabia and, it is hoped, throughout the region, valuable databases need to be generated using the simple classifications outlined in SACAP guidelines, enhancing understanding of this important area. Databases detailing microbiological, clinical and mortality data looking at CAP in Saudi Arabia will prove essential to any focused and intelligent modification of this statement and, in turn CAP management practices in the future. Saudi Arabia and the Middle East region can then expect to make valuable contributions to CAP management worldwide, particularly in light of the unusual antibiotic resistance patterns found in Saudi Arabia.

Guidelines, it must be emphasized, are just that they are useful tools to be applied in conjunction with good clinical acumen. Combining good principles of therapy, and clinical experience with managing CAP patients, can only lead to more effective management. Furthermore, SACAPWG recognizes that guidelines are 'documents in evolution' and will need regular revisions. Revision must reflect the changing microbiological and clinical environment, which now characterizes the rapidly developing Saudi Arabian health care system. The tremendous health care resources that the Kingdom enjoys can be best utilized only through judicious management principles; admitting those who will benefit from admission and identifying those who do not need inpatient management are examples of sensible resource use.

Exactly how these guidelines will impact CAP management in Saudi Arabia will be of great interest and need exists for the development of audit systems to measure and evaluate for any changes in practice engendered by this document. Audit of the content, utility and impact of these guidelines are essential and will contribute to the revision of these guidelines. Saudi Arabia's first step towards guideline-driven therapy and, in the future, guideline-driven policy making, is sure to become benchmarks towards to health care provision throughout the Middle East.

## Appendix A: Saudi Arabia Community-Acquired Pneumonia (SACAP) Working Group

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